APPROVED: 27 June 2024

Annex A

Public consultation on the draft scientific opinion on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283

European Food Safety Authority (EFSA)

Abstract

In line with the EFSA's policy on openness and transparency, EFSA conducts public consultations on draft scientific outputs in order to receive input from the scientific community and stakeholders. EFSA conducted a public consultation to receive input from interested parties on the draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. The draft guidance was prepared by the Working Group on Novel Foods of the EFSA Panel on Nutrition, Novel Foods and Food allergens (NDA Panel). The NDA Panel endorsed the draft guidance for public consultation at the 145th Plenary meeting on 31 January 2024. The public consultation was open from 15 February 2024 until 14 April 2024, hosted on the Open EFSA website and supported by an electronic comment submission tool including instructions to stakeholders for comment submission. EFSA received 715 comments from 47 interested parties. EFSA and its NDA Panel wish to thank all commentors for their contributions to this work. The present Annex contains the comments received and responses from the NDA Panel on how they have been taken into consideration towards finalising the guidance. The final guidance was adopted at the 150th NDA Panel Plenary meeting on 27 June 2024 and will be published in the EFSA Journal.

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1 Introduction

1.1 Rationale for the public consultation and summary of its outcome

In line with European Food Safety Authority (EFSA)'s policy on openness and transparency, and for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key topics. Accordingly, the draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 together with its Appendices was released electronically for public consultation from 15 February 2024 until 14 April 2024 by means of an e-submission tool. The comments were made publicly available immediately after the closure of the public consultation in Open EFSA.

Comments were received in the electronical tool from 47 interested parties from 14 countries. Table 1 provides an overview on the interested parties that have submitted comments through the electronic submission.

Table 1: Overview of stakeholder comments

Stakeholder	Category[(a)]	Country
Aletheia: Il Segreto Del Buon Vivere	Other	Italy
Analyze & Realize GmbH	/	Germany
AseBio - Spanish Bioindustry Association,	NGO	Spain
Atova Regulatory Consulting Sl	/	Spain
BaseClear	Industry - SME	Netherlands
Bene Meat Technologies A.S.	Industry - SME	Czech Republic
Bonumose, Inc.	Industry - SME	United States
Cellular Agriculture Europe	/	Belgium
Dwayne Holmes	Personal capacity	Netherlands
EU Specialty Food Ingredients	EFSA Registered Stakeholder	Belgium
EuropaBio	EFSA Registered Stakeholder	Belgium
European Industrial Hemp Association – EIHA	EFSA Registered Stakeholder	Belgium
Food Fermentation Europe	EFSA Registered Stakeholder	France
Food Safety & Nutrition Consultancy	Consultant	Netherlands
Food Safety Authority of Ireland	Public Authority in EU Member State	Ireland
Food Supplements Europe	EFSA Registered Stakeholder	Belgium
FoodchainID	Consultant	France

Stakeholder	Category[a]	Country
FoodDrinkEurope	/	Belgium
Gaiker	Academia/Research Institute	Spain
German Federal Institute for Risk Assessment	Public Authority in EU Member State	Germany
International Probiotic Association - Europe (IPA Europe)	EFSA Registered Stakeholder	Belgium
Intertek	/	United Kingdom (excluding Northern Ireland)
Istituto Zooprofilattico Sperimentale Delle Venezie	Public Authority in EU Member State	Italy
Jeremy Coller Foundation	NGO	United Kingdom (excluding Northern Ireland)
Katharina Julia Brenner	Personal capacity	Germany
Mario Stahl	Personal capacity	Germany
Medfiles Ltd	Consultant	Finland
Ministry of Regional Affairs and Agriculture	Public Authority in EU Member State	Estonia
National Food Institute, Technical University of Denmark	EFSA Registered Stakeholder	Denmark
Novonesis (merger of former Novozymes and Chr. Hansen)	Industry - Multinational	Germany
Nutraveris - A FoodchainID Company	/	France
Pen & Tec Consulting S.L.U. (Trading As Argenta®)	/	Spain
PETA Science Consortium International E.V.	EFSA Registered Stakeholder	Germany
Planet A Foods GmbH	Industry - SME	Germany
Ronald van Ree	Personal capacity	Netherlands
Solar Foods	Industry - SME	Finland
Specialised Nutrition Europe (SNE)	/	Belgium
Swedish Food Agency	Public Authority in EU Member State	Sweden
Synpa, French association of specialty food ingredients manufacturers and distributors	Industry - SME	France
The Good Food Institute Europe	NGO	Belgium
Undisclosed	Personal capacity	United Kingdom (excluding Northern Ireland)
Undisclosed	Personal capacity	Germany
Undisclosed	Personal capacity	Netherlands

Stakeholder	Category[(a)]	Country
University Medical Center Utrecht	Academia/Research Institute	Netherlands
Vaclav Bazata	Personal capacity	Czech Republic
VTT, Technical Research Centre of Finland	Academia/Research Institute	Finland
SME: Small Or Medium-Sized Enterprise; NGO: Non-Governmental Organisation (a) as indicated by the stakeholder.		

1.2 Assessment of comments and use for finalisation of the Opinion

The comments received were duly considered by the EFSA WG on Novel Foods and the EFSA NDA Panel and wherever appropriate taken into account for the finalisation of the draft Guidance. Tables 2 to 78 provide a detailed list with all comments received from interested parties together with EFSA NDA Panel responses and explanations how the comments were considered in the final Guidance. Some comments, especially those suggesting editorial changes, have been directly addressed in the text of the Guidance, if they were considered appropriate. Duplicate comments have been removed from this Annex (duplication was identified when the following conditions occurred simultaneously: the same commenter, the same comment, and in the same section of the Guidance).

EFSA wishes to thank all commentors for providing comments during the public consultation of the draft Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283.

2 Comments received and responses.

Table 2: General principles

Comment number	Commentor	Comments	EFSA NDA Panel responses
7	Undisclosed (personal capacity)	Lines (322-323) Point 9 'Deviations from the requirements specified in the respective sections of this guidance document must be justified' should be highlighted in its own right as its the fundamental principle of the guidance.	The Panel acknowledges the concerns expressed. This point is already a well-established element among the Guidance's general principles and is sufficiently emphasised.
39	Intertek	Lines 329 to 333 – Regarding use of New Approach Methodologies (NAMs), there are no specific references to these methods in the toxicological testing section of this guidance (Section 8). Recommend to include examples of NAMs that could be used to complement the existing classical toxicological testing methods, within the Section 8 sub-sections.	The Panel acknowledges the concerns expressed. Sections 7 (Absorption, Distribution, Metabolism, and Excretion) and 8 (Toxicological Information) of the Guidance highlight where additional animal studies may be relevant or even necessary. Methods evolve, and examples can quickly become outdated. The key takeaway is that a NAM must be validated.
48	Specialised Nutrition Europe (SNE)	Page 10 line 308 and page 11 line 320 It would be recommended to EFSA to phrase this as comprehensive review of 'all scientific evidence' relevant to the safety appraisal of the novel food. The terminology 'in favour' 'not in favour' bears some subjectivity in interpretation. Page 11 line 330-335 It would be strongly recommended to EFSA to allow for the definition of minimum requirements and a process making applicants eligible to raise the question to EFSA prior submission to have the discussion on the decision or not to run an in vivo/animal study. It is about animal protection/welfare but also scientific relevance and costs.	The Panel considers that no change to the Guidance is needed with regard to the terminology 'in favour' and 'not in favour'. With regard to the in vivo studies, the Panel acknowledges the concerns expressed, and wishes to highlight that the tiered approaches proposed across different sections of the Guidance address this point.
62	Nutraveris - A FoodchainID company	Section 6: EFSA clarifies the requirements for an application related to the modifications of the conditions of use. However, in the case of a change has no impact on bioavailability, safety testing, exposition, etc, is it acceptable for EFSA to provide an application covering only the section of the application affected	The example provided in the comment concerns not only the conditions of use and anticipated intakes but also the production process. Even with a highly purified

Comment number	Commentor	Comments	EFSA NDA Panel responses
		by the modification? Example: for an application requesting a new food category for an ingredient already authorised, would it be possible to present data only for the sections 'proposed uses and use level and anticipated intake', stability in the food matrix and ADME if not already assessed, and a discussion on the safety of this new use, and not to provide data for other sections not affected by the change (identity, production process, compositional data, specifications, history of use, nutritional information, toxicity, human data and allergenicity).	substance, factors such as residual substances, the presence of small particles, and allergenicity risks could differ. Moreover, even if the main substance is already authorised, an update of the available literature is required. Additionally, regarding toxicological data, the applicant must provide a justification for the absence of toxicological studies using the novel food as test material. The Panel considers that no change to the Guidance is needed.
83	BaseClear	1) In lines 295-300 mentioned 'data and information should be provided concerning the history of use ... to support the safety of the novel food.'. Clarify the specific criteria or standards for determining when scientific justification and argumentation are sufficient to waive the requirement for certain data or information in sections such as the history of use, toxicological information, nutritional information, and allergenicity. This could include providing examples of scenarios where such waivers may be appropriate. Besides, it will be very helpful to offer guidance on what constitutes adequate scientific justification and argumentation, including the types of evidence or reasoning that should be provided to support the decision to omit certain data or information. 2) In lines 324-328 mentioned quality systems and the accreditation of involved facilities. Provide clear guidance on the qualifications and standards required for facilities conducting analyses/tests on the novel food. This could include specifying the necessary accreditations, certifications, and quality systems, such as GLP, GMP, GCP, and applicable ISO systems.	The Panel acknowledges the concerns expressed. It should be highlighted that when there is no 'history of use' data, this criterion can be waived. The requirement for toxicological studies depends on factors such as compositional data, details of the production process, the extent and quality of 'history of use' data, anticipated intake, and available toxicological and/or human studies in the literature. Typically, it is a combination of these factors. It is recommended that applicants review EFSA opinions on previously evaluated, ideally relevant, novel foods.
90	Undisclosed (personal capacity)	Systematic Review Criteria (Lines 311ff, page 10). It would be beneficial for EFSA to outline specific cases or criteria under which a systematic review, following the 2010 EFSA guidance, is mandatory. This clarity will help stakeholders prepare more thoroughly for compliance.	'General principles' are inherently broad. The purpose and objective of a systematic review can be found in the referenced EFSA Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel responses
			The guidance outlines across its various sections when the principles of EFSA (2010) should be considered. Applicants may also opt to apply these principles to additional areas not explicitly specified in the guidance to further enhance the quality of their application dossier. The Panel considers that no change to the Guidance is needed.
96	The Good Food Institute Europe	Line 301-303: Applications which concern an already authorised novel food may relate to changes of the production process, specifications, or the conditions of use, e.g. adding a target population, adding uses (add new food categories to which a novel food is intended to be added) or use levels. Comments: EFSA should clarify what specific elements of 'changes of the production process' would make re-authorisation necessary. For example, whether a material input change would always reflect a production process change. EFSA should also urgently consider the imposition of 'amendment notification processes', such as those used by the US Food and Drug Administration, which provide clarity on the path to notification for pre-authorised products with amendments to production processes or input materials.	The decision on whether a change in the production process requires an application must be made by the European Commission and the competent national authorities, which should be consulted in such cases. The Panel considers that no change to the Guidance is needed.
117	Medfiles Ltd	Point 11) Comment P11 L329-345: Medfiles welcomes strengthening of the 3R principle throughout the guidance and that a comprehensive/detailed chemical characterisation, literature review for toxicologically (and nutritionally) relevant substances identified in the characterisation and in vitro studies should be conducted prior to any animal studies. Nevertheless, EFSA notes that 'a subchronic study is often needed', which gives the impression that even if the Applicant provided a proper data based on the 3R principles (but not its own 90-day study), there is a great chance that 90-day study would be requested anyhow by EFSA. Thus, could EFSA consider reflecting in its guidance better that in fact the 90-day study could be waived and give examples when and based on which	The Panel considers that all comments regarding component-based risk assessment, the compositional comparison of the novel food to a known safe food or ingredient (e.g., using omics and/or fingerprinting techniques), in silico studies, TTC, omics, NAMs, and the use of data on MOAs/mechanisms are well-founded. These approaches have already been applied in previous Novel Food assessments conducted by the EFSA NDA Panel. It is

Comment number	Commentor	Comments	EFSA NDA Panel responses
		data this could be possible? E.g. Medfiles assumes that if the applicant is able to carry out a component-based risk/safety assessment concluding the safety of a novel food, this could be one way to avoid a 90-day study. Similarly, Medfiles assumes that if the Applicant was able to conduct a compositional comparison of the novel food to a food/food ingredient known to be safe e.g. by using omics and/or fingerprinting techniques a 90-day study could be omitted. Hence, could EFSA consider adding this type of guidance in order to waive the 90-day study, please. We also noted that guidance also incorporates better the use of read-across, in silico (QSAR), TTC, omics, (in chemico could be added) and other NAMs as well as use of data on MOAs/mechanisms. In line with 3Rs, Medfiles proposes that the guidance should take more stock about that component-based mixture risk assessment as this could be very relevant in case of simple mixtures. Feedap is using this approach e.g. for botanicals. Much toxicological literature data are already available. In addition, Medfiles notes that TKplate and its use is not considered in this guidance. Therefore, Medfiles proposes to add it to the guidance in view that it would become available for all to use. P9 L329-335 11) Referring to Directive 2010/63/EU12 329 , Regulation (EU) 2015/2283 emphasises the 3 Rs, i.e. replacing, reducing, refining animal studies. This goal to reduce animal studies to the minimum needed is also in line with the EU's chemicals strategy for sustainability and EFSA's Strategy 2027 to develop and integrate new scientific developments focusing on NAM -based methods and the minimisation of animal testing. When these methodologies are qualified or become validated as alternative approaches, applicants are encouraged to make use of them to provide data on the safety the novel food. Comment: Medfiles notes that the fact is that as far as the EFSA Scientific Committee (which deals with horizontal EFSA Guidance documents), does not update its Guidance on default values and the toxicological approach, these new toxicological approaches will not be accepted in novel food safety assessments. It is clear that new toxicological methods will not be included to the guidance before they are	recommended that applicants review EFSA opinions on previously evaluated, ideally relevant, novel foods. The Panel agrees that exploring component-based risk assessment and other suggested methods could help reduce or avoid the need for a 90-day study, depending on the level of compositional characterisation, knowledge of the novel food source, exposure data, and other relevant information. The Panel notes the recommendation to provide examples but considers it impractical given the vast array of potential scenarios and factors that need to be considered. Horizontal guidance documents may evolve over time. The Panel aims to avoid frequent revisions of specific guidance documents, such as the Guidance on Novel Foods, in response to changes in horizontal guidance documents. It is essential to consult and carefully consider the applicable horizontal guidance documents in their entirety whenever relevant.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		validated. In principle, the EFSA Panels cannot accept the new methods not yet included to the horizontal EFSA Guidance documents. So, why to mention them here? To follow the scientific development it would be essential to update also that horizontal Guidance as soon as possible.	
139	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Lines 301-310 : Point 6 There is no explanation of what constitutes a production process change that might result in a qualitative or quantitative change. Suggest further explanation or guidance on level of changes that would require updates, i.e., anything that produces significant change to the specification would be a significant change. This is not clear how the determination will on which guidances will be applicable. The EFSA Food contact guidance (https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4357) states that polymers >1000 Da are not absorbed in the intestinal tract. This current guidance does not address polymer molecular weight and absorption leading to the question of which guidance is correct when considering absorption of large molecular weight polymers. Suggest that a definition of production process changes is needed, i.e., anything that produces significant change to the specification would be a significant change similar to enzyme guidance (https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2021.6851) ` 2. Lines 301-310 : Point 6 : on process changes requirements - we don't know the novel food production processes because they are covered by confidentiality. How can we know the novel food we are making has a different process? 3. Lines 322-323 Point 9 : on deviations should be clarified or adhered to in each section unless justified is a good `catch all` statement and could be highlighted in its own right? 4. Lines 329-345 Point 11 : encouraging the use of alternative methods and avoid animal testing is welcomed and in line with EFSA's Strategy 2027 but contradictory with the toxicology section which does not sufficiently encourage alternative methods and requires animal testing even at Tier I for certain section.	1. The decision on whether a change in the production process requires the submission of an application falls under the competence of the European Commission. Generally, if a food business operator (FBO) places a novel food on the EU market, the novel food must comply with the EU Union List, which outlines specific requirements. All novel foods must adhere to these requirements. If the FBO is confident that their food meets these standards and is safe, there is no need to submit an application. 2. However, if the FBO has any doubts, they should consider contacting the competent national authorities and the European Commission. 3. Please refer to the response to comment 7. 4. Please refer to the response to comment 117.

Comment number	Commentor	Comments	EFSA NDA Panel responses
184	Istituto zooprofilattico sperimentale delle venezie	Point 6) The need to apply for any change in production process can have effect on innovation and competitiveness. In addition it sound quiet inconsistent in regulatory context characterised by FBO's responsibility on food safety. At least for production process change that do not affect final composition maybe some amendment could be done. Another point is linked to the difficulty in enforcing such requirements.	Not every change requires an application. Whether a change in the production process necessitates submitting an application is a decision within the competence of the European Commission. Please refer to the response to comment 139.
192	EU Specialty Food Ingredients	1. Lines 301-310: The applicability of the EFSA guidances is not very clear. For instance, the EFSA Food contact materials guidance (https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4357) states that polymers >1000 Da are not absorbed in the intestinal tract. This current guidance does not address polymer molecular weight and absorption leading to the question of which guidance is correct when considering absorption of large molecular weight polymers. 2. Lines 330-335: We appreciate EFSA's efforts to minimise animal testing and the advocacy to use NAM-based methods once they are validated as alternative approaches. However, EFSA's initiative will have only limited impact, if it is limited only to the EU, as many products are intended for global authorisation. We therefore encourage EFSA to advocate for this approach and promote it also to other authorities around the globe. EFSA being the pioneer in this topic is great but we need authorities from other to accept NAM-based methods as well in order to minimise animal testing globally.	1. Absorption aspects are addressed in the ADME (Absorption, Distribution, Metabolism, and Excretion) section of the guidance. The applicability of specific requirements, including those related to the absorption of large molecular weight polymers, can vary depending on the identity and characteristics of the novel food. Applicants should refer to the ADME section for relevant criteria and tailor their investigations based on the specific nature of their novel food. 2. The Panel appreciates the recognition of EFSA's ongoing efforts to consider NAMs in its assessments. However, promoting the use of NAMs in the risk assessment of regulated products is outside of EFSA's remit. Please refer to the response to comment 39.
263	Dwayne Holmes (personal capacity)	Page 11, Line 315 – Clearly define cases or criteria when systematic review following EFSA (2010) guidance would be applicable.	Please refer to the response to comment 90.
281	Katharina Julia Brenner (personal capacity)	Systematic Review Criteria (Line 315, page 11) Comment: The guidance should clearly outline the situations in which a systematic review is necessary. Providing explicit criteria or cases for when to follow EFSA (2010) guidance on systematic	Please refer to the response to comment 263.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		reviews would help ensure consistency and comprehensiveness in novel food assessments.	
306	Food Safety & Nutrition Consultancy	1. Following lines 254-256: if the composition of the novel food is not essentially different from existing foods then the prior approach of 'substantial equivalence' should be re-introduced. It is not needed to re-invent the wheel. Rather EFSA should make use of existing data. Such would allow a fast(er) track towards authorisation. Hence if the composition is qualitatively comparable to existing foods and grossly also quantitatively please unlock the door (again) for substantial equivalence. This is a real opportunity for EFSA and for innovation. [this comment towards re-introducing substantial equivalence can also deserve a place elsewhere: by preference as a separate chapter] 2. lines 329 ss: whereas I agree, this would also ask EFSA to not demand animal studies in case these are not needed. Example: 90-d studies and genotoxicity studies for alternative proteins. Realise that if EFSA demands then this can be a hollow phrase.	1. It should be noted that the substantial equivalence notification procedure is no longer in place since the concept of 'substantial equivalence' has not been retained in Regulation (EU) 2015/2283. The Panel considers that this comment goes beyond the scope of this Guidance. 2. The guidance outlines a tiered approach to toxicity testing for animal studies. Applicants have the option to present arguments justifying why certain studies may not be necessary for assessing the safety of their product(s).
317	EuropaBio	We consider that this guidance should be aligned across different EFSA guidance documents, including references whenever necessary.	The Panel would like to highlight that this aspect has already been considered in the Guidance.
432	Food Supplements Europe	1. Lines 278-280 When new or updated guidance is published, it would be good to specify from what moment the guidance will apply to ensure a smooth transition. Especially where the changes relate to fields where the principles have already a long history of application (like most of the novel food requirements), not applying new or updated guidance on applications that have been submitted already or have been compiled in accordance with the previous guidance should not lead to delays or requests for additional data that was not required before. 2. Lines 325-328 It is not clear from the guideline if analytical labs should always be accredited, or if there are exemptions, e.g. internal labs, … It would appear not, as in lines 671-672 it is indicated that if analyses are not performed in accredited laboratories, justification should be provided. Could the	1. The guidance will be implemented from 1 February 2025. 2. Certificates of analyses, along with information on the matrix accreditation and scope of accreditation of laboratories, should be provided. If analyses are conducted in non-accredited laboratories, a justification for this choice must be included. Accreditation of laboratories ensures the quality of data, and data from accredited labs are preferred and more readily accepted by experts during the assessment.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		guidance elaborate as to what would be acceptable justification?	
526	FoodchainID	1. Section 11: While EFSA encourages applicants to follow the 3 R's principles in order to reduce animal studies to the minimal needed, in reality, animal studies are required in the vast majority of NF application in order to determine the safety of the NF and the NOAEL. The current tendency with the in vivo studies required for NF application does not reflect the EFSA's Strategy 2027, and in practice, animal studies are requested for novel food approval. 2. Could EFSA develop the alternative methodologies that EFSA accept in order to follow the 3R's principles? 3. How is the validity of in vivo toxicological studies on a NF conducted without following OECD guidelines?	The Panel acknowledges the concerns expressed. 1. Please refer to the response to comment 306. 2. Additionally, it should be noted that method development is outside the scope of this guidance. 3. The validity of the provided studies is assessed by the Panel through a thorough evaluation process. Although OECD guidelines are highly regarded for their comprehensive and current standards on conducting toxicity studies, the Panel recognises that alternative standards and frameworks may be applicable depending on the nature and specifics of the study and the test item. When such alternative approaches are used, the Panel reviews the studies alongside other submitted evidence to ensure they meet the necessary scientific and regulatory criteria. It is crucial that all aspects of the studies are transparently documented to facilitate a complete and accurate assessment of the evidence provided.
547	Novonesis (merger of former Novozymes and Chr. Hansen)	page 11, lines 330-335: We appreciate EFSA's efforts to minimise animal testing and the advocacy to use NAM-based methods once they are validated as alternative approaches. However, EFSA's initiative will have only limited impact, if it is limited only to the EU, as many products are intended for global authorisation. We therefore encourage EFSA to advocate for this approach and promote it also to other authorities	Please refer to the reply to comment 192.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		around the globe. EFSA being the pioneer in this topic is great but we need authorities from other jurisdictions to accept NAM-based methods as well in order to minimise animal testing globally.	
561	International Probiotic Association - Europe (IPA Europe)	line 329 par11) lines 329 to 345 IPAEU: the aim is to reduce and replace animal testing; this is welcomed and in line with EFSA Strategy 2027. We lose this notion in the guidance, which is not mentioned in the toxicology sections, where animal testing is requested from Tier I for repeated-dose toxicity. In addition, no alternative methods are mentioned.	Please refer to the response to comments 139 and 306.
578	AseBio - Spanish Bioindustry Association,	We consider that this guidance should be aligned across different EFSA guidance documents, including references whenever necessary.	Please refer to the response to comment 317.
593	Cellular Agriculture Europe	1. Lines 315-317: 'Where applicable, the published literature is to be reviewed taking into account systematic review principles (EFSA, 2010). Full study reports should be provided if available'. We invite EFSA to define cases when systematic review following EFSA's (2010) guidance would be applicable. We assume when literature is used to support safety. 2. Lines 322-323: The Guidance clarifies especially in point 9 that 'Deviations from the requirements specified in the respective sections of this guidance document must be justified'. In our view, this sentence is a good 'catch-all' statement and we would suggest highlighting it in its own right. 3. Line 324: The text should further specify the term 'qualified'. In our opinion, it should mean 'accredited'.	1. Please refer to the response to comment 263. 2. The Panel appreciates the recognition of EFSA's ongoing efforts for flexible yet comprehensive scientific requirements. The General Principle mentioned in this comment is outlined as a distinct point in the Guidance. 3. The term 'qualified' is broader than 'accredited' and is intended to address all situations, including cases where e.g., a non-established analytical method needs to be developed. Additionally, please refer to the response to comment 432.
638	Pen & Tec Consulting S.L.U. (trading as Argenta®)	1. Line 272. 'Article 32b of the General Food Law': 'Regulation (EC) No 178/2002 (hereinafter 'General Food Law')' or similar introduction to what General Food Law stands for is missing from the guidance. 2. Line 274. '…provisions of transparency and confidentiality (Article 39 of the General Food Law)': Add '(Article 38 of the	1. The text has been revised in line with the comment. Please note that the full title of the Regulation is also available in a footnote in that section of the Guidance. 2. The text has been revised in line with the comment.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		General Food Law)' after the word 'transparency'. Article 39 relates to confidentiality only. 3. Lines 325-326. 'Information on the accreditation of involved facilities and certificates of analyses should be provided': Which kind of accreditation does EFSA consider adequate? 4. Line 345. 'in accordance with international guidelines such as OECD or ICH16': The reference No 16 provided is for OECD and therefore should be next to 'OECD'. A footnote with a reference/link to ICH guidelines should be provided after 'ICH'. Also note that the link in the footnote is not working.	3. Please refer to the response to comments 83 and 432. 4. The text has been revised.
660	Atova Regulatory Consulting SL	1. (Line 315, page 10) 'Where applicable, the published literature is to be reviewed taking into account systematic review principles (EFSA, 2010). Full study reports should be provided if available.' Please can EFSA define cases when systematic review following EFSA (2010) guidance would be applicable. We assume when literature is used to support safety. 2. (Line 335, page 10) 'safety the novel food.' Typo – missing 'of'	1. Please refer to the response to comment 90. 2. The text has been revised in line with the comment.
686	FoodDrinkEurope	1. [Lines 301-310] Concerning the production process, we would like to underline that in many cases the production process of currently authorised novel foods (NF) is not sufficiently described, and in some cases it is even absent. Therefore, when the Food Business Operator (FBO) is not the applicant of that already approved NF, in many cases has no possibility to assess a change in the production process and therefore know whether the suggested process is divergent from the process that has been initially assessed by EFSA – except of course obvious differences. Does this mean that any FBO that would like to benefit from a generic NF approval, and produce on its own an already approved NF, would have to file an application to have its production process to be assessed and validated? That would become a major obstacle to innovation and we doubt was the intention of this EFSA guidance. We therefore suggest to qualify the change as 'significant change' in the current text, to align also with the requirements in other legislative frameworks such as food	1. Please refer to the response to comment 139 2. Please refer to the response to comment 593 3. Please refer to the response to comment 139 4. The text has been revised in line with the comment.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		additives (A food additive already approved under this Regulation which is prepared by production methods or using starting materials significantly different from those included in the risk assessment of the Authority, or different from those covered by the specifications laid down, should be submitted for evaluation by the Authority) 2. [Line 324] The text should clarify the meaning of the term 'qualified'. To our opinion, it should mean 'accredited' 3. [Lines 329 – 345] Point 11 encouraging the use of alternative methods and avoid animal testing is welcomed and in line with EFSA's Strategy 2027 but contradictory with the toxicology section which does not sufficiently encourage alternative methods and requires animal testing even at Tier I for certain section. 4. [Lines 335] Typo error: on the safety 'of' the novel food	

Table 3: Definitions

Comment number	Commentor	Comments	EFSA NDA Panel responses
82	BaseClear	At line 237, there is a lack of clarity for applicants in distinguishing between 'novel food' and 'food ingredients' when their products are derived from microorganisms, fungi, or algae. Providing clear guidance on this distinction would aid applicants in accurately categorising their products and navigating the authorisation process effectively. Provide examples or case studies for each category to illustrate how they apply in practical terms. This can help clarify the criteria for determining whether a food falls under the definition of 'novel food.'	In case where a novel food is used for the production of other food products, it can be considered as a food ingredient. The term 'novel foods' in the regulation can refer to, for example, whole foods, food ingredients, ingredients for food supplements, and food for special groups. The Panel considers that no change to the Guidance is needed. If a product falls under the Novel Food Regulation, it is up to the risk managers, not within EFSA's remit and out of the scope of this Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel responses
			As part of this reply, the following cases can be considered as examples: Whole Food: An algal species intended to be consumed as such can be considered a whole food. Food Ingredient: A novel protein extract from a fungus used as an ingredient in bakery products can be considered a food ingredient. Ingredient for Food Supplements: Substances extracted from a novel yeast source are used as ingredients in food supplements. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.
89	Undisclosed (personal capacity)	General Definitions and Clarity (Lines 232, page 8): The term 'significant degree' used in the EFSA draft lacks precise definition which may lead to varied interpretations. It is suggested that EFSA provides a clearer definition or examples to ensure consistency in interpretation. The addition of references to existing literature where this term is well-defined would also be beneficial.	The term 'significant degree' appears as such in Regulation (EU) 2015/2283 and its interpretation also it is a risk management decision, thus it is outside EFSA's remit. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.
262	Dwayne Holmes (Personal Capacity)	Page 8 Page 8, Line 232 – The meaning of 'significant degree' is not clear and further definition with references or examples could be used.	Please refer to the response to comment 89.
571	Aletheia: il segreto del buon vivere	As defined in the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) guidelines 'Food safety aspects of cell-based food' (https://www.fao.org/3/cc4855en/cc4855en.pdf) the most appropriate terminology for classifying food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, microorganisms, fungi or algae ARE CELL-BASED PRODUCTS OR LAB-GROW PRODUCTS.	The Panel acknowledges the proposal by FAO as well as nomenclature proposals by other national and international entities. However, for this guidance and other relevant activities such as the EFSA Scientific Colloquium 27 on 'Cell culture-derived foods and food ingredients' (EFSA, 2024), EFSA has decided to use the

Comment number	Commentor	Comments	EFSA NDA Panel responses
			term 'cell culture-derived foods,' in analogy to terms such as 'animal-derived' and 'plant-derived'. The Panel considers that no change to the Guidance is needed.

Table 4: Objectives

Comment number	Commentor	Comments	EFSA NDA Panel responses
138	Synpa, French association of specialty food ingredients manufacturers and distributors	Regulation 178/2002 on the general principles and requirements of food law repeatedly defines the responsibilities of the food and feed business operators and that their responsibilities include that they ensure that foods or feeds satisfy the requirements of food law (Art. 3§3, Art. 17, art. 19). It also defines the role of member states to monitor and verify that the relevant requirements are fulfilled. In various new requirements, the novel food guidance draft, EFSA overreaches and infringes on these principles. Not only do they take the responsibility from the food and feed business operator to ensure the requirements of food law are satisfied away, but they also take away the role of member states as defined in Art. 17 §2 and take it upon them in the context of a novel food. We do ask to reconsider and align this novel food guidance to follow the general requirements of food law.	The Panel acknowledges the concerns expressed. It should be highlighted that the guidance aims to ensure comprehensive information is available for informed risk assessments. In the European Union, the functions and roles of risk management and risk assessment are distinctly separated. EFSA's role in the context of novel foods is to conduct safety assessments, provide scientific guidance, communicate findings transparently, and facilitate scientific co-operation in the field. The Panel considers that no change to the Guidance is needed.
354	Vaclav Bazata (Personal Capacity)	Technical remark	No further feedback can be provided because the comment is unclear.
431	Food Supplements Europe	1. Food Supplements Europe represents food supplement manufacturers and ingredient providers in Europe. The novel food process is one of the most important gateways for product innovation in our sector, both covering authorisation of new ingredients as well as new nutritional substances. We welcome that EFSA continuously updates its scientific guidance to keep track of new developments in the area of risk assessment. We	The Panel appreciates the recognition of EFSA's ongoing efforts to update its scientific guidance in line with developments in risk assessment. It is crucial to note that comprehensive information on the aspects outlined in the guidance is essential for hazard

Comment number	Commentor	Comments	EFSA NDA Panel responses
		note however that with each new edition, more data requirements are being specified covering areas where in principle no changes have occurred and where novel foods in the past have been positively assessed on the basis of previous data requirements. As a sector where over 95% of companies are SMEs, we would ask EFSA to consider for each new element if it is really essential for the risk assessment. In principle the data essential for the risk assessment should relate to the specifications of the novel food and the intake assessment as determined by the levels of use. Any information that for instance relates to quality assurance measures that are intended to ensure that existing legal requirements are met, would not add to the safety data. The information about the manufacturing process and in-process controls should be sufficient to cover that aspect. In the area of novel foods, the applications can cover a wide range of products going from simple plant preparations to sophisticated intentionally manufactured substances. It is logic to assume that these should each meet the data that are tailored to their nature. We therefore very welcome the statement in lines 292-300 on which data is essential (information on the identity, production process, compositional data, specifications, proposed uses and use levels and anticipated intake) and which data can be waived based on scientific justification and argumentation from the applicant (e.g. data on absorption, distribution, metabolism and excretion, toxicological information, nutritional information and allergenicity). Care should be taken obviously that this is consistently applied to relevant applications. Certain comments are also appropriate for the guidance on traditional foods from a third country and we would ask EFSA to retain consistency between both documents.	identification and for conducting well-informed risk assessments. Applicants are encouraged to provide scientifically substantiated arguments explaining why specific scientific requirements may not be necessary for the safety assessment of their product, which will be evaluated by the Panel. Regarding the alignment of information between the novel food guidance and the traditional food guidance, consistency is ensured where applicable, while acknowledging that these documents pertain to different product categories.
540	European Industrial Hemp Association - EIHA	Preserving innovation while ensuring safety.	Consumers' safety is indeed the primary goal, ensuring that innovation in food products progresses alongside rigorous safety assessments.

Comment number	Commentor	Comments	EFSA NDA Panel responses
559	International Probiotic Association - Europe (IPA Europe)	Line 204 to 206 IPA Europe, the association representing the interest of the European manufacturing of probiotic food and food supplements, welcome the opportunity to publicly comment the revision of the novel food guidance, PC-0824. Also, we noticed that during the EFSA webinar held on 21 March 2024 EFSA referred to a project for microorganisms' requirements for all sectors including food – by end 2024 and we would be interested to learn more about the background and the term of references of this report.	The Panel appreciates the recognition of EFSA's ongoing efforts for stakeholder engagement and openness, and acknowledges the interest in the cross-sectoral guidance on the risk assessment of microorganisms intentionally added to the food chain. However, providing information on advances in other guidance documents goes beyond the scope of this Guidance.
569	Aletheia: il segreto del buon vivere	A transparent, science-based and comprehensive approach is necessary to assess the development of artificial cell-based meat production, which does not constitute a sustainable alternative to primary farm-based production. In this direction EFSA guidelines must be characterised by a comprehensive approach like pharmaceutical products, including pre-clinical and clinical studies that will be used as safety criteria for an opinion of EFSA.	The Panel would like to highlight that scientific requirements to assess the safety of such products are already comprehensively covered in the Guidance.

Table 5: Scope

Comment number	Commentor	Comments	EFSA NDA Panel responses
116	Medfiles Ltd	Comment P8 L211: Medfiles notes that in several sections EFSA goes beyond its risk assessment remit and mentions the needs by the EC and MSs within their novel food authorisation process (e.g. p 21, 27, 30, 33) or labelling considerations. While we note that these pieces of information are useful for the Applicant, they also add confusion which body is responsible for risk assessment and which for risk management in the EU, particularly for non-EU Applicants. Therefore, we propose first to add a brief discussion of the responsibilities as regards risk assessment and risk management in the EU to the beginning of the guidance, and secondly mentioning that the guidance also	Please refer to the response to comment 138. Furthermore, the Panel acknowledges the proposal for a brief discussion regarding the roles of risk assessors and risk managers within the EU novel food regulatory framework. However, it is deemed that this goes beyond the scope of this Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		reflects risk management needs where they are considered relevant. Medfiles views that in this way the risk management does not appear 'out of the blue' in the body text.	
191	EU Specialty Food Ingredients	According to the EFSA Administrative guidance for the processing of applications for regulated products 'in adopting new EFSA policies, decisions, approaches, or scientific methodologies that affect the assessment of an application for regulated products, EFSA ensures that a reasonable transitional period is granted'. We are aware that EFSA set a transitional period of 6 months for the application of the guidance concerning food enzymes dossiers. Is EFSA planning a similar transitional period for the updated guidance concerning novel foods?	Please refer to the response to comment 432.
560	International Probiotic Association - Europe (IPA Europe)	Lines 211, 212,213,214 Overall, the revision proposed fulfil the objective to assist applicants with the scientific requirements providing clarification to the previous guidance. Also, in the context of the scientific requirements for the taxonomic and hazard identification of microorganisms as novel foods or used in the production of novel foods: the Annex A differentiates microorganisms as novel foods from microorganisms used in the production of novel food.	The Panel appreciates the recognition of EFSA's ongoing efforts to update its scientific guidance.
570	Aletheia: il segreto del buon vivere	The guidance presented in this document is provided to assist applicants with the scientific requirements in preparing applications for authorisation of a novel food under Article 10 of Regulation (EU) 2015/2283. A separate EFSA guidance document is available to assist applicants in preparing and presenting a notification dossier for a traditional food from a third country under Article 14 of Regulation (EU) 2015/2283 (EFSA NDA Panel, 2021). The latter document specifically addresses the data required to substantiate the 'history of safe food use in third country' of a traditional food, as defined by Article 3 of Regulation (EU) 2015/2283. Under the notification procedure, Regulation (EU) 2015/2283 foresees that a Member State or EFSA may submit to the Commission duly reasoned safety objections to the placing on the market within the Union of the traditional food concerned. In such cases, the present guidance should also serve applicants in preparing an	It should be highlighted that the applicant should consider any applicable guidance documents when preparing their application dossier(s). Food processing can potentially impact on the allergenic potential of a complex food (decreased, unchanged, or even increased). Considering the multitude of allergenic structures potentially present in novel foods and the differential impact of treatments on various proteins, predicting the effect of food processing on the structural and allergenic properties of allergenic

Comment number	Commentor	Comments	EFSA NDA Panel responses
		application under Article 16 of Regulation (EU) 2015/2283, where the application concerns data other than those on the 'history of safe food use in a third country. Procedural aspects linked to the submission of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 are not in the scope of this guidance document. Instead, applicants are advised to consult the EFSA Administrative guidance for the preparation of applications on novel foods pursuant to Article 10 of Regulation (EU) 2015/2283 (EFSA, 2021a), the EFSA Administrative guidance for the processing of applications for regulated products (EFSA, 2021b), and the EFSA Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA, 2021d). Health considerations When introducing proteins from novel sources into the human diet, it is essential to take in consideration their behaviour and bioavailability throughout the gastrointestinal tract and also assess their possible cytotoxic effects or other negative impacts on human health (e.g. allergic reactions). In general, in different studies changes induced by processing on the ability of IgE antibody to bind to a food protein do not necessarily indicate a change in the allergenicity of that protein and its ability to cause the acquisition of sensitisation. Processing may not only alter epitopes (changes in IgE antibody-binding properties), but may also create new epitopes, that might have the potential to induce sensitisation and food allergy. For this reason, it is important to consider whether processing has had an impact on the inherent allergenicity of a food protein.	foods or ingredients is challenging. Moreover, the extent of protein modification during processing depends on the type and conditions of the process, protein structure, and matrix composition. While the effects of different technological and cooking treatments on the IgE-binding capacity of several allergens have been studied, there is less information available on the impact of processing on clinical reactivity (EFSA NDA Panel, 2014). Therefore, even though processing may alter the 'inherent allergenicity' of novel food proteins, predicting clinical reactivity to these proteins is difficult. As a result, the default assumption is that they retain their allergenic potential (EFSA NDA Panel, 2014). The Panel considers that no change to the Guidance is needed.
637	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 216. 'EFSA NDA Panel, 2021': To be updated once the draft traditional food guidance is finalised.	The reference has been updated in line with the proposal in the comment.

Table 6: Characterisation of the novel food, technical and scientific data

Comment number	Commentor	Comments	EFSA NDA Panel responses
91	Undisclosed (Personal capacity)	Characterisation of Novel Foods (Lines 347ff, page 12) Comment: For complex mixtures, such as cultured meat, the requirement for 'full characterization' could be better defined. Including examples from previously assessed novel foods might help clarify the expectations and implications of incomplete characterisation.	The paragraph has been removed because it was considered redundant with the information provided in section 3.3, 'Complex Mixtures and Whole Foods,' which already describes the elements needed for the comprehensive characterisation of the composition of complex mixtures and whole foods. Examples of requirements applicable to the characterisation of specific novel foods are provided in the Guidance.
107	Food Fermentation Europe	Line 347 page 12 requires 'full characterisation' of the novel food. It would be helpful if this section referred to section 3 on compositional data requirements, and provided further guidance on what constitutes a suitable 'full characterization'. For example, should it systematically include full chemical, nutritional, and physical characterisation? It would also be very helpful if EFSA could provide examples of acceptable levels of characterisation of various novel foods. Food Fermentation Europe there respectfully requests that the draft guidance be revised to provide further advice and examples of what may constitute acceptable levels of characterisation for a novel food.	Please refer to the response to comment 91.
222	Food Safety Authority of Ireland	Please check the text (422-427) regarding GMM use in food production and the Commission report to the Council and Parliament of 2006 clarifying the use of GMMs as processing aids in fermentation where the GMMs are not present in the final product. The definition of 'processing aid' allows for the unintended presence of safe residues without a technological function and so it at variance with this text.	The legal classifications of regulated products are outside EFSA's remit. Regulations 1829/2003 on GMOs and 2015/2283 on novel foods are mutually exclusive. For the definitions of GMM categories relevant to risk assessment, please refer to the EFSA GMO Panel (2011) and the EFSA Scientific Committee (2022a); only GMM categories 1 and 2 fall under the

Comment number	Commentor	Comments	EFSA NDA Panel responses
			remit of Regulation 2015/2283 on novel foods. For information on new developments in biotechnology applied to microorganisms and the adequacy of the current EFSA risk assessment guidance, refer to the EFSA GMO Panel (2024). The Panel considers that no change to the Guidance is needed.
238	The Good Food Institute Europe	Line 347: The full characterisation of the novel food under assessment is a key element of the risk assessment. Comments: EFSA should consider adding further specificity on the characterisation metrics necessary as part of the risk assessment process, including whether it should include chemical, nutritional and/or physical characterisation. EFSA could even provide examples on acceptable degrees or thresholds for the characterisation for novel foods.	Please refer to the response to comment 91.
264	Dwayne Holmes (Personal capacity)	Page 12, Line 347 – For complex mixtures or whole foods (e.g. cultured meat and seafood) qualify what is meant by 'full characterization'. It would also be helpful to provide some examples based on previously assessed novel foods and outline the implications of when a novel food cannot be 100% fully characterised.	Please refer to the response to comment 91.
282	Katharina Julia Brenner (Personal capacity)	Full Characterization of Complex Mixtures (Line 347, page 12) Comment: The term 'full characterization' is ambiguous, especially for complex mixtures or whole foods like cultured meat. The document should specify what constitutes complete characterisation and offer examples from previously assessed foods. Additionally, it should address scenarios where a novel food cannot be fully characterised and the implications of such cases.	Please refer to the response to comment 91.
594	Cellular Agriculture Europe	Line 347: The full characterisation should be further specified in the text. For example, should it cover chemical, nutritional, physical full characterisation? The full characterisation should also refer to section 3 and be fully aligned with compositional data. We would suggest to EFSA to provide also examples on	Please refer to the response to comment 91.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		what are acceptable degree/threshold of characterisation for a novel food.	
661	Atova Regulatory Consulting SL	(Line 347, page 12) 'The full characterisation of the novel food under assessment is a key element of the risk assessment.' Please can EFSA qualify what they mean by 'full characterisation'. It would also be helpful if EFSA could provide some examples based on previously assessed novel foods and outline the implications of when a novel food cannot be 100% fully characterised.	Please refer to the response to comment 91.
687	FoodDrinkEurope	[Line 347] The full characterisation should be further specified in text. For example, should it cover chemical, nutritional, physical full characterisation? The full characterisation should also refer to section 3 and be fully aligned with compositional data. We think the guidance would benefit from examples on what are acceptable degree/threshold of characterisation for a novel food, by, for example, referring to past novel foods assessments.	Please refer to the response to comment 91.

Please note that this section has been removed from the final version of the Guidance.

Table 7: 1. Identity of the novel food

Comment number	Commentor	Comments	EFSA NDA Panel responses
8	Undisclosed (Personal Capacity)	Lines 366-370 'and must bear no nutrition or health claims according to Regulation (EU) 2015/2283' It is not EFSA's job/remit to decide this, it is a regulatory issue on a case-by-case basis and that is part of the administrative process upon submission of the dossier. If a material is e.g. a 'protein-rich biomass' then there is no reason why this name is not appropriate so long as it meets the requirement of the nutrition claims annex. It would also be scientifically correct.	The text has been revised.
63	Nutraveris – A FoodchainID company	- For ingredients for which the use of excipients is mandatory, can the application be made on the combination ingredient and excipient? For example, EFSA opinion on Phaeodactylum	The Guidance states that non-novel compounds should not be considered for the identity of the novel food, the compositional analyses, and the

Comment number	Commentor	Comments	EFSA NDA Panel responses
		tricornutum for which MCT oil is mandatory to be able to manipulate the novel food.	proposed specifications, unless they are essential to maintain specific characteristics of the novel food. The Panel considers that no change to the Guidance is needed.
118	Medfiles Ltd	Comment P12 onwards: Medfiles welcomes the extension of deception for the characteristics required, noting also the requirements needed for cell-cultured materials.	No further feedback can be provided because the comment is unclear.
140	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Line 352 It appears that the guidance is designed to not want mixtures, blends of novel and not novel ingredients, i.e., the application for a herbal extract should be for the pure form without addition of carriers. If a plant extract requires carriers for stability, would the extract plus carrier be a novel food? This section should be clarified. 2. Lines 354 – 359 Some non-novel components can have a double function. For example they can be added for stability or physical form and also added for the standardisation of a product. Could you please confirm that even if these components are both added for the physical form and the standardisation, they can be kept in the product for the characterisation? During the webinar, EFSA mentioned that 'if a non-novel ingredient is used, explain and clarify its purpose and its interaction with the novel food.'. The notion of 'interaction' should be clarified.	Please refer to the response to comment 63.
193	EU Specialty Food Ingredients	It appears that the guidance is designed to not want mixtures, blends of novel and not novel ingredients, i.e., the application for an herbal extract should be for the pure form without addition of carriers. If a plant extract requires carriers for stability, would the extract plus carrier be a novel food? This section should be clarified.	Please refer to the response to comment 63.
239	The Good Food Institute Europe	Line 367-370 …and must bear no nutrition or health claims according to Regulation (EU) 2015/2283 Comment: EFSA should reconsider whether such a blanket approach to nutritional or health claims is appropriate within the confines of the novel food authorisation process. It could be considered that these aspects are regulatory issues which can be deliberated on a case-by-case basis as part of dossier evaluation. On some occasions, the scientifically accurate name of a novel food could include	Please refer to the response to comment 8.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		nutrition or health claims, and these should be permitted if fully compliant with applicable regulations and not misleading to consumers.	
283	Katharina Julia Brenner (Personal Capacity)	1. Clarification on Non-novel Ingredients' Impact (Page 12, Lines 352-359): Comment: The section could be enhanced by specifying which characteristics necessitate the inclusion of non-novel ingredients in the identity definition. It should explicitly define conditions under which non-novel ingredients significantly affect the novel food's stability or physical form, thereby necessitating their inclusion in identity assessments. This would provide clearer guidance to applicants on how to handle such ingredients in their submissions. 2. Detailing Scientific Nomenclature Requirements (Page 12, Lines 366-370): Comment: While the requirement for scientific nomenclature is mentioned, the document could benefit from a more detailed explanation or examples of acceptable nomenclature. This should include guidance on how to select appropriate scientific names and how these names reflect the characteristic elements of the novel food. This enhancement would aid applicants in accurately naming their products, ensuring consistency and avoiding regulatory discrepancies.	1. Please refer to the response to comment 63. 2. The requirements for scientific nomenclature are addressed on a case-by-case basis, depending on the specific characteristics of each novel food. The Panel considers that providing an exhaustive list of acceptable nomenclature is not feasible and falls outside the scope of this document.
307	Food Safety & Nutrition Consultancy	If the mass balance is grossly complete and with adequate qualitative and quantitative data then EFSA should consider a rapid risk assessment such as using the substantial equivalence route.	The Panel does not agree with the proposal, as the approach 'Mass balance grossly complete' could potentially obscure substances of concern. Therefore, the Panel considers that no change to the Guidance is needed.
340	Jeremy Coller Foundation	1. Line 422 – page 14 - Would genetically edited organisms fit within the novel food guidance also/would there be different regulatory requirements compared with GMO? 2. Line 463-464, page 15 - Clarity on percentage by what - mass, volume? 3. Line 510 – page 17 - Do certificates of meeting animal welfare requirements during biopsy also need to be provided (as required in other jurisdictions)?	1. The legal classifications of regulated products are beyond EFSA's remit. Please note that Regulations 1829/2003 on GMOs and 2015/2283 on novel foods are mutually exclusive. Please refer to the EFSA GMO Panel (2011) and EFSA Scientific Committee (2022a) for the definitions of GMM categories for the purpose of the risk

Comment number	Commentor	Comments	EFSA NDA Panel responses
			assessment (only GMM categories 1 and 2 fall under the remit of Regulation 2015/2283 on novel foods), and to the EFSA GMO Panel (2024) for new developments in biotechnology applied to microorganisms and adequacy of the current EFSA risk assessment guidance. Therefore, the Panel considers that no change to the Guidance is needed. 2. The text has been revised. 3. The text has been revised, making reference to the specific requirements in the applicable EU regulations, i.e., Regulation (EU) 2017/625 on official controls and other official activities and, where applicable, Regulation (EC) No 853/2004 on specific hygiene rules for food of animal origin.
346	GAIKER	The novel food status (whether a food is novel or non-novel) of all major alternative proteins should be clarified by the EFSA without request. For example: protein extracts obtained from legumes (pea, faba) or edible mushrooms	The determination of a product's 'novel status' falls under the responsibility of risk managers, not EFSA. For specific guidance, please consult the competent authority in your Member State. The Panel considers that this comment goes beyond the scope of this Guidance.
355	Vaclav Bazata (Personal Capacity)	in abstract	No further feedback can be provided because the comment is unclear.
433	Food Supplements Europe	Lines 353-359 The legal definition of novel food does not specify that novel foods should not be mixtures in which also non-novel ingredients may be present. In addition, studies could have been undertaken with the mixture including the non-novel constituents. Can the guidance explain why this new requirement	EFSA's mandate for the safety assessment of novel foods does not extend to non-novel ingredients that do not fall under the novel food definition, except in specific

Comment number	Commentor	Comments	EFSA NDA Panel responses
		has been introduced and why this is important for the safety assessment?	circumstances. Please refer to the response to comment 63.
527	FoodchainID	For ingredients composed of several extracts/mixtures that undergo additional mixing, drying and standardisation processing. Is the novel food defined as the blend or the former individual extracts/mixtures?	In the case of a mixture, the definition of novel foods applies to the fraction of the mixture that is considered novel. Please refer to the response to comments 63 and 433.
595	Cellular Agriculture Europe	1. Lines 367-368: 'and must bear no nutrition or health claims according to Regulation (EU) 2015/2283' In our view, it is not EFSA's job/remit to decide this. It is a regulatory issue on a case-by-case basis and that is part of the administrative process upon submission of the dossier. If a material is e.g. a 'protein-rich biomass' then there is no reason why this name is not appropriate so long as it meets the requirement of the nutrition claims annex. It would also be scientifically correct. We believe that on some occasions, the name of a novel food could bear nutrition or health claims, if fully compliant with applicable regulations and not misleading. We suggest that the sentence is rephrased or deleted. 2. Lines 368-370: We propose to add: 'commercial names including trademarks are to be avoided'	1. Please refer to the response to comment 8. 2. The text has been revised in line with the comment.
639	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 364. 'Regulation (EU) 2283/2015': It should say 'Regulation (EU) 2015/2283'.	The text has been revised in line with the comment.
662	Atova Regulatory Consulting SL	(Line 367-368, page 12) 'and must bear no nutrition or health claims according to Regulation (EU) 2015/2283'. In the case of a 'protein-rich biomass' there should be no issue with using this as the descriptive name as long as the protein content of the biomass meets the appropriate conditions laid out in the Annex to Regulation (EC) 1924/2006.	Please refer to the response to comment 8.
688	FoodDrinkEurope	1. [Lines 367-368] We believe that on some occasion, the name of a novel food could bear a nutrition or health claims if fully compliant with applicable regulations and not misleading. For example, a protein-rich concentrate would be an appropriate	1. Please refer to the response to comment 8. 2. Please refer to the response to comment 595

Comment number	Commentor	Comments	EFSA NDA Panel responses
		descriptor for a novel food ingredient if compliant with regulation (EU) 1924/2006 (High in Protein) 2. [Line 368] The guidance specifies that commercial names are to be avoided. We suggest including also 'trademarks' here. 3. [Line 380] Please provide a citation for IUPAC nomenclature. In the past the rules applied by EFSA have not been applied in the same way as the applicant. A common reference source should be provided. 4. [Lines 531-532] We observed that there is no section in the guidance document related to novel food category (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.	3. The text has been revised in line with the comment, including additional references. 4. It is highlighted in the Guidance that the subsections within 'Identity' are to be distinguished from the categories outlined in Article 3 of Regulation (EU) 2015/2283, to which the applicant must assign their novel food upon submission of the application dossier. Specific provisions for micronutrients i.e., vitamins and minerals, are provided in Section 9.3 'Specific considerations for novel foods proposed as new sources of micronutrients'.

Table 8: 1.1 Chemical substances, products of mineral origin and polymers

Comment number	Commentor	Comments	EFSA NDA Panel responses
1	Analyze & Realize GmbH	line 406/407 Do we understand correctly that natural polysaccharides and proteins are considered polymers?	The text has been revised, specifying that, for the purpose of this Guidance, the term 'polymers' does not include proteins.
12	Undisclosed (Personal Capacity)	Line 380 EFSA should provide a citation for IUPAC nomenclature. In the past the rules applied by EFSA have not been applied in the same way as the applicant, and EFSA has arguably not always been correct. So a common reference source should be provided here.	Please refer to the response to comment 688.
67	Nutraveris - A FoodchainID company	o in case of identity test performed by NMR or LCMS is it necessary to add comparison with certified chemical standards? o CAS number and other identification numbers are not always available for chemical substances, is the list a mandatory list of information to provide?	The text has been revised to emphasise that, when available, comparison with chemical standards, certified reference materials, authentic biological specimens,

Comment number	Commentor	Comments	EFSA NDA Panel responses
		o Similarly, chemical standard are not always available, notably when compounds are isolated from natural sources, or are natural compounds obtained by chemical synthesis. What is EFSA recommendation when comparison with validated standard is not possible?	naturally occurring compounds, or other relevant materials may be pertinent for the characterisation of the novel food's identity. The revision also addresses situations where such identifiers or standards are unavailable.
148	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Line 380 Please provide a citation for IUPAC nomenclature. In the past the rules applied by EFSA have not been applied in the same way as the applicant. A common reference source should be provided. 2. Line 386 'As written it appears to be a ratio of Molar:Molecular mass. Should read: 'Molecular weight: either molar mass (g/mol) or molecular mass (Da).'	1. Please refer to the response to comment 688. 2. The text has been revised in line with the comment.
199	EU Specialty Food Ingredients	Line 386: As written, it appears to be a ratio of Molar:Molecular mass. Should read: 'Molecular weight: either molar mass (g/mol) or molecular mass (Da).'	Please refer to the response to comment 148.
225	Planet A Foods GmbH	- ll371 ff. What fault to frame is accepted here? Is 99 % identified components (keep in mind that purities are always <100 %, which should be reflected in the allowed fault to frame of identified compounds in the final product?	A specific cut-off for purity cannot be set, as this must be determined on a case-by-case basis. The acceptable level of identified components is more closely linked to the overall composition and the nature of the components identified in the final product rather than being defined by a fixed percentage threshold for purity. The Panel considers that no change to the Guidance is needed.
528	FoodchainID	For powder soluble in water (> 33.3g/L), are particle size, shape and distribution required?	No additional assessment of the fraction of small particles is required by default if the substance's solubility in water is equal to or greater than 33.3 g/L. This requirement is applicable when the EFSA Scientific Committee (2021a) Guidance applies.

Comment number	Commentor	Comments	EFSA NDA Panel responses
601	Cellular Agriculture Europe	Line 380: We suggest that EFSA provides a citation for IUPAC nomenclature. In the past, EFSA and applicants applied different rules. So a common reference source should be provided here, for clarity and consistency.	Please refer to the response to comment 688.
641	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 388. 'SMILES Canonical and SMILES Isometric': It should rather say Canonical SMILES and isomeric SMILES. Note the typo in 'isomeric'. Lines 410-411. 'the ECHA guidance for identification and naming of substances under REACH and CLP should be followed.19': The link in the footnote is not working.	The text has been revised in line with the comment.
695	FoodDrinkEurope	1. [Line 389] Typo error: relevant constituents should… 2. [Lines 395-397] We would suggest moving these lines to ADME section given they relate to bioavailability	1. The text has been revised in line with the comment. 2. The indicated part of the text will remain in its current position, but the concept is also reiterated in the ADME section for emphasis and clarity.

Table 9: 1.2 Foods consisting of, isolated from or produced from microorganisms

Comment number	Commentor	Comments	EFSA NDA Panel responses
13	Undisclosed (Personal Capacity)	Lines 412-458 Annex A This section and Annex have been comprehensively expanded and are now very useful. How QPS relates to toxicology and allergenicity requirements is not clearly defined (it is for food enzymes)	The Panel appreciates the recognition of EFSA's ongoing efforts to provide up-to-date guidance. Please refer to EFSA BIOHAZ Panel (2023a) and https://www.efsa.europa.eu/en/applications/qps-assessment for additional information on the criteria for the QPS approach to safety assessment. The Panel considers that no change to the Guidance is needed in relation to the QPS approach and allergenicity requirements since 'the potential allergenicity of the microorganism, its residual components, or produced metabolites are not covered by the QPS status of the taxonomic unit and

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			have to be separately assessed by the EFSA Panel responsible for assessing the application (i.e., EFSA NDA Panel)`. Section 8 `Toxicological Information` has been clarified in relation to the QPS approach and toxicological requirements on the novel food.
50	Specialised Nutrition Europe (SNE)	Page 15 line 446: anti-microbial Anti-microbial is a very broad term. Alcohol, acids, and certain ingredients can be antimicrobial. Many microorganisms can produce acids. Is the intent that this should not lead to antibiotic resistance? If that is the case, this should be said. Anti-microbial is not necessarily bad, increasing antibiotic resistance in the population is. The word anti-microbial should be changed since the term is too broad.	It should be noted that the term `antimicrobial` is widely recognised by the scientific community and aligns with the nomenclature used in other relevant EFSA scientific outputs. Antimicrobials are defined as `active substances of synthetic or natural origin that destroy microorganisms, suppress their growth, or inhibit their ability to reproduce in animals or humans, excluding antivirals and antiparasitic agents.` For the purpose of assessing antimicrobial susceptibility and production in this Guidance, only antimicrobial substances of clinical relevance are considered (EUCAST, 2024). Section 1.2 and Appendix A have been updated, and the term `antimicrobial` has been defined in the Glossary.
72	Bene Meat Technologies A.S.	line 426: please ad (category) `cisgenic organisms from category 3` after the words `(`complex products in which both GMMs and newly introduced genes are no longer present'),` Reasoning: We suggest keeping category 3 (according to the EFSA GMO Panel, 2011) in the microorganism category, however, only cisgenic organisms. All the food we consume originates from either plants, animals, or microbes. All this food contains DNA, RNA, and nucleotides and in our usual diet, we typically ingest grams of DNA and RNA on a daily basis.	Please refer to Regulation 1829/2003 on genetically modified organisms (GMOs) and Directive 2001/18/EC (Article 2(2) and Annex I B) for the definition of GMOs. It should be noted that Regulations 1829/2003 on GMOs and 2015/2283 on novel foods are mutually exclusive. For definitions of GMM categories relevant to risk

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		Additionally, all forms of DNA, including any recombinant or synthetic DNA, consist of the same four nucleotides (Jonas et al., 2001; Nawaz et al., 2019). Any form of DNA is completely broken down in the digestive tract (Rizzi et al., 2012). Genetically Modified Organisms (GMOs) have sparked intense debate, primarily concerning their safety for human consumption. However, numerous reputable organisations, such as the World Health Organization, the American Medical Association, the U.S. National Academy of Sciences, and the British Royal Society, have extensively researched the biosafety of GMOs. Based on over 130 research projects spanning more than 25 years and involving 500 independent research groups, these organisations collectively conclude that biotechnology, particularly GMOs, pose no greater risk than conventional breeding technologies (AAAS, 2012). Claims of adverse effects in animals fed genetically modified food, such as digestive disorders or tumours, have been sensationalised but lack scientific support. We understand that there are several concerns regarding GMOs and human health. One major concern is the potential for GMOs to introduce new allergens into the food supply (Herman et al., 2022). It has been demonstrated that allergens can be transferred from one plant to another via genetic modification (Nordlee et al., 1996). However, rigorous testing can identify such issues early, before they enter the food chain (DeFrancesco, 2013). With modern omics analysis tools readily available, any new product can undergo thorough testing (DeFrancesco, 2013). Another concern is horizontal genetic transfer, which involves the non-sexual movement of genetic information between genomes of different species (Keeling and Palmer, 2008). Although no studies have confirmed such genetic transfer so far, there is a need for proper, long-term, well-designed, and independent studies (Nawaz et al., 2019). Genetic engineering encompasses two main categories: transgenic and cisgenic methods. Transgenic genetic engineering involves transferring genetic material from unrelated species into a target organism, thereby expanding the gene pool of the recipient organism (Schouten et	assessment, refer to EFSA GMO Panel (2011) and EFSA Scientific Committee (2022a), as well as Section 1.2 of the Guidance, which addresses GMM categories (1 and 2) that fall under the remit of Regulation 2015/2283 on novel foods. Products not covered by Regulation 2015/2283 on novel foods (Article 10) are outside the scope of this Guidance. The Panel considers that no change to the Guidance is needed.

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		al., 2006). This type of genetic modification imparts a new trait to the recipient organism that is not naturally occurring in the species nor can be introduced through classical breeding. Conversely, cisgenic genetic modification involves either inducing direct mutations in the recipient genome (Ahmad et al., 2023) or introducing a gene that is present in the genome of the species or its close relatives. This method likely poses no additional risks beyond those associated with conventional breeding methods, such as effects on non-target organisms or soil ecosystems, toxicity, or potential allergy risks (Schouten et al., 2006). When it comes to microorganisms, adaptation, basically direct evolution – selection of desired mutations, can be employed to achieve desired traits in some cells. Another method to attain desired cell line characteristics or eliminate unwanted genes or DNA segments (knock-out), such as prions or viruses, is genetic engineering. Genetic modification offers more control than traditional crossbreeding of plants or animals and allows precise changes in the genome (Ishino et al., 2018). Cisgenic genetic modification can be for example employed to attain cell immortality, closely mimicking natural processes and potentially mitigating risks associated with introducing foreign genetic material or producing new allergens (Schouten et al., 2006). The debate surrounding GMOs encompasses various considerations, from the origin of introduced genes to their potential implications for human health and the environment. Regulatory processes for cisgenic and/or CRISPR-edited organisms lag behind the rapid pace of scientific advancement, posing challenges for regulatory authorities in effectively addressing complexities and evaluating risks. Regulatory processes often trail the swift progress in scientific advancements across many jurisdictions (Ahmad et al., 2023). Understanding the nuances of genetic modification techniques and their specific applications is essential in navigating these complex discussions and shaping the future of food production. REFERENCES: Ahmad, A., et al. ‘GMOs or non-GMOs? The CRISPR Conundrum.‘ Frontiers in plant science vol. 14 1232938 (2023). doi:10.3389/fpls.2023.1232938 American Association	

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		for the Advancement of Science. 'Statement by the AAAS board of directors on labeling of genetically modified foods.' American Association for the Advancement of Science. http://www.aaas.org/sites/default/files/AAAS GM statement.pdf (2012). DeFrancesco, Laura. 'How safe does transgenic food need to be?' Nature biotechnology vol. 31,9 (2013): 794-802. doi:10.1038/nbt.2686 Herman, Rod A., and Ping, S. 'Comprehensive COMPARE database reduces allergenic risk of novel food proteins.' GM Crops & Food 13.1 (2022): 112-118. doi:10.1080/21645698.2022.2079180 Ishino, Y., et al. 'History of CRISPR-Cas from encounter with a mysterious repeated sequence to genome editing technology.' Journal of bacteriology 200.7 (2018): 10-1128. doi:10.1128/JB.00580-17. Jonas, D. A., et al. 'Safety considerations of DNA in food.' Annals of Nutrition and Metabolism 45.6 (2001): 235-254. doi: 10.1159/000046734. Keeling, P., J, and Palmer, J. D. 'Horizontal gene transfer in eukaryotic evolution.' Nature reviews. Genetics vol. 9,8 (2008): 605-18. doi:10.1038/nrg2386 Nawaz, M., et al. 'Addressing concerns over the fate of DNA derived from genetically modified food in the human body: A review.' Food and Chemical Toxicology 124 (2019): 423-430. doi: 10.1016/j.fct.2018.12.030 Nordlee, J A et al. 'Identification of a Brazil-nut allergen in transgenic soybeans.' The New England journal of medicine vol. 334,11 (1996): 688-92. doi:10.1056/NEJM199603143341103 Rizzi, A., et al. 'Stability and recovery of maize DNA during food processing.' Italian journal of food science 15.4 (2003): 499-510. Schouten, H., J et al. 'Cisgenic plants are similar to traditionally bred plants: international regulations for genetically modified organisms should be altered to exempt cisgenesis.' EMBO reports vol. 7,8 (2006): 750-3. doi:10.1038/sj.embor.7400769	
84	BaseClear	In lines 436-438 and 453-458, scientific requirements were outlined for the taxonomic and hazard identification of microorganisms. It would be beneficial to provide clear descriptions of the methods and protocols for each	The Panel notes the recommendation but considers that a detailed expansion of methods, protocols, and validation procedures goes beyond the scope of this Guidance. Please

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		analysis/test, along with any related validation procedures that meet the qualification demands.	refer to EFSA FEEDAP Panel (2018), EFSA (2021e), EFSA BIOHAZ Panel (2023a, b), and EFSA GMO Panel (2024) for additional information on the scientific requirements for the taxonomic and hazard identification of microorganisms intentionally used in the food chain, including microorganisms as novel foods (active agents or biomasses) or used in the production of novel foods (production strains).
120	Medfiles Ltd	Comment: P15L458: The referred section 2.1.3 of EFSA FEEDAP Panel (2018) does not exist. Should it be replaced by section 2.2.2 instead?	The corresponding reference has been amended in section 1.2.
149	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Line 412 When will the new guidance or reference document for microorganism be published ? Will it concern all the microorganisms or only genetically modified microorganisms ? 2. Line 417-452 'In the context of novel foods, microorganisms can have different roles : 1) as novel food consisting of viable or non-viable cells 2) as source of novel food, i.e., novel food is isolated or produced from the microorganism. ' In case of GMMs, only products in 2) fall under novel food Regulation unless falling under other Regulations (e.g., food improvement agents). Products in 1) fall under GMFF Regulation. In some cases, more than one Regulation applies. Please make it clearer which kind of products are included in or excluded from Novel Food Regulation in case of GMMs. Please mention the alternative regulation for approval of these kinds of products. How are the products to be approved that do not fall within the scope of Novel Food Regulation or Regulation 1829/2003? ' 3. Line 420 'produced from' should be replaced by 'produced with' or 'produced by' 4. Lines 430-435 'Suggested change ' ... and confirmation of deposition . . .'. The culture collection depositary may not be able to provide a certificate of deposit format for customer-owned non-patent deposits, but will be able to provide an	1. For additional information on the 'EFSA Guidance on the Characterisation and Risk Assessment of Microorganisms Used in the Food Chain,' please refer to the Open EFSA portal (EFSA-Q-2024-00438). 2. The roles of microorganisms in the context of novel foods and for the purpose of this Guidance have been clarified in Section 1.2 and Appendix A. Please refer to the response to comment 72 for details on regulatory provisions concerning novel foods and GMOs, as well as relevant GMM categories for the risk assessment of novel foods. 3. The text regarding novel foods produced with GMMs has been revised. 4. The text in Section 1.2 and Appendix A concerning the certificate of deposition for the microbial strain

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		official statement confirming safe deposit / long-term preservation of the organism in their biorepository under an accession number. The term 'certificate of deposition' may cause confusion regarding the requirement. ' 5. Lines 439-442 The Certification of deposition is now a normal requirement for food and feed dossiers. However, it will be important to watch what the Commission will make out of it. Currently, quite some Novel Food approvals are not strain-specific, but cover entire strain lineages (e.g. genetically modified strains of E. coli K12 in general; e.g. HMOs). This practice should be maintained. We are not sure whether this should already be emphasised at this stage of the process. 6. Line 451 'if applicable' should be added at the beginning of the sentence. 7. Lines 451-452 Provision of providing WGS raw data and FASTA-files of the WGS: The submission of these data should not be systematically requested for production strains used in contained use fermentation processes and for microorganisms used as Novel Food, as each application should be considered on a case-by-case basis, where a safety concern is demonstrated by EFSA. We still maintain and support the position expressed previously through the industry associations AMFEP, EuropaBio and FEFANA that: - EFSA guidance documents are not legally binding but a flexible tool to support applicants in the authorisation procedure and that, therefore, deviations from the requirements are allowed, if duly justified; - Submission and/or checks of raw data must not be part of risk assessment, but can be addressed by risk management measures; and - Submission of FASTA files represents a significant threat for the competitiveness of the fermentation industry, particularly for production microorganisms used under containment, as outlined in detail by AMFEP/EuropaBio/FEFANA before. Even if under the new Transparency rules, applicants can make confidentiality requests on the FASTA files when submitting dossiers, every disclosure represents a potential risk of accidental dissemination to unauthorised parties. Moreover, the FASTA files constitute processed data and do not per se	under assessment has been updated. For further information, please refer to EFSA FEEDAP Panel (2018), Section 2.1. It is up to the applicant to determine the most appropriate type of deposition (e.g., open, safe, or patent deposit). 5. The characterisation and risk assessment of microorganisms used as novel foods or in the production of novel foods are conducted at the strain level (taxonomic identification at the species level). The specific microbial strain should be listed in the specifications of the novel food, as detailed in Section 4. The Panel considers that no change to the Guidance is needed. 6. For information on the presence of viable cells of the production strain in the novel food, please refer to EFSA FEEDAP Panel (2018), Section 3.1. Strains belonging to species with QPS status and meeting QPS qualifications are considered as 'qualifying for QPS approach' (EFSA FEEDAP Panel, 2018; EFSA BIOHAZ Panel, 2023a). The Panel considers that no change to the Guidance is needed. 7. According to EFSA (2021e), WGS-based data analysis can provide definitive taxonomic identification of strains and insight into their potential functional traits of concern. Further details on conducting and reporting sequencing and WGS-based analyses are available in EFSA (2021e). By the

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		allow to draw any conclusions from a risk perspective and therefore, they should not be requested for such purpose. Risk assessment is not based on such data, but on final analysis/reports provided. ‘ 8. Lines 457 - 458 AMR is too broad also here Annex A (cited line 437) Viable cells: if the novel food is an extract, the test should be done on the extract or on the biomass? This should be clarified Annex A (cited line 437) What does ‘not qualifying for the QPS status‘ mean?	end of 2023, EFSA will introduce a new bioinformatics tool, the Microorganisms Pipelines Service (MoPS) portal, which will allow EFSA to independently verify WGS data submitted as part of novel food applications involving microorganisms (bacteria, yeasts, and filamentous fungi). This tool is designed to comply with EFSA’s strict IT security requirements to ensure a secure and confidential environment. As communicated by EFSA’s Front-Desk and Workforce Planning Unit, ‘effective 1 May 2024, EFSA will request applicants to submit WGS data (FASTA files) on a routine basis during the suitability/completeness check phase, if not already included in the application dossier.‘ Applicants may request confidential status for WGS data in accordance with the applicable legal framework, particularly Articles 39 to 39e of Regulation (EC) No 178/2002. Section 1.2 and Appendix A have been updated accordingly. 8. Please refer to the response to comment 50.
200	EU Specialty Food Ingredients	Lines 417-427: Please make it clearer which kind of products are included in or excluded from Novel Food Regulation in case of GMMs. Please mention the alternative regulation for approval of these kinds of products. How are the products to be approved that do not fall within the scope of Novel Food Regulation or Regulation 1829/2003? Line 420: ‘produced from‘ should be replaced by ‘produced with‘ (or ‘produced by‘). ‘Produced from‘ has a different meaning in the context of the EU GMO	Please refer to the response to comments 50 and 149.

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		regulations. Lines 439-442: - The Certification of Deposition is now a normal requirement for food and feed dossiers. However, it will be important to watch what the Commission will make out of it. Currently, quite some Novel Food approvals are not strain-specific, but cover entire strain lineages (e.g. genetically modified strains of E. coli K12 in general; e.g. HMOs). This practice should be maintained. We are not sure whether this should already be emphasised at this stage of the process. - Suggested change '... and confirmation of deposition …'. The culture collection depositary may not be able to provide a certificate of deposit format for customer-owned non-patent deposits, but will be able to provide an official statement confirming safe deposit / long-term preservation of the organism in their biorepository under an accession number. The term 'certificate of deposition' may cause confusion regarding the requirement. Lines 446-448: Anti-microbial is a very broad term. Alcohol, acids, and certain ingredients can be antimicrobial. Many microorganisms can produce acids. Hence, this broad and imprecise wording could be interpreted as a request to analyse all these components for their potential effect. In the past, EFSA's concern was rather related to the production of antibiotics or the spread of antibiotic resistance in the environment. This focus should be kept and the wording should be amended accordingly. Lines 451-452: 1. We would add 'if applicable' at the beginning of the sentence. 2. Provision of providing WGS raw data and FASTA-files of the WGS: The submission of these data should not be systematically requested for production strains used in contained use fermentation processes and for microorganisms used as Novel Food, as each application should be considered on a case-by-case basis, where a safety concern is demonstrated by EFSA. We would like to point out that: - EFSA guidance documents are not legally binding but a flexible tool to support applicants in the authorisation procedure and that, therefore, deviations from the requirements are allowed, if duly justified; - Submission and/or checks of raw data must not be part of risk assessment, but can be addressed by risk management measures; and - Submission	

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		of FASTA files represents a significant threat for the competitiveness of the fermentation industry, particularly for production microorganisms used under containment. Even if under the new Transparency rules, applicants can make confidentiality requests on the FASTA files when submitting dossiers, every disclosure represents a potential risk of accidental dissemination to unauthorised parties. Moreover, the FASTA files constitute processed data and do not per se allow to draw any conclusions from a risk perspective and therefore, they should not be requested for such purpose. Risk assessment is not based on such data, but on final analysis/reports provided.	
226	Planet A Foods GmbH	1. - ll. 439-442: meaning the applicant needs to publicly deposit the strain prior to the application? 2. - ll. 453-455: thresholds for acceptable live cell counts per g of product - ll. 456-458: thresholds for acceptable DNA amounts per g of product are missing	1. Please refer to the response to comment 149 in relation to the certificate of deposition of the microbial strain under assessment 2. Please refer to EFSA FEEDAP Panel (2018), sections 3.1 and 3.2, for additional information on the presence of viable cells and DNA from the production strain, in relation to the requirements for the analytical determination. The Panel considers that no change to the Guidance is needed.
237	VTT, Technical Research Centre of Finland	Page 14, Lines 424-426: 'only GMM categories 1 ('chemically defined purified compounds and their mixtures in which both GMMs and newly introduced genes have been removed') and 2 ('complex products in which both GMMs and newly introduced genes are no longer present'), ' Comment: Newly introduced genes 'no longer present' is without the GMM residue limit and refers to zero tolerance. We consider that this could be more specific and presented in a quantifiable limit and the requirement should be the at the same level as given to traditional foods and food ingredients. Among traditional foods the presence of GMOs is below 0.9% of the food/feed, or if the ingredient is adventitious or technically unavoidable, labelling of	Please refer to EFSA FEEDAP Panel (2018), section 3.2, for additional information on the presence of DNA from genetically modified production strains, in relation to the requirements of the analytical determination. The wording has been improved in section 1.2 in relation to GMM categories (1 and 2) falling under the remit of the Regulation 2015/2283 on novel foods.

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		GMO is not required. We propose that the same threshold of GMM content is used for novel foods as for conventional foods. Page 15, Lines 439-442 'Unambiguous taxonomic identification at species level and certificate of deposition (including accession number) in an internationally recognised culture collection having acquired the status of International Depositary Authority under the Budapest Treaty (EFSA FEEDAP Panel, 442 2018; EFSA, 2021e);' The text in the current version is suggested to be reconsidered. There are two issues that should be addressed: 1. The necessity of proper taxonomic identification and request to deposit in collection with International Depositary Authority (IDA) status should not be combined, but rather stated separately. 2. The issue of mandatory deposit to the collection with IDA status. As formulated now in the draft document it can be a public deposit, safe deposit or patent deposit. The Budapest Treaty governs the procedure for the deposit of biological material solely for patent purposes and IDA status is given to the collection that performs deposits of the microorganisms under the Budapest Treaty rules. 1. If patenting is obligatory for Novel Food applications, this should be stated in the document. If filing a patent is not obligatory for an application for authorisation, but EFSA prefers the deposit to be done in IDA, we advise clarifying this in the guidance. We proposed to mention, for instance, that 'Safe Deposit' or 'Confidential Deposit' should be done in IDA.	It should be noted that both requirements (taxonomic identification and certificate of deposition) relate to the identification of the microbial strain under assessment, as per EFSA FEEDAP Panel (2018), section 2.1. The Panel considers that no change to the Guidance is needed. Regarding the certificate of deposition of the microbial strain under assessment, please refer to the response to comment 149.
242	The Good Food Institute Europe	Line 412-418: Foods consisting of, isolated from or produced from microorganisms Comment: We would like to put on record our firm support for the inclusion and expansion of section 1.2 on Foods consisting of, isolated from or produced from microorganisms. Line 456-458: The presence of DNA from the production strain in the novel food has to be tested for i) GM production strains, and ii) non-GM production strains harbouring acquired AMR genes (additional requirements in section 2.1.3 of EFSA FEEDAP Panel (2018). Comment: It should be noted that FEEDAP gives two protocols that need to be satisfied, phenotype testing and whole-genome sequencing. Equally EFSA could	The text has been revised in relation to the presence of DNA from the production strain in the novel food.

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		consider replacing the term 'tested' with 'analysed' to enable a greater scope of methodological approaches.	
310	Food Safety & Nutrition Consultancy	QPS status: guidance (reference to procedure) is needed on how applicants can strive for QPS. This is frequently an unclear procedure.	Please refer to the response to comment 13.
321	EuropaBio	Lines 417-427 Proposed amendment '…roles: 1) as NF consisting of viable or non-viable cells 2) as source of NF, i.e., NF is isolated or produced from the microorganism. In case of GMMs, only products in 2) fall under NF Regulation unless falling under other Regulations (e.g., food improvement agents). Products in 1) fall under GMFF Regulation. In some cases, more than one Regulation applies.' Please make it clearer which kind of products are included in or excluded from Novel Food Regulation in case of GMMs. Please mention the alternative regulation for approval of these kinds of products. How are the products to be approved that do not fall within the scope of Novel Food Regulation or Regulation 1829/2003? Lines 451-452 Provision of providing WGS raw data and FASTA-files of the WGS: The submission of these data should not be systematically requested for production strains used in contained use fermentation processes and for microorganisms used as Novel Food, as each application should be considered on a case-by-case basis, where a safety concern is demonstrated by EFSA. We still maintain and support the position expressed previously through the industry associations AMFEP, EuropaBio and FEFANA that: - EFSA guidance documents are not legally binding but a flexible tool to support applicants in the authorisation procedure and that, therefore, deviations from the requirements are allowed, if duly justified; - Submission and/or checks of raw data must not be part of risk assessment, but can be addressed by risk management measures; and - Submission of FASTA files represents a significant threat for the competitiveness of the fermentation industry, particularly for production microorganisms used under containment, as outlined in detail by AMFEP/EuropaBio/FEFANA before. Even if under the new Transparency rules, applicants can make confidentiality requests on the FASTA files when	Please refer to the response to comment 149. Regarding 'inspection requirements', please note that the text has been revised, retaining this point under section 1.4.

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		submitting dossiers, every disclosure represents a potential risk of accidental dissemination to unauthorised parties. Moreover, the FASTA files constitute processed data and do not per se allow to draw any conclusions from a risk perspective and therefore, they should not be requested for such purpose. Risk assessment is not based on such data, but on final analysis/reports provided. Line 513: 'inspection requirements' as defined in the Food Hygiene Regulation.	
349	GAIKER	Interested in knowing legal limits for nucleic acid content, and how these reference limits are calculated (for example, there might be a big difference between 2% on a dry weight basis, or 2% on a total volume basis Interested in knowing legal limits for exotoxins and endotoxins	The Panel considers that this goes beyond the scope of this Guidance.
435	Food Supplements Europe	Lines 451-452 We fail to see why whole-genome sequence data should systematically be provided for any micro-organism used in addition to the other data requirements that enable already to establish the identity of the micro-organism. In particular for QPS microorganism, this is a requirement that should be waived.	Please refer to the response to comment 149 It should be noted that the criteria for the QPS (Qualified Presumption of Safety) approach to safety assessment include unambiguous taxonomic identification as belonging to a species listed in the QPS list, as well as meeting the corresponding QPS qualifications, such as the absence of acquired antimicrobial resistance for bacteria. For further details on the scientific requirements for taxonomic identification and the analysis of genes of potential concern, which necessitate whole-genome sequencing (WGS) data analyses, please refer to the EFSA FEEDAP Panel (2018) and EFSA (2021e).
550	Novonesis (merger of former Novozymes	page 14-15, lines 428-433: From line 428 to 433 it is explained that for a product consisting of live microorganisms belonging to the QPS taxonomic unit with 'qualifications' may benefit from risk approach based on safety preassessment from QPS.	Please refer to the response to comment 13.

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	and Chr. Hansen)	However, impact of risk assessment approach based on QPS is not further defined for a strain that has QPS taxonomic unit and fulfills 'qualifications'. It could benefit to spell it out similar to the approach in Scientific Guidance for the submission of dossiers on Food Enzyme, EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (EFSA CEP Panel) 2021, p 22, 4.1 Exemptions from toxicity testing (other than allergenicity).	
575	Aletheia: il segreto del buon vivere	Section 1.1.3 contains several limitations in the case of foods of animal origin produced by microorganisms, such as milk proteins derived from genetically modified yeasts: • the level of microorganism characterisation required in this respect by the Guidance is very limited, especially when compared to the information required for risk assessment of microorganisms in products subject to pre-market authorisation carried out by EFSA itself. For example, the 'Guidance for the evaluation of food enzymes'(EFSA, Scientific Guidance for the submission of dossiers on Food Enzymes. EFSA Journal 2021;19(10):6851) like protein compounds produced by microorganisms, requires an accurate evaluation of the producing microorganism, also based on genome analysis for taxonomic identification, a search for virulence factors, toxins, and antimicrobial resistance genes, and a characterisation and risk analysis of genetic modification. • precision fermentations for animal protein production use genetically modified microorganisms ('GMM's). GMM assessment follows the criteria defined by the 'Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use'(EFSA, Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use. EFSA Journal 2011;9(6):2193) that defines four different categories: - Category 1: Chemical-defined purified compounds and mixtures thereof in which both GMMs and newly introduced genes have been removed (e.g., amino acids, vitamins); - Category 2: complex products in which both GMMs and newly introduced genes are no longer present (e.g., cell extracts, most enzyme preparations); - Category 3: GMM-derived products in which	The overall scientific requirements for the taxonomic and hazard identification of microorganisms, whether used as novel foods (active agents and biomasses) or in the production of novel foods (production strains), including those produced through precision fermentation, are detailed in Section 1.2 and Appendix A. These sections also make reference to the most up-to-date EFSA scientific outputs (EFSA FEEDAP Panel, 2018; EFSA, 2021e; EFSA BIOHAZ Panel, 2023a; EFSA GMO Panel, 2024) for additional information on the scientific requirements for risk assessment. It should be noted that EFSA has initiated activities to centralise the different sector-specific guidance documents in this area into one single overarching Guidance on the characterisation of microorganisms (EFSA-Q-2024-00438) to be finalised in the next months. For regulatory provisions on the interplay between NFs and GMOs, as well as relevant categories of

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		there are no GMMs capable of multiplying or transferring genes, but in which newly introduced genes are still present (e.g., heat-inactivated starter cultures); - Category 4: Products consisting of or containing GMMs capable of multiplying or transferring genes (e.g., live starter cultures for fermented food and feed). Products derived from microorganisms belonging to Cat. 1 and 2 do not fall under the scope of Regulation (CE) 1829/2003 on GMO foods. Differently, foods in Cat. 3 that may include food products containing milk proteins produced by microorganisms, are considered GMO foods. A similar example of proteins produced from GMM yeasts is the production of soybean leghemoglobin in Pichia pastoris, a product currently being evaluated by EFSA, as reflected in the minutes of GMO Panel meetings. (https://www.efsa.europa.eu/sites/default/files/event/gmo-134-m.pdf). In the case of Cat. 3 foodstuffs, the evaluation must follow the EFSA guidance for GMMs. This guidance is a document written in 2011 before the development of omics techniques for risk assessment and it presents some limitations, as highlighted in the opinion on Synthetic Biology of the EFSA Scientific Committee. In conclusion, the current Guidance for Novel Foods requirements are not in accordance with EFSA most up-to-date guidance for risk assessment of microorganisms and their products intentionally introduced into foods.	genetically modified microorganisms (GMM) for risk assessment purposes, please refer to Regulation 1829/2003 on genetically modified organisms (GMOs) and Directive 2001/18/EC (Article 2(2) and Annex I B) for the definition of GMOs. It should be noted that Regulations 1829/2003 on GMOs and 2015/2283 on novel foods are mutually exclusive. For definitions of GMM categories relevant to risk assessment, refer to EFSA GMO Panel (2011) and EFSA Scientific Committee (2022a), as well as Section 1.2 of the updated novel foods Guidance, which addresses GMM categories (formerly called 1 and 2) that fall under the remit of Regulation 2015/2283 on NFs. Products not covered by Regulation 2015/2283 on novel foods (Article 10) are outside the scope of this Guidance. Please note that the overarching Guidance on the characterisation of microorganisms (EFSA-Q-2024-00438), under development, will provide further horizontal guidance across EFSA also on this matter. Please also refer to the response to comment 72. The Panel considers

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			that no change to the Guidance is needed.
583	AseBio - Spanish Bioindustry Association,	1. Line: 417-427 Proposed amendment ' ... roles: 1) as NF consisting of viable or non-viable cells 2) as source of NF, i.e., NF is isolated or produced from the microorganism. In case of GMMs, only products in 2) fall under NF Regulation unless falling under other Regulations (e.g., food improvement agents). Products in 1) fall under GMFF Regulation. In some cases, more than one Regulation applies.' Please make it clearer which kind of products are included in or excluded from Novel Food Regulation in case of GMMs. Please mention the alternative regulation for approval of these kinds of products. How are the products to be approved that do not fall within the scope of Novel Food Regulation or Regulation 1829/2003? 2. Line: 451 - 452 Provision of providing WGS raw data and FASTA-files of the WGS: The submission of these data should not be systematically requested for production strains used in contained use fermentation processes and for microorganisms used as Novel Food, as each application should be considered on a case-by-case basis, where a safety concern is demonstrated by EFSA. We still maintain and support the position expressed previously through the industry associations AMFEP, EuropaBio and FEFANA that: - EFSA guidance documents are not legally binding but a flexible tool to support applicants in the authorisation procedure and that, therefore, deviations from the requirements are allowed, if duly justified; - Submission and/or checks of raw data must not be part of risk assessment, but can be addressed by risk management measures; and - Submission of FASTA files represents a significant threat for the competitiveness of the fermentation industry, particularly for production microorganisms used under containment, as outlined in detail by AMFEP/EuropaBio/FEFANA before. Even if under the new Transparency rules, applicants can make confidentiality requests on the FASTA files when submitting dossiers, every disclosure represents a potential risk of accidental dissemination to unauthorised parties. Moreover,	Please refer to the response to comment 149.

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		the FASTA files constitute processed data and do not per se allow to draw any conclusions from a risk perspective and therefore, they should not be requested for such purpose. Risk assessment is not based on such data, but on final analysis/reports provided.	
602	Cellular Agriculture Europe	1. Lines 412-458: This section and Annex have been comprehensively expanded and are now very useful. However, in our opinion, how QPS relates to toxicology and allergenicity requirements is not clearly defined (it is for food enzymes). 2. Line 418: 'or non-viable cells (biomasses), including or not their spent fermentation media.' Clarification is needed if the novel food from microorganism may consist as well of media. 3. Line 430: We invite EFSA to specify the meaning of the term 'Unambiguously' (e.g., Taxonomy). 4. Line 456: 'The presence of DNA from the production strain in the novel food has to be tested': We would recommend using the term 'analysed' instead of 'tested'.	1. Please refer to the response to comment 13. 2. It should be noted that Regulation 2015/2283 on novel foods, Article 3, refers to novel foods 'consisting of, isolated from or produced from microorganisms'. Please refer to section 3 in this Guidance, in relation to the scientific requirements for the compositional characterisation of the novel food. The Panel considers that no change to the Guidance is needed. 3. Please refer to EFSA FEEDAP Panel (2018), section 2.1, and EFSA (2021e) for additional information on the scientific requirements for the taxonomic identification of the microorganisms under assessment, and to the 'Guidelines and Good Practices for Taxonomies' by the Semantic Interoperability Centre Europe. The Panel considers that no change to the Guidance is needed. 4. Please refer to the response to comment 242.
642	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Lines 453-455. 'Additionally, the presence of viable cells in the novel food has to be tested in the case of i) biomasses as novel foods, ii) QPS TUs with the qualification 'for production purposes only', and iii) non-QPS or GM production strains (EFSA FEEDAP Panel, 2018)': Does the presence of viable cells also have to be tested in the case of NFs that have been produced by a non-QPS strain (non GM), but the strain has been proven safe by	It should be emphasised that Whole-Genome Sequencing (WGS) data alone may be inadequate for addressing potential safety concerns in microbial strains that do not fulfil the Qualified Presumption of Safety (QPS) criteria, particularly in cases

Comment number	Commentor	Comments	EFSA NDA Panel responses
		analysing WGS data? What would be the implications of presence (in low amounts) of these cells?	where there is limited existing knowledge or ongoing safety concerns. The Panel considers that no change to the Guidance is needed.
666	Atova Regulatory Consulting SL	1. (Line 412-458, page 14-15) We welcome the update to this section and to Annex 4. However, we suggest that it is made clearer how the QPS requirements relate to toxicology and allergenicity as per the latest food enzyme guidance (EFSA, 2021). 2. (Line 422-427, page 14) For clarity and consistency, we request that EFSA refers to the terminology/definitions used lines 418-421 to qualify GMM Category 1 (chemically defined purified compounds…. e.g. when the microorganism is used as the novel food itself) and Category 2 (complex products in which….. e.g. when the microorganism is used in the production of novel foods). 3. (Line 451-452, page 15) In other applicable EFSA guidance documents such as (EFSA FEEDAP Panel, 2018 and 2021e as cited in this draft) WGS data is recommended but not required for filamentous fungi. Same comment is relevant for Annex A 4. (Line 453, page 15) Can EFSA provide some more clarity on the test item (s) (or manufacturing process step) that would be acceptable to show absence of viable cells and DNA.	1. Please refer to the response to comment 13. 2. Please refer to the response to comment 149. It should be noted that GMMs could be used in the production of novel foods (i.e., as production strains) provided that no presence of viable cells and DNA from the GM production strain in the novel food (GMM categories 1 and 2) is demonstrated according to EFSA FEEDAP Panel (2018) 3. Please refer to the response to comment 149. 4. Please refer to EFSA FEEDAP Panel (2018), sections 3.1 and 3.2, for additional information on the presence of viable cells and DNA from the production strain. The Panel considers that no change to the Guidance is needed.
696	FoodDrinkEurope	1. [Line 418] We would suggest to add '…including or not their spent fermentation media', since the novel food from microorganism may consist as well of media. 2. [Line 430] The meaning of the term 'Unambiguously' should be specified (e.g., Taxonomy) for better clarity in the text 3. [Line 446] Anti-microbial is a very broad term. Alcohol, acids, and certain ingredients can be antimicrobial. Many microorganisms can produce acids. Is the intent that this should not lead to antibiotic resistance? If that is the case, this should be said. Anti-microbial is not necessarily bad, increasing	1. Please refer to the response to comment 602. 2. Please refer to the response to comment 602. 3. Please refer to the response to comment 50. 4. Please refer to EFSA FEEDAP Panel (2018), section 3.2, for additional information on the presence of DNA from the production strain, which has to be analysed for a) GM production

Comment number	Commentor	Comments	EFSA NDA Panel responses
		antibiotic resistance in the population is. The word anti-microbial should be changed since the term is too broad. 4. [Line 456] To be able to retain protein quality (for novel food proteins), absolute DNA absence is not possible. Furthermore, some of the microorganisms used will have QPS status. In other jurisdictions (e.g. the US), the presence of small amounts of DNA is not considered a safety concern. The safety concern should be about absence of viable cells, not about DNA (reference: Recombinant DNA in fermentation products is of no regulatory relevance, Food Control 141 (2022) 109170.). We question under what safety parameter is the presence of DNA based on?	strains and b) non-GM production strains carrying acquired antimicrobial resistance (AMR) genes. For a), this is a requirement related to legal classifications since the Regulations 1829/2003 on GMOs and 2015/2283 on novel foods are mutually exclusive. In relation to b), novel foods consisting of, isolated from or produced from microorganisms should not add to the pool of AMR genes already present in the gut bacterial population or otherwise increase the spread of AMR (EFSA FEEDAP Panel, 2018). The Panel considers that no change to the Guidance is needed.

Please note that in final version of the Guidance, the section title has been changed to 'Foods consisting of, isolated from or produced with microorganisms'.

Table 10: Food consisting of, isolated from or produced from plants, macroscopic fungi and algae, or their parts

Comment number	Commentor	Comments	EFSA NDA Panel responses
2	Analyze & Realize GmbH	line 478-481 For commodity plant raw materials sourced on the global market (e.g., plant seeds), this information might not be available at all or cannot be verified by the applicant. What is the minimum requirement that would be acceptable?	The applicant is required to provide all available information. If any part of the information is not available or cannot be retrieved, the applicant must provide a justification for the missing details. This justification will be assessed by the Panel.

Comment number	Commentor	Comments	EFSA NDA Panel responses
14	Undisclosed (Personal Capacity)	Lines 459-460 Should this read: Food consisting of, isolated from or produced from plants, macroscopic fungi, macroscopic algae, or their parts. Do these groups belong together?	The text has been revised.
68	Nutraveris - A FoodchainID company	1. o Is world flora online an appropriate and valid source alternative to plants of the world online? 2. o The draft guidance states that '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 Scientific Committee, 2009)'. However, DNA-based authentication is not stated in the EFSA botanical guidance. While established and validated identification methods exist for plants enabling to determine the plant identity by macro and microscopic assessment with no doubt, why would a DNA-based authentication be required for uncomplicated cases? 3. o Why is the identification approach for macroscopic fungi and algae different than for plants?	1. The appropriate database of reference is Plants of the World Online. The text has been revised in line with the comment, replacing the previous hyperlink with the correct one. 2. The text presents a non-exhaustive list of alternatives for the experimental verification of the identity of plants. 3. The text reflects the difference in scientific knowledge and resources currently available for the characterisation of plants compared to algae and fungi.
85	BaseClear	In lines 465-467 and 474-476, the necessity of providing taxonomy and identity for macroscopic fungi and algae was emphasised. However, it remains unclear whether specific methods, such as WGS, should be employed for this purpose.	WGS is only required in the case of bacteria, yeasts, filamentous fungi and viruses (EFSA WGS, 2021e).
121	Medfiles Ltd	Comment: P15-16 L465-467: The provided link for plants21 goes to the web page http://www.theplantlist.org/ which states that the plant list is superseded and is replaced with The World Flora Online (WFO) Plant List https://wfoplantlist.org/. However, the EFSA Draft novel food guidance refers to the 'Plants of the World Online', for which the correct link is https://powo.science.kew.org/. Please check the provided link presented in the guidance.	Please refer to the response to comment 68.
150	Synpa, French association of specialty food ingredients manufacturer	1. Line 459: For NF derived from wild plants, how can verification of identity be performed, considering natural hybridisation? 2. Lines 470-473 As written, there appears to be a lack of understanding on how the botanical supply chain works. The guidance assumes that the plant and its parts are only single-sourced. For example, many non-GMO statements could be	1. In the case of novel foods derived from wild plants, information on the identity can be obtained through chemical fingerprinting. 2. The applicant is requested to provide a non-GMO statement, accompanied by information on the

Comment number	Commentor	Comments	EFSA NDA Panel responses
	s and distributors	needed from multiple suppliers and locations depending on where the plant or plant part is grown and harvested. 3. Line 482 Can EFSA clarify which kind of non-GMO statement is expected? Is it an official document or statement from e.g. the plant or extract suppliers sufficient?	source material. The guidance acknowledges that the plant and its parts may come from multiple sources. Products derived from GM plants may be subject to Regulation 1829/2003 on GMOs. 3. The text has been revised, further specifying the requirements for the non-GMO statement.
201	EU Specialty Food Ingredients	Lines 470-473: As written, this paragraph does not reflect the practical management of the botanical supply chain. The guidance assumes that the plant and its parts are only single-sourced. For example, many non-GMO statements could be needed from multiple suppliers and locations depending on where the plant or plant part is grown and harvested. Line 482: Can EFSA clarify which kind of non-GMO statement is expected? Is it an official document or statement from e.g. the plant or extract suppliers sufficient?	The applicant is required to provide a non-GMO statement along with information on the source materials used in the production of the novel food. Products derived from genetically modified plants may be subject to Regulation (EC) No 1829/2003 on GMOs.
243	The Good Food Institute Europe	Line 459: Food consisting of, isolated from or produced from plants, macroscopic fungi and algae, or their parts Comment: EFSA should provide greater clarity on the meaning of the term '...or their parts', including potentially including examples for specific reference points.	The text has been revised in line with the comment.
350	GAIKER	The novel food process should be fast and easible for alternative proteins obtained from fermentation with fungi authorised by EFSA (EFSA LIST OF QUALIFIED PRESUMPTION OF SAFETY (QPS) : Fusarium venenatum. whereas fungal protein, Quorn (commercial product) has been consumed for many years	Please refer to section 1.2 where the interplay between the QPS for microorganisms, including fungi, and the present guidance is described.
373	Vaclav Bazata (Personal Capacity)	please, see abstract	No further feedback can be provided because the comment is unclear.
436	Food Supplements Europe	1. Lines 478-481 The provision of growing region(s) of the source organism (continent, country, region) and, when relevant, season of harvesting and growing conditions to produce the source organism (i.e., cultivated or from the wild, conditions of cultivation) are parameters that are applied during	1. No changes were implemented, as information on growing regions and harvesting seasons may be relevant for the safety assessment. If the applicant deems these requirements

Comment number	Commentor	Comments	EFSA NDA Panel responses
		quality control when sourcing raw materials. They will not be part of the specifications. In particular if the source materials are general food commodities the provisions of these details would not be of relevance for the safety assessment. It is suggested to add 'where relevant'. 2. Line 482 The submission of a Non-GMO statement is. a new requirement, but the form under which this must be provided is not specified. We believe that this information is part of the production process and should not be in addition be certified or confirmed in official ways.	not relevant to the safety assessment of the specific product, they may provide a scientific rationale for not including the data. 2. Please refer to the response to comment 201.
459	Undisclosed (Personal Capacity)	The guidance would benefit by including what type of GMO statement is needed. Is an internal statement valid or should this be externally validated?	Please refer to the response to comment 150.
542	Bonumose, Inc.	We request some clarity on how the identity of a novel food derived from a processed plant material such as maltodextrin should be identified. Some of the requested information in Section 1.3 does not seem relevant for highly-processed food ingredients that are already widely used in the industry. For example, experimental verification of the identity of the plant would not be possible due to the high amount of processing that is performed in the isolation of plant starch and its conversion to maltodextrin. DNA from the crop source would not persist in the final materials. Similarly, the growing conditions used to produce the source organism may not be relevant to the safety of the material when it undergoes extensive processing.	This section of the Guidance outlines the principles for defining the identity of plants, macroscopic fungi, and macroalgae. If the applicant considers certain requirements to be irrelevant for the safety assessment of the specific product, they may provide a scientific rationale for not including the data.
603	Cellular Agriculture Europe	Lines 459- 460: Should this read: Food consisting of, isolated from or produced from plants, macroscopic fungi, Macroscopic algae, or their parts? Do these groups belong together? Line 477: 'Part(s) used' : For better clarity in text, we would suggest adding examples of the meaning of the term 'Part(s)s used' (e.g., flower, seed, root, etc..)	The text has been revised in line with the comment.
643	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 482. 'Non-GMO statement': Is it sufficient to provide a statement by the applicant, or do EFSA expect a more official document?	Please refer to the response to comment 150.

Comment number	Commentor	Comments	EFSA NDA Panel responses
697	FoodDrinkEurope	[Line 477] We think the guidance would benefit if some examples of the meaning of the term 'Part(s) used (e.g., flower, seed, root, etc..)' were added	The text has been revised, specifying examples of the part(s) used.

Please note that in final version of the Guidance, the section title has been changed to 'Food consisting of, isolated from or produced from plants, macroscopic fungi and macroalgae, or their parts'.

Table 11: 1.4 Food consisting of, isolated from or produced from animals or their parts

Comment number	Commentor	Comments	EFSA NDA Panel responses
3	Analyze & Realize GmbH	lines 492-496: For commodity animal-derived raw materials that are sourced on the global market, this information is often unavailable or cannot be verified by the applicant. What type of documentation has to be provided? In which level of detail?	The applicant is required to provide all available information. If any part of the information is missing and cannot be retrieved, the applicant must provide a justification for the absence of this information, which will be assessed by the Panel.
15	Undisclosed (Personal Capacity)	Lines 483-497 See section 1.5.1 The general food hygiene requirements and traceability, veterinary checks etc under Regulation 853/2004 should be harmonised	The text has been revised in line with the comment.
151	Synpa, French association of specialty food ingredients manufacturers and distributors	Line 497 Can EFSA clarify which kind of non-GMO statement is expected? Is it an official document or statement from e.g. the plant or extract suppliers sufficient?	The text has been revised, further specifying the requirements for the non-GMO statement.
265	Dwayne Holmes (Personal Capacity)	Page 16, Line 495-496 – The original sources of cells for cultured meat and seafood products may not be traditional livestock or obtained from vendors. Guidance would be useful to include cells sourced from animals, or animal materials, obtained in the wild (e.g. wild animals sampled, fish caught, eggs found, etc.) or from non-vendor entities (e.g. non-commercial laboratorial stocks, donations, etc.).	It should be noted that compliance with applicable EU regulations is requested. The Panel considers that no change to the Guidance is needed.

Comment number	Commentor	Comments	EFSA NDA Panel responses
460	Undisclosed (Personal Capacity)	The guidance would benefit by including what type of GMO statement is needed. Is an internal statement valid or should this be externally validated?	Please refer to the response to comment 151.
529	FoodchainID	Are other identity verification method accepted (i.e. certification by expert)? Or other recognised databases and identification methods?	The text has been revised in line with the comment.
538	Undisclosed (Personal Capacity)	Source and Quality of Cells for Cultured Meat (Lines 495-496ff, page 16) Comment: The guidance could include specific considerations for cultured meat regarding the source and quality of cells, especially from non-traditional sources like wild animals or non-commercial entities. Issues such as genetic stability, cell line authentication, and absence of pathogens should be addressed, reflecting concerns raised in the Humbird document on cultured meat economics, which highlights the challenges in scaling and maintaining cell quality.	It should be noted that these aspects have already been addressed in the Guidance, specifically in the sections on identity and production process. Please also refer to the response to comment 265.
604	Cellular Agriculture Europe	Lines 483-497: See section 1.5.1 The general food hygiene requirements and traceability, veterinary checks etc under Regulation 853/2004 should be harmonised.	The text has been revised in line with the comment.
644	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 497. 'Non-GMO statement': Is it sufficient to provide a statement by the applicant, or do EFSA expect a more official document?	Please refer to the response to comment 151.
698	FoodDrinkEurope	[Lines 483-497] Section 1.5.1 and 1.4 should also require hygiene compliance requirements to Regulation 853/2004 Reference to hygiene regulations is missing in the text	Please refer to the response to comment 604.

Table 12: 1.5 Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, macroscopic fungi or algae

Comment number	Commentor	Comments	EFSA NDA Panel responses
289	Katharina Julia Brenner	Sourcing of Cells for Cultured Meat (Lines 498ff, page 17) Comment: Current guidance may not adequately cover the sourcing of cells from non-traditional livestock or non-vendor	For the characterisation of animal sources, including less common species, the text refers to the

Comment number	Commentor	Comments	EFSA NDA Panel responses
	(Personal Capacity)	sources such as wild animals or lab stocks. It would be beneficial to include specific guidelines for cells obtained from these unconventional sources.	requirements outlined in section 1.4. The text has been revised.
576	Aletheia: il segreto del buon vivere	The information considered necessary in this point, but may not be sufficient for a characterisation of a meat product derived from bioreactor cell products. Indeed, in the case of cell-based meat, scaffolds are frequently used to allow aggregation of animal cells. These components become an integral part of the food and, consequently, they require a detailed characterisation to provide an accurate risk assessment. For cell-based products, EFSA guidelines should cover certain aspects of evaluation currently provided for new pharmaceutical products, including pre-clinical and clinical studies that will be used as safety criteria for an opinion of EFSA.	Scaffolding structures are part of the production process and, depending on their characteristics and functionality, may or may not be considered an integral component of the NF. As extensively discussed at the "EFSA Scientific Colloquium 27: Cell Culture-Derived Foods and Food Ingredients" (EFSA, 2024), scaffolding structures are used to enable the three-dimensional growth of cultivated cells, aimed to increase the yield, and improve the texture in cell culture-derived products, and can also be intentionally part of the final product. The production process, including all input materials, must be thoroughly described, as highlighted in the NF Guidance. Human intervention studies, if available, should be provided and are considered by EFSA, regardless of the primary objective of the study, as long as safety aspects are also investigated. It is to be noted in the context of safety studies, that the NF Guidance makes use of a tiered approach for ADME (Absorption, Distribution, Metabolism and Excretion) studies, genotoxicity and repeated-dose toxicity testing. This ensures that should there any safety concerns for the consumer that cannot be

Comment number	Commentor	Comments	EFSA NDA Panel responses
			addressed by in vitro or animal studies, evidence for safety may also require data from human intervention studies as it already occurred for the risk assessment of other novel foods.
699	FoodDrinkEurope	[Line 519] Further clarifications would be welcomed in the text for the use of the term 'Macroscopic' We understood that EFSA is making a distinction between microalgae (1.2) and macroscopic algae (1.3)	The text has been revised in line with the comment.

Please note that in final version of the Guidance, the section title has been changed to 'Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, macroscopic fungi or macroalgae'.

Table 13: 1.5.1 Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals

Comment number	Commentor	Comments	EFSA NDA Panel responses
16	Undisclosed (Personal Capacity)	Lines 512-513 This new section is very much welcomed. It is recommended that information to attest that the animal cells and tissues used for the preparation of the novel food comply with inspection requirements, with reference to cell-lines established from organ biopsies and eggs, the traceability and veterinary requirements laid down under Regulation (EC) No 853/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin should be considered A veterinary certificate and identification number (where applicable) is required for the source animal which must meet or exceed the same standard required for food producing animals in the EU.	The phrase 'Information to attest that the animal cells and tissues used for the preparation of the novel food comply with inspection requirements' has been removed from section 1.5.1, as it was deemed redundant with the requirements already outlined in section 1.4, 'Food consisting of, isolated from, or produced from animals or their parts.' This section references the following regulations: Commission Regulation (EU) No 2015/1162; Regulation (EU) 2017/625; Regulation (EC) No 853/2004; Regulation (EU) 2019/627 on official controls of products of animal origin.

Comment number	Commentor	Comments	EFSA NDA Panel responses
73	Bene Meat Technologies A.S.	line 512: change the word 'animal' for 'primary'. Reasoning: the change is proposed to make clear that inspection requirements relate to primary cells and tissues (as they must comply with all hygienic and other requirements in the same way as a slaughter animal).	The text has been revised in line with the comment.
152	Synpa, French association of specialty food ingredients manufacturers and distributors	Line 512-513 It is recommended that information to attest that the animal cells and tissues used for the preparation of the novel food comply with inspection requirements, with reference to cell-lines established from organ biopsies and eggs, the traceability and veterinary requirements laid down under Regulation (EC) No 853/2004 laying down specific hygiene rules for food of animal origin should be considered. A veterinary certificate and identification number, where applicable is required for animal source which must meet or exceed the same standard required for food producing animals in the EU. Line 513 'inspection requirements' as defined in the Food Hygiene Regulation. Line 517-518 'Information on whether the cells or tissues sourced from a non-GM [animal, plant, fungus, alga] have been genetically modified.' Either they are genetically modified or not – they cannot be both at the same time.	The text has been revised in line with the comment.
246	The Good Food Institute Europe	1. Line 512-513: Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals Comment: We would like to put on record our firm support for the inclusion and expansion of section 1.5.1 Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals. EFSA could consider including a further bullet point requirement in this section, stating that 'A veterinary certificate and identification number is required for the source animal which must meet or exceed the same standard required for food producing animals in the EU.' 2. Line 517-518: Information on whether the cells or tissues sourced from a non-GM animal have been genetically modified. Comment: EFSA should further clarify the definition of 'genetically modified' in this section, with references or	1. Please refer to the response to comment 16. 2. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		examples which could cross-reference the techniques listed in Part 1 of Annex 1A of Dir. 2001/18/EC).	
266	Dwayne Holmes (Personal Capacity)	1.Page 17, Line 508 – Cells used for cultured meat or seafood may come from exotic species, or technologies used to produce cells from novel species that are not well characterised. It may be useful for guidance to consider when sources are not common species. 2. Page 17, Line 513 – In case there is an EU/EC regulation related to inspection requirements, the number could be mentioned. 3. Page 17, Line 515 – Regarding testing for prions, it is suggested to rephrase as 'testing for prions in the case of limited health information on the source animal where relevant and where recognised methods exist'.	1. Please refer to the response to comment 289. 2. The text has been revised in line with the comment. 3. The applicant has the opportunity to argue why prion testing may not be relevant in their specific case and can highlight any challenges faced, such as the availability of recognised testing methodologies. This requirement will be considered on a case-by-case basis, taking into account the overall documentation and evidence provided by the applicant. The Panel considers that no change to the Guidance is needed.
290	Katharina Julia Brenner (Personal Capacity)	1. Regulatory References for Inspection Requirements (Line 513, page 17) Comment: If there are specific EU/EC regulations related to inspection requirements, mentioning the relevant regulation numbers directly in the text could enhance clarity and ensure compliance. 2. Prion Testing Guidance (Line 515, page 17) Comment: The recommendation for prion testing should clarify the circumstances under which such testing is required, focusing on situations with limited health information on the source animal and where recognised testing methodologies are available.	1. Please refer to the response to comment 266. 2. Please refer to the response to comment 290.
584	AseBio - Spanish Bioindustry Association,	Line: 513 'inspection requirements' as defined in the Food Hygiene Regulation.	Please refer to the response to comment 266.
605	Cellular Agriculture Europe	1. Lines 512-513: This new section is very much welcomed. It is recommended that information to attest that the animal cells and tissues used for the preparation of the novel food comply with inspection requirements, with reference to cell-lines established from organ biopsies and eggs, the traceability and	1. The text has been revised in line with the comment. 2. Please refer to the response to comment 246.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		veterinary requirements laid down under Regulation (EC) No 853/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin should be considered. A veterinary certificate and identification number (where applicable) is required for the source animal which must meet or exceed the same standard required for food producing animals in the EU. The term 'inspection requirements' (513) should be better defined, as per above for example. 2. Lines 517-518: We invite EFSA to specify what 'genetically modified' means (i.e. by techniques listed in Part 1 of Annex 1A of Dir. 2001/18/EC)	
645	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 513. 'inspection requirements': Please clarify these requirements.	The text has been revised in line with the comment.
667	Atova Regulatory Consulting SL	(Line 512-518, page 17) We welcome the addition of this section to the guidance. We suggest that animal cells and tissues used in the production process of the novel food the inspection requirements, the traceability and veterinary requirements laid down under Regulation (EC) No 853/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin should be considered.	The text has been revised in line with the comment.

Table 14: 1.5.2 Foods consisting of, isolated from or produced from cell culture or tissue culture derived from plants, macroscopic fungi or algae

Comment number	Commentor	Comments	EFSA NDA Panel responses
17	Undisclosed (Personal Capacity)	See comment 1.3. Should is state ...or macroscopic algae - just to avoid confusion and making clear microscopic algae are microorganisms	The text has been revised in line with the comment.

153	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 525-526 'Information on whether the cells or tissues sourced from a non-GM [animal, plant, fungus, alga] have been genetically modified.' Either they are genetically modified or not – they cannot be both at the same time	The text has been revised in line with the comment.
606	Cellular Agriculture Europe	Lines 519-526 see comment to 1.3. Clarify that this means macroscopic algae (e.g.. sea weeds) rather than microalgae	The text has been revised in line with the comment.

Please note that in final version of the Guidance, the section title has been changed to 'Foods consisting of, isolated from or produced from cell culture or tissue culture derived from plants, macroscopic fungi or macroalgae'.

Table 15: 1.6 Foods containing or consisting of engineered nanomaterials

Comment number	Commentor	Comments	EFSA NDA Panel responses
154	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 527-531 The Guidance on technical requirements for nanomaterials (EFSA, 2021) should be addressed here as there are specific nano tests that may apply such as solubility and bridging toxicology data.	This section focuses solely on the identity of engineered nanomaterials and does not provide specific testing strategies for products that contain nanoparticles. The Panel considers that no change to the Guidance is needed.
202	EU Specialty Food Ingredients	Lines 527-531: EFSA should also refer to the Guidance on technical requirements for nanomaterials (EFSA Journal 2021;19(8):6769) as it provides exemptions for specific nano testing that may still be applicable to novel foods falling into this category (solubility, bridging existing toxicology data).	Please refer to the response to comment 154.
248	The Good Food Institute Europe	Line 527: Foods containing or consisting of engineered nanomaterials Comment: EFSA should clarify whether protein molecules from precision fermentation could be included in the definition of 'engineered nanomaterials' if they are less than 100nm, or whether they would fall into conventional materials risk assessment as long as they lose nano-specific properties as per Guidance on risk assessment of nanomaterials to be applied	Unmodified proteins (including enzymes) do not require a nano-specific risk assessment. However, modified proteins may require an assessment according to the Guidance on risk assessment of nanomaterials to be applied in the

Comment number	Commentor	Comments	EFSA NDA Panel responses
		in the food and feed chain: human and animal health. This is particularly pertinent for proteins with localisation or trafficking tags that are not a 1:1 copy of a food protein.	food and feed chain. This assessment can be necessary when nano-specific properties are retained.

Table 16: 2 Production process

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49	Specialised Nutrition Europe (SNE)	Page 18 Line 583-586: enzymes as processing aids If enzymes are used, does this text mean to say that these enzymes need to be removed/inactivated? If the enzymes are approved, do they need to be removed or inactivated? Is this different from enzymes used in traditional foods?	The text in section 2.2 has been revised in relation to the scientific requirements for food enzymes used in the production of novel foods, in order to establish the safety of the novel food.
64	Nutraveris - A FoodchainID company	- Is a non-confidential description of the production process still mandatory?	Clarification on the matter has been provided in section 2.1. The text has been revised.
141	Synpa, French association of specialty food ingredients manufacturers and distributors	Line 532 How to ensure that all confidential data will be kept confidential even for the scientific advice publication? Lines 533-534 'The process(es) employed to produce the novel food (e.g., chemical synthesis, enzyme catalysis, fermentation, or isolation from a natural source) should be thoroughly and completely described.' This is disproportionate and can lead to onerous reporting requirements. Proposal to replace by: […] should be described at a sufficient level of detail to allow identification of all potential safety risks. Lines 533-536 What is the definition of 'thoroughly and completely described.'? That definition could be different for different reviewers leading to some thorough and complete novel foods dossiers to be rejected while other with less information being accepted. Also, it could be quite burdensome to compile thorough and complete description. Perhaps, 'sufficient level of detail to allow identification of all potential safety risks' with a description of 'sufficient detail' would be a better approach.	Please refer to Regulation 2015/2283 on novel foods (article 23), in relation to the provisions on transparency and confidentiality. Confidentiality of submitted information can be requested. Moreover, additional information can be found on the respective EFSA webpage. https://www.efsa.europa.eu/en/applications/confidentiality-sanitisation. Additionally, please refer to the response to comment 64. The Panel acknowledges the concern expressed. It should be highlighted that it is crucial to ensure that the assessment of novel foods is conducted with a comprehensive understanding of the production

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			processes involved. Detailed descriptions of the processes employed are essential for identifying and evaluating all potential safety risks associated with the novel food. Therefore, the Panel considers that it is necessary to maintain the requirement for thorough and complete descriptions of the production processes. Considering the proposals in the comment, the wording has been improved to provide further clarity. Please refer to the response to point 2 of this comment.
185	Istituto zooprofilattico sperimentale delle venezie	Does this part cover farming (for example in the case of edible insects)? It is important to let space in the dossier description for post-approval modification of the production process if these does not affect identified risks. Or to have a fast procedure for approval of such changes.	Farming covers all animals, including those for edible insects. As outlined in Article 25 (a) of Regulation (EU) 2015/2283, any changes that occur after the risk assessment or eventual authorisation of the novel food, which could affect its safety, must be promptly notified to the European Commission. Upon notification of such changes, appropriate risk management decisions will be made, with the possibility of additional risk assessment if deemed necessary. The Panel considers that no change to the Guidance is needed.
194	EU Specialty Food Ingredients	Lines 533-534: 1. This is disproportionate and can lead to onerous reporting requirements. Proposal to replace by: […] should be described at a sufficient level of detail to allow identification of all potential safety risks. We appreciate that the content of this section may be covered by confidentiality as per the practical arrangements of the	Please refer to the response to comment 141. Please refer to the response to comment 64.

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		Transparency Regulation, as recognised in the EFSA webinar March 21 2024, where EFSA experts noted that evaluation of impact requires all details of the production process, and that content in this section is covered by confidentiality.	
284	Katharina Julia Brenner (Personal Capacity)	Comprehensive Description and Validation of Production Process (Page 18, Lines 532-536): Comment: The guidance specifies that the production process must be thoroughly described, including methods like chemical synthesis, enzyme catalysis, fermentation, or isolation. However, it could benefit from explicitly requiring the validation of each process step to demonstrate control and consistency. Detailed protocols for process validation should be included, ensuring that each stage meets predetermined specifications contributing to the final product's safety and efficacy. This would enhance the robustness of the production process evaluation and ensure reliability across different production batches. Detailed Reporting on Input Materials and Contact Materials Compliance (Page 18, Lines 538-542): Comment: While the document mandates reporting on all input materials and their compliance with EU regulations, it could be improved by specifying the required details for these reports. For each input material, the guidance should request information on source, quality, safety data, and regulatory compliance documentation. Additionally, for materials in contact with the food during production, detailed justifications for their use and data on their non-reactivity and non-contamination potential should be provided. This ensures that all materials meet safety standards and do not adversely affect the novel food's safety and quality.	The description of the production process should indeed be detailed. The applicant can provide additional evidence to further substantiate the quality of the production process. The Panel notes the recommendations but considers that a detailed expansion of the section referred to goes beyond the scope of this Guidance. Regarding raw materials, please refer to the response to the comment 155. With regard to materials in contact with the food during production, please refer to comment 4. The text has been revised.
341	Jeremy Coller Foundation	Line 556, page 18 - Should this include considerations of employee safety during the production process? E.g. management of risk of transfer of zoonotic disease when culturing cell lines Line 605, page 20 - Particularly those which could be biologically active? Line 640, page 21 - How much detail is required on the manufacturing centres?	Any information relevant to the safety of the product shall be presented. No change to the Guidance is needed. All potential risks, including those that could be biologically active, should be considered. No change to the Guidance is needed.

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			Please refer to the response to comment 325.
347	GAIKER	It would be interesting to draw up a list of EFSA-recognised processes that do not apply under the Novel food regulation. Something like EFSA List of conventionally applied processing methods	The Panel notes that this is a risk management decision, and it is considered outside the scope of this Guidance.
572	Aletheia: il segreto del buon vivere	The requested information on the production process for precision fermentation products is more limited than what is required for food enzymes by the EFSA guidance for the evaluation of food enzymes. In the case of cell-based meat, Section 1.2.1 presents some limits to make an accurate risk assessment. Indeed, nutrient sources and growth factors are required for cell multiplication. In most cases these are either fetal bovine serum (FBS) or a mixture of hormones, vitamins, amino acids and, in some cases, antimicrobial compounds. Regarding these components of the growth substrate, it should be noted that: • in all cases, these compounds should be characterised as ingredients, food additives or processing aids. Thus, compounds/agents not falling into one of these categories are not allowed to be used in food production stages; • FBS is a by-product of cattle slaughtering. For the purpose of food use as an ingredient in cell-based meat, it is necessary to assess whether this growth substrate component is considered an edible part of the animal and whether it maintains hormonal actions in the feed (see next section); • a mix of hormone-acting growth factors can be used instead of FBS. In this specific case two aspects should be considered: ▪ the origin of these growth factors: if from animal, it applies what has highlighted in the case of FBS. Differently, if they are of biotechnological origin, these ingredients fall under Regulation (EC) 1829/2003 and a risk assessment is needed before their use in food. ▪ the potential residues of hormonal activity. In 1981, under Directive 81/602/EEC and the subsequent Directive 2003/74/EC (Directive 2003/74/EC of the European Parliament and of the Council of 22 September 2003 amending Council Directive 96/22/EC concerning the prohibition	It should be noted that general provisions included in sections 2, 2.1, 2.4 as well as Appendix B, and relevant specific considerations included in sections 2.2 and 2.3 apply to the production process of novel foods consisting of, isolated from or produced with microorganisms, including those produced by 'precision fermentation'. Moreover, scientific requirements for the taxonomic and hazard identification of microorganisms used as novel foods (active agents and biomasses) or in the production of novel foods (production strains) are listed in section 1.2 and Appendix A, according to relevant EFSA guidance documents (EFSA FEEDAP Panel, 2018; EFSA, 2021e). The Panel considers that no change to the Guidance is needed. Please refer to the response to comment 98 in relation to scientific requirements for growth factors of microbial origin used in the production of novel foods, in order to establish the safety of the novel food. Please refer to the general provisions included in sections 2, 2.1, 2.4 and Appendix B, and relevant specific

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		on the use in stock farming of certain substances having a hormonal or thyreostatic action and of beta- agonists) the EU banned the use of substances with hormonal action for fostering animal growth livestock, with the aim of avoiding consumer exposure to these compounds. If these substances are banned in animal feed, where only indirect consumer exposure is possible, it is conceivable that their direct use in the production of a food product may not be allowed or should require a specific risk assessment and authorisation; • vitamins and amino acids are frequently produced by GMMs, with the possible consequences outlined previously; • antimicrobial compounds of clinical interest (WHO Medically Important Antimicrobial) frequently used in animal cell production stages, may not be used in food production. As an example, EFSA recently provided a negative opinion on the safety of a food enzyme due to the presence of traces of bacitracin in the food product,8 as the presence of this antibiotic in the food enzyme poses risks for the development of resistance in bacteria.	considerations included in sections 2.2 and 2.3 in relation to the production process of the novel food. It should be highlighted that information on substances used in the manufacturing process (e.g., reagents, additives), residues remaining in the final product, potential by-products, impurities, or contaminants should be provided. Formation of processing contaminants should be also considered based on the processes applied and a description of the parameters that may lead to the formation of a given processing contaminant should be included. This includes also the presence/absence of antimicrobial substances of clinical relevance in the novel food.
579	AseBio - Spanish Bioindustry Association,	Line: 533 - 534 533 - 534 'The process(es) employed to produce the novel food (e.g., chemical synthesis, enzyme catalysis, fermentation, or isolation from a natural source) should be thoroughly and completely described.' This is disproportionate and can lead to onerous reporting requirements. Proposal to replace by: ' […] should be described at a sufficient level of detail to allow identification of all potential safety risks.' Line: 533 - 536 533 – 536 The content in this section may be covered by confidentiality as per the Practical Arrangements of the Transparency Regulation. This was also recognised in the webinar organised on 21 March 2024, where EFSA experts noted that evaluation of impact requires all details in the production process, and that content in this section is covered by confidentiality.	Please refer to the response to comments 64 and 141.
689	FoodDrinkEurope	1. [Line 540] Annex B is referring to COA while the text is referring to specification of all raw materials inputs used in the	It has been clarified that the information will be obtained through

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		manufacturing process Suggestion is made to add specification as text rather than COA in the annex B 2. [Lines 541 - 543] Materials in contact with food shall always be compliant with the applicable food contact material framework and regulations. These requirements are applicable for all food business operators and fall under the control of local authorities in the EU member states. Therefore, we suggest deleting the reference in this text to share declaration of compliances (or other relevant legal documents) for all food contact materials. This is an additional administrative burden for the applicant with no additional value to the novel food dossier and overlapping with the official controls by local authorities. 3. [Line 551] ' The applicant has to inform whether a production process is novel, i.e., not used for food production within the EU before 15 May 1997, and characterize the novel aspects of the process. ' In practice, this is rare that the production process has never been used in food production before 1997. In general, this is the combination a food production process (used before 1997) applied to a new food that makes the novelty. We would welcome an example of EFSA of past novel food assessment for novel production process 4. [Lines 554-559] The needs for providing detail on HACCP system and quality systems is not clear. These requirements are already put in place for food companies in compliance with the EU General Food Law and the Hygiene regulation; and mandatory for food business operators. These requirements are controlled by the local authorities in the EU member states. Our suggestion is to rewrite this paragraph so that not all those details have to be provided to EFSA. There is no added value for the dossier and there is overlap with the official control by local authorities.	the Specification documentation and/or Certificates of Analysis (CoAs). Additionally, the footnote 'Quality of the input material can be proven for commercial products by the certificates of analysis of the purchased products or by specifications for non-commercial products and certificates of analysis that prove the product complies with specification' should be considered. The text has been revised to provide further clarity. Please note that novel foods must comply with the applicable EU regulatory requirements before entering the EU market. Proof of such compliance can reduce the need for additional testing during the risk assessment, for example, for substances that may migrate into the novel food from contact materials used during production, such as tanks, pipes, hoses, or components like heat exchangers, extractors, or filter cages. Regarding conformity declarations, it is important to note that EU Regulations are the primary standard, and other relevant legal documents, such as conformity declarations with non-EU regulations, might also be considered as additional evidence. The text has been revised to provide further clarity. It should be noted that there are certain production process aspects

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			that can be indeed novel for food production. The requirement refers solely to such cases. The Panel considers that no change to the Guidance is needed. The details requested regarding production control and quality and safety assurance are reviewed to identify potential hazards linked to the production process. Understanding how the food business operator applies mitigation measures may, in certain cases, reduce the need for generating new analytical data on the novel food for specific aspects. This approach ensures that safety is maintained while potentially minimising the need for additional data generation. Therefore, the Panel considers that no change to the Guidance is needed.

Table 17: 2.1 General provisions

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4	Analyze & Realize GmbH	line 542-544 is 'other relevant legal document' limited to EU Regulations, or would a conformity declaration with, e.g., US or Chinese Regulations be accepted? What about production equipment like tanks, pipes, hoses, or components like heat exchangers, extractors or filter cages? Which kind of conformity declaration is accepted?	Please note that novel foods must comply with the applicable EU regulatory requirements before entering the EU market. Proof of such compliance can reduce the need for additional testing during the risk assessment, for example, for substances that may migrate into the novel food from contact materials

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			used during production, such as tanks, pipes, hoses, or components like heat exchangers, extractors, or filter cages. Regarding conformity declarations, it is important to note that EU Regulations are the primary standard, and other relevant legal documents, such as conformity declarations with non-EU regulations, might also be considered as additional evidence. The text has been revised to provide further clarity.
18	Undisclosed (Personal Capacity)	Line 557 (Annex B) 'Additionally, information on the specification…' Annex B says COA not specification. Annex B needs to be amended to replace COA with 'Specification'. See also comment for Annex B below. Lines 551-552 'The applicant has to inform whether a production process is novel, i.e., not used for food production within the EU before 15 May 1997, and characterise the novel aspects of the process.' This is ambiguous because most individual steps in the process of novel foods are already used in the food industry. It is their combination that is novel. Suggest deletion of this sentence.	1. Please refer to the response to comment 689. 2. Please refer to the response to comment 689.
51	Specialised Nutrition Europe (SNE)	Page 18 Line 541-543 Materials in contact with food shall always be compliant with the applicable food contact material regulations. These requirements are applicable for all food companies and fall under the control of local authorities in the EU member states. Therefore, we suggest deleting the reference in this text to share declaration of compliances (or other relevant legal documents) for all food contact materials. This is an additional administrative burden for the applicant with no additional value to the novel food dossier and overlapping with the control by local authorities. Page 18 Line 554-559 More detailed information is requested in this paragraph about the HACCP system, prerequisite programs, etc. These requirements fall under EU regulations,	1. Please refer to the response to comment 4. 2. Please refer to the response to comment 689.

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		like General Food Law, Hygiene regulation and other general regulations in place for food companies. These requirements are under the control of local authorities in the EU member states. Our suggestion is to rewrite this paragraph so that not all those details have to be provided to EFSA. There is no added value for the dossier and there is overlap with the control by local authorities	
97	Undisclosed (Personal Capacity)	Production Process and Hygiene (Lines 556, page 18) Comment: Updates to the regulation on the hygiene of foodstuffs should be clearly reflected in the guidance, with annotations regarding any amendments, such as EC 2021/382 amending EC 852/2004.	Please kindly note that amendments to Regulation (EC) No 852/2004 on the hygiene of foodstuffs are directly included in its consolidated version. The Panel considers that no change to the Guidance is needed.
122	Medfiles Ltd	Comment: P18 L538: We would suggest to add the information that only authorised food additives under Regulation (EC) No 1333/2008 and extraction solvents comply with Directive 2009/32/EC can be used in novel foods. Information on those should be provided. - Any unauthorised food additive use will lead to the rejection of the novel food until the food additive is authorised. The same applies to extraction solvents. Only the extraction solvents that. If any other extraction solvent is used, the authorisation is needed also for that before the novel food may be authorised. P18 L541-544: Medfiles acknowledges that FCM Regulations have to be adhered to. However, to reduce Applicant's burden to provide DoCs or other legal documents, as this can be a substantial number of documents, could EFSA agree that the titles of these documents together with the links to the FCM-suppliers websites (to prove that an existing company has provided the documents) is listed to one document instead to provide the actual legal docs. Furthermore, quite often the FCM-companies have DoCs on their website to which a link could be provided by the Applicant. In addition, in view that the EC has plans to develop an electronic tool for DoCs, Medfiles would appreciate if an easier approach than providing the actual documents would be taken by EFSA NDA Panel.	With regard to the use of food additives in the production of a novel food, please note that such additives must be authorised and listed with conditions of use in the EU's positive list based on Regulation (EC) No 1333/2008. Any unauthorised additives cannot be used. Regarding the use of solvents, please consider Directive 2009/32/EC on extraction solvents used in the production of foodstuffs and food ingredients. The text in section 2.2 and section 2.3 has been revised. Please refer to the response to comment 689.

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155	Synpa, French association of specialty food ingredients manufacturers and distributors	1. What is considered 'changes' in production process that need to be notified? - Are minor changes that do not impact the composition of the NF need to be notified? 2. Lines 544-546 'Considering all steps during the production process, the production yield, i.e., the resulting amount of a novel food from its raw materials, should be calculated, providing also the 'processing factors', when applicable.' This comes pretty close to disclosing production costs which should be a no-go. We assume this 'requirement' comes from the discussions that also the environmental impact should be a point of attention. However, the Commission and EFSA should come up with a concrete, meaningful proposal on this, rather than this pretty generic statement that would not be in our interest … Therefore, suggestions to delete, emphasising that EFSA should continue to focus on safety. 3. Lines 551-559 As raw material suppliers may change over time, the source of raw materials may also change. However, specifications generally remain the same or vary slightly in ways that do not affect safety or function. The guidance should indicate that examples of raw material sources and specifications be provided when submitting the novel foods dossier. As safety is the main goal, providing the impurities, potential by-products and contaminants (Line 546-550) should be sufficient. The potential safety concerns of these materials can be addressed in the exposure assessment and toxicology review. Otherwise, this large dataset could provide confidential information (e.g., production costs and materials) and require large amounts of time and capital while not advancing consumer safety. It is important that production process information be confidential to a great extent. Additionally, local authorities in the EU member states control compliance to General Food Law, Hygiene Regulation and others. Where there is overlap (e.g., providing HACCP, prerequisite programs, etc.) the guidance should be written to clarify these materials do not need to be provided to EFSA in the dossier. '	1. The Panel wishes to highlight that what constitutes 'changes' can vary depending on the specific circumstances of each case. Notification of all changes during the risk assessment ensures that the Panel can assess the representativeness of the compositional data provided during the evaluation process. It is essential to understand that notifying a change does not necessarily imply any additional requirements but rather facilitates transparency and thorough evaluation. Moreover, as stipulated in Article 25 (a) of Regulation (EU) 2015/2283, changes occurring after the risk assessment or the eventual authorisation of the novel food 'which might influence the evaluation of the safety of the novel food 'must be immediately notified to the EC. The text has been revised to provide further clarity. 2. The requirement to calculate production yield and provide processing factors serves to assess potential hazards posed by the raw material in the final novel food. Regarding confidentiality aspects, Please refer to the response to comment 141 (part 1). Providing such information may, in certain cases, reduce the need for generating new analytical data on the novel food. The Panel considers that no change to the Guidance is needed.

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			3. Providing information on raw material sources and their specifications at the time of submission is crucial to the safety assessment process. The Panel acknowledges that changes to the production process, including those related to raw materials, may occur both during the risk assessment and after authorisation. This is why the guidance has included provisions for handling such changes. Specifications on raw materials are essential for identifying impurities, contaminants, and other substances of potential concern, ensuring the safety of the novel food. Detailed information on the composition and production process can indeed play a critical role in the safety evaluation. In some cases, this information may even reduce or waive the need for conducting toxicological studies, as it provides a robust understanding of the potential risks associated with the novel food. The Guidance aims to balance the need for transparency and safety while protecting proprietary information to the extent possible. Regarding the HACCP considerations, please refer to the response to comment 689. The Panel considers that no change to the Guidance is needed.

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203	EU Specialty Food Ingredients	1. Lines 540-541: We would like to point out that suppliers for the input/raw materials and fermentation aids oftentimes change over time. This means that the source of the raw material might change, although the specifications remain the same or change only in some (non-safety-relevant) parameters. Therefore, it would only be possible to give examples for the raw material sources and respective specifications at the time of submitting the application. This should be stated in the guidance, accordingly. 2. Lines 541-544: 1. We would like to stress that materials in contact with food shall always be compliant with the applicable food contact material regulations. These requirements are applicable for all food companies and fall under the control of local authorities in the EU member states. Therefore, we suggest deleting the reference in this text to share declaration of compliances (or other relevant legal documents) for all food contact materials. This is an additional administrative burden for the applicant with no additional value to the novel food dossier and overlapping with the control by local authorities. 3. 2. Should EFSA insist on keeping this reference, we would like to ask for clarification on the exact way how this proof should be provided. As there can be a considerable number of materials involved in the production of a Novel Food, we propose that a statement by the applicant, confirming that all materials in contact with the Novel Food are compliant with Regulation (EC) No 1935/2004 should be sufficient to fulfil this request. This should be stated in the guidance, accordingly. 4. Lines 544-546: We are concerned that a huge set of data would be needed to calculate and show the production yield (e.g. for fermentation-derived Novel Foods), leading to a lot of additional work for the applicant and EFSA, while not contributing to the assessment of the safety of the novel food. Moreover, this comes pretty close to disclosing production costs, which is not acceptable. We propose that providing information on potential by-products, impurities, or contaminants and on the formation of processing contaminants	1. Please refer to the response to comments 4, 52 and 155. 2. Please refer to the response to comment 689. 3. Please refer to the response to comment 689. 4. Please refer to the response to comment 155. 5. Please refer to the response to comment 141. 6. Please refer to the response to comment 689. 7. Please refer to the response to comments 4 and 689.

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		(as written in lines 546-550) would be more relevant for the safety assessment and that providing these data makes the calculation of the production yield and the provision of processing factors unnecessary. The potential safety concerns of these materials can be addressed in the exposure assessment and toxicology review. 5. Lines 551-559: 1. While we do appreciate the effort to clarify the requirements needed for the safety assessment of novel foods, we also are concerned about the confidentiality of the data submitted. In this draft version of the guidance more details are requested (not only in this chapter) and we are concerned that some of these details might not be considered confidential according to Regulation (EC) No 178/2002, Article 39, leading to more information on e.g., the production process becoming public. Therefore, we suggest to clarify that all information provided for the production process (and especially detailed information on process parameters and similar data) can be kept confidential, as it is very sensitive information. 6. 2. Instruction states that HACCP, GMP or ISO should already be implemented and describing all steps and details of HACCP plus all possible producers, which would basically block every development batch and requires a full production set-up before the novel food dossier can be filed. 7. 3. In addition, more detailed information is requested in this paragraph about the HACCP system, prerequisite programs, etc. These requirements fall under EU regulations, like General Food Law, Hygiene regulation and other general regulations in place for food companies. These requirements are under the control of local authorities in the EU member states. Our suggestion is to rewrite this paragraph so that not all those details have to be provided to EFSA. There is no added value for the dossier and there is overlap with the control by local authorities.	
227	Planet A Foods GmbH	ll. 538 ff.: Input materials do not need to be food grade? Some input materials in fermentations of microorganisms may even be toxic, but are required in the fermentation as trace elements. Can these - including suggested measures - please	In the EU food regulatory framework, the term 'food grade' does not appear explicitly. All input materials used in food production must be reported.

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		be addressed as well? Or is this included in section 3.3. Under Ll. 774 ff.? If so, please specify 'fermentation media components' in the example list as well ll- 560/561: 'Standardisation criteria (e.g., chemical markers for the novel food)'. If the novel food has the same chemical composition as a known foodstuff, but is isolated from another source, then no chemical marker can be provided. Would this be a problem?	When reporting components used in e.g., fermentation media, it is essential to include both the initial concentration of these inputs and their final concentration in the novel food. For specific components that may be considered hazardous, hazard characterisation may be required. The text has been revised to provide further clarity.
249	The Good Food Institute Europe	Line 541-544 Moreover, every material in contact with food during the production process (e.g., plastic containers) should comply with Regulation (EC) No 1935/2004… Comment: EFSA should clarify whether 'every material' in this section refers to packaging materials, or has a broader scope to include materials used during production processes. Line 551-552 The applicant has to inform whether a production process is novel, i.e., not used for food production within the EU before 15 May 1997, and characterise the novel aspects of the process. Comment: EFSA should clarify the definition of 'novel aspects of the process.' Many of the steps involved in the production of novel foods are already found in other food industry settings - it is the combination of these steps into one process that defines them as 'novel'. EFSA should provide greater clarification on the specific aspects of processes that are necessary to characterise, or consider deleting this sentence.	Please refer to the response to comment 689. Please refer to the response to comment 689.
267	Dwayne Holmes (Personal Capacity)	Page 18, Line 556 – The most updated regulation on hygiene of foodstuffs is EC 2021/382 which amended the EC 852/2004. If the reference in this section is to language from the original document, it may still be useful to add a notation 'as amended by EC 2021/382.'	Please refer to the response to comment 97, in relation to Regulation (EC) No 852/2004 on the hygiene of foodstuffs.
322	EuropaBio	533 - 534: 'The process(es) employed to produce the novel food (e.g., chemical synthesis, enzyme catalysis, fermentation, or isolation from a natural source) should be thoroughly and completely described.' This is disproportionate and can lead to onerous reporting requirements. Proposal to replace by: ' […]	Please refer to the response to comment 141. Please refer to the response to comment 64.

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		should be described at a sufficient level of detail to allow identification of all potential safety risks.‘ 533 – 536: The content in this section may be covered by confidentiality as per the Practical Arrangements of the Transparency Regulation. This was also recognised in the webinar organised on 21 March 2024, where EFSA experts noted that evaluation of impact requires all details in the production process, and that content in this section is covered by confidentiality. 540-541: ‘Additionally, information on the specification and quality of the input/raw materials and fermentation aids has to be provided.‘ While the specifications for input/raw materials and/or fermentation aids remain the same (or change only in some non-safety relevant parameters), it is likely that the source or suppliers of input/raw materials may change over time. Therefore, it would only be possible to give examples for raw material sources and respective specifications at the time of submitting the application. This should be stated in the guidance accordingly. 541 – 544: Please provide clarification on the way for applicants to provide proof of compliance. As there can be a considerable number of materials involved in the production of a Novel Food, our proposal is that a statement by the applicant, confirming that all materials in contact with the Novel Food are compliant with Regulation (EC) No 1935/2004, should be sufficient to fulfil this requirement. 544 – 546: Please note that calculation of production yield is confidential information. This requirement is not safety related. A concrete proposal for calculating production yield is needed.	Please refer to the response to comment 203. Please refer to the response to comment 689. Please refer to the response to comment 155 and comment 141.
437	Food Supplements Europe	Lines 541-544 Compliance with applicable legislation is a condition that must be met in all cases. It is therefore not of particular relevance for the safety assessment. Can the guidance explain why a declaration of compliance with this regulation or any other relevant legal document with regards to food contact material is required and specify under what form this need to be provided. i.e. what is meant by ‘legal document’? Line 558-559 Surely the purpose and risk	1. Please refer to the response to comment 4. 2. A statement would not be sufficient, please refer to the response to comment 689.

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		assessment of a novel food should not equate a control of compliance with the provisions of Regulation (EC) 852/2004. It is a legal requirement to have such procedures in place. The requirement of information on the quality assurance system should be restricted to those parameters that are essential for risk assessment. It should be kept in mind that all information provided could end up in the public domain if the request for confidentiality would not be accepted. Elements that are not essential should not systematically be requested. In this case, a statement confirming conformity with legislation should suffice (e.g. HACCP).	
530	FoodchainID	Is it acceptable if the novel food is produced in a non-certified facility where food safety management systems based on HACCP principles are in place (i.e all procedure and documentation can be provided but no HACCP certification)	Food production must comply with EU food law, which requires that food safety management systems be in place and follow HACCP principles. For non-EU facilities, certification is not obligatory, but there must be a comparable system in place. The Guidance does not require certification; however, the applicant must submit the HACCP plan itself, not the certification.
551	Novonesis (merger of former Novozymes and Chr. Hansen)	1. page 18, lines 540-541: We would like to point out that suppliers for the input/raw materials and fermentation aids oftentimes change over time. This means that the source of the raw material might change, although the specifications remain the same or change only in some (non-safety-relevant) parameters. Therefore, it would only be possible to give examples for the raw material sources and respective specifications at the time of submitting the application. This should be stated in the guidance, accordingly. 2. page 18, lines 541-544: We would like to ask for clarification on the exact way how this proof should be provided. As there can be a considerable number of materials involved in the production of a Novel Food, we propose that a statement by the applicant, confirming that all materials in contact with the Novel Food are compliant with Regulation (EC) No 1935/2004 should	1. Please refer to the response to comments 155 and 689. 2. Please refer to the response to comments 437 and 689. 3. Please refer to the response to comment 155. 4. Please refer to the response to comment 141.

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		be sufficient to fulfil this request. This should be stated in the guidance, accordingly. 3. page 18, lines 544-546: We are concerned that a huge set of data would be needed to calculate and show the production yield (e.g. for fermentation-derived Novel Foods), leading to a lot of additional work for the applicant and EFSA, while not contributing to the assessment of the safety of the novel food. Furthermore, we consider information on the yield intellectual property for which we see no need to disclose. We understand that EFSA is concerned about the accumulation of contaminants, depending on the yield, but we would like to highlight, that the levels of contaminants or by-products etc. are already managed by the specifications of the novel food, as well as the regulation on contaminants (EU) 2023/915. We propose that providing information on potential by-products, impurities, or contaminants and on the formation of processing contaminants (as written in lines 546-550) would be more relevant for the safety assessment and that providing these data makes the calculation of the production yield and the provision of processing factors obsolete. 4. page 18, lines 551-559: While we do appreciate the effort to clarify the requirements needed for the safety assessment of novel foods, we also are concerned about the confidentiality of the data submitted. In this draft version of the guidance more details are requested (not only in this chapter) and we are concerned that some of these details might not be considered confidential after Regulation (EC) No 178/2002, Article 39, leading to more information on e.g., the production process becoming public. Therefore, we suggest to clarify that all information provided for the production process (and especially detailed information on process parameters and similar data) can be kept confidential, as it is very sensitive information.	
585	AseBio - Spanish Bioindustry Association,	1. Line: 540-541 'Additionally, information on the specification and quality of the input/raw materials and fermentation aids has to be provided.' While the specifications for input/raw materials and/or fermentation aids remain the same (or change only in some non-safety relevant parameters), it is likely that	1. Please refer to the response to comments 155 and 689. 2. Please refer to the response to comments 437 and 689.

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		the source or suppliers of input/raw materials may change over time. Therefore, it would only be possible to give examples for raw material sources and respective specifications at the time of submitting the application. This should be stated in the guidance accordingly. 2. Line: 541 – 544 Please provide clarification on the way for applicants to provide proof of compliance. As there can be a considerable number of materials involved in the production of a Novel Food, our proposal is that a statement by the applicant, confirming that all materials in contact with the Novel Food are compliant with Regulation (EC) No 1935/2004, should be sufficient to fulfil this requirement. 3. Line: 544 – 546 Please note that calculation of production yield is confidential information. This requirement is not safety related. A concrete proposal for calculating production yield is needed.	3. Please refer to the response to comment 155.
607	Cellular Agriculture Europe	Lines 537-540: 'Additionally, information on the specification…' Annex B says certificate of analysis (CoA), and not specification. We propose that Annex B is amended to replace CoA with 'Specification'. 2. Lines 541-544: Footnote 25 also refers to: CoAs for commercially available products, specifications and CoAs for non-commercial products, so it would need to be modified too. 'every material in contact with food during the production process' does EFSA refer to packaging material only (like it used to be in the past) or every piece of equipment that gets in contact with the cells throughout the entire production process, from cell banking to harvesting? In addition, can EFSA provide a definition for 'production process'? 3. Lines 551 - 552: 'The applicant has to inform whether a production process is novel, i.e., not used for food production within the EU before 15 May 1997, and characterise the novel aspects of the process.' This is ambiguous because most individual steps in the process of novel foods are already used in the food industry. It is their combination that is novel. We therefore suggest deleting this sentence.	1. Please refer to the response to comment 689. 2. Please refer to the response to comment 689. 3. Please refer to the response to comment 689.

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646	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 568. 'Description of feed': Please clarify what information is required here, e.g. is it the nutritional profile or composition, or something else.	Please refer to the response to comment 5.

Table 18: 2.2 Considerations for specific production process steps

Comment number	Commentor	Comments	EFSA NDA Panel responses
5	Analyze & Realize GmbH	line 568-571 What type of documentation has to be provided? In which level of detail?	The description should be as detailed as possible. Any available certificates (e.g., from feed producers) should contain comprehensive information on the compositional characteristics (e.g., nutrient profile, contaminant levels). The level of detail should be sufficient to ensure assessment of the compliance with relevant EU safety standards. The Panel considers that no change to the Guidance is needed.
86	BaseClear	Line 572-578: Clarify the requirements for describing cultivation, breeding, rearing, and farming practices, including the use of pesticides, hormones, veterinary drugs, antimicrobials, and feed additives. Offer examples or case studies to illustrate how to effectively document these practices and their potential impact on the safety of the novel food.	The Panel acknowledges the comment. The primary objective of the Guidance is to establish overarching principles and key considerations rather than prescribing specific methodologies or case studies. This approach is intended to provide flexibility and adaptability, accommodating the diverse range of novel food applications and production processes. Applicants are strongly encouraged to thoroughly document their practices, including any changes to raw material sources, production

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			processes, and the potential impact on the safety of the novel food. This documentation should be comprehensive, specific, and tailored to the unique characteristics of each novel food and its production process. The Panel considers that no change to the Guidance is needed.
98	Undisclosed (Personal Capacity)	1. Recombinant Technologies and Safety (Lines 593ff, p.19) Comment: The guidance should consider the use of recombinant proteins as processing aids in cultured meat production. 2. Additionally, the establishment of a Qualified Presumption of Safety (QPS) list, similar to that used for microorganisms, could be suggested to streamline the safety documentation process.	1. Please kindly note that currently there is not a regulatory framework in the EU for growth factors (e.g., recombinant proteins, vitamins, amino acids, etc.) used in the production of, e.g., novel foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, microorganisms, fungi or algae. Therefore, in order to establish the safety of the novel food, growth factors of microbial origin will be assessed taking into consideration the scientific requirements for the taxonomic and hazard identification of microorganisms intentionally used in the food chain as listed in section 1.2 and Appendix A according to relevant EFSA guidance documents (EFSA FEEDAP Panel, 2018; EFSA, 2021e). The text in section 2.3 has been revised for clarity. 2. It should be noted that that EFSA's QPS approach for safety assessment is intended for microbial taxonomic units. The Panel notes the recommendation on the QPS list for culture components but considers that

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			it goes beyond the scope of this Guidance.
156	Synpa, French association of specialty food ingredients manufacturers and distributors	1. 583-586 'In cases when food enzymes of microbial origin are used as processing aids for the production of a novel food, the processes and operational conditions in place for the inactivation/removal of these enzymes are to be provided and the presence or absence of these enzymes in the novel food has to be demonstrated experimentally along with their enzymatic activity, if present (EFSA CEP Panel, 2021).' Proposal to emphasise that inactivation should not be a must. Instead, the applicant should demonstrate that the enzyme is inactivated or has no technological function in the final food. 2. 591-593 It appears that two regulatory approvals are needed when a novel food is produced biocatalytically. This seems conflicting when only one approval would be needed for a novel food produced by a micro-organism. Only one approval should be needed for both cases. 3. 591-593 : 'Food enzymes used in the production of novel food should preferably have been already assessed with a positive outcome by the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (EFSA CEP Panel).' I feel it is largely overdone to request that for a novel food produced biocatalytically, you need two approvals, but for a novel food produced by a microorganism (i.e. whole-cell biocatalysis), you only need one. At the very least, both options should be allowed, without any preference. So, if an applicant describes the enzyme as part of the production process, this should be sufficient. 4. 593-596 the producer of the novel food will not have access to detailed and confidential information about the enzyme production. Authorised food enzymes should continue to be assumed to be safe for their intended use until they are re-evaluated.	Please refer to the response to comments 49 and 259 in relation to scientific requirements for food enzymes used in the production of novel foods, in order to establish the safety of the novel food. Please kindly note that the safety of food enzymes in foods, including such enzymes used as processing aids, is subject to the provisions of Regulation (EC) No 1332/2008. Therefore, the Panel notes the comment but considers that it goes beyond the scope of this Guidance. Please kindly note that, when necessary, additional data on the food enzyme(s) to establish the safety of the novel food will be requested to the novel food business operator and it is their responsibility to contact the food enzyme producer in order (a) to grant EFSA's Working Group on Novel Foods (WG NF) access to the food enzyme dossier under evaluation by EFSA's WG on Enzymes or (b) to provide to EFSA's WG NF the additional data needed to establish the safety of the novel food, in case the food enzyme is not under assessment by EFSA's WG on Enzymes yet. Please kindly note that only enzymes that have been evaluated by EFSA with a positive outcome and subsequently listed in the Union list of food enzymes will be authorised to be used in the

Comment number	Commentor	Comments	EFSA NDA Panel responses
			production of the novel food. The Panel considers that no change to the Guidance is needed.
204	EU Specialty Food Ingredients	It appears that two regulatory approvals are needed when a novel food is produced bio-catalytically. This seems conflicting when only one approval would be needed for a novel food produced by a microorganism. Only one approval should be needed for both cases. Lines 583-586: If enzymes are used, does this text intend to say that these enzymes need to be removed/inactivated? If the enzymes are approved, do they need to be removed or inactivated? Is this different from enzymes used in traditional foods? We propose to emphasise that inactivation should not be a must. Instead, the applicant should demonstrate that the enzyme is inactivated or has no technological function in the final food. Lines 591-593: We feel it is largely overdone to request that for a novel food produced bio-catalytically, you need two approvals, but for a novel food produced by a microorganism (i.e. whole-cell biocatalysis), you only need one. At the very least, both options should be allowed, without any preference. So, if an applicant describes the enzyme as part of the production process, this should be sufficient. Lines 593-596: The producer of the novel food will not have access to detailed and confidential information about the enzyme production. Authorised food enzymes should continue to be assumed to be safe for their intended use until they are re-evaluated.	Please refer to the response to comments 49, 156, and 259.
228	Planet A Foods GmbH	ll. 580-582: Can the process description also include an optional step (such as freeze-drying for storage/transport in the first few years of production (e.g. because the microorganisms (as raw material) has to be transported from the fermentation/propagation site to another location for extraction of the final product?)	The production process should be accurately described as it stands during the submission. Any modifications during the risk assessment process or post approval must be promptly reported, as specified in the response to comment 155. Regarding the addition of an optional step, the applicant must carefully assess its potential impact on the identity of the novel food and

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			identify any additional hazard posing safety concerns. Depending on the circumstances, providing analytical data may be necessary to substantiate the safety and identity of the novel food after undergoing this optional step.
259	VTT, Technical Research Centre of Finland	Page 19, Lines 593-595: 'In case the food enzymes have not been assessed or the risk assessment is still in progress, additional data on the microorganisms used to produce the food enzymes could be requested to establish the safety of the novel food, in line with the scientific criteria outlined in relevant EFSA guidance documents' Comment: We consider it challenging to request an applicant to provide safety data on food enzymes which are in the prolonged risk assessment process in the EU. These food enzymes are available for food grade use as processing aids for traditional food ingredients. Moreover, the applicant of novel food is demanding to response on safety on behalf of another party i.e. enzyme manufacturer.	It should be noted that, in case the food enzymes have not been assessed by EFSA yet or the risk assessment is still in progress, the additional data on the microorganisms used to produce the food enzymes that could be requested during the risk assessment of the novel food are limited to those necessary to establish the safety of the novel food, as listed in section 1.2 and Annex A according to relevant EFSA guidance documents (EFSA FEEDAP Panel, 2018; EFSA, 2021e). Please refer to the response to comments 49 and 156 for additional information.
268	Dwayne Holmes (Personal Capacity)	Page 19, Line 593-596 – What about recombinant proteins used as processing aids that are not enzymes (e.g. recombinant growth factors for use in cultured meat and seafood production). Should applicants follow the same approach outlined for enzymes? Further, as such culture components are identified and safety documented, it could be useful to produce and maintain a qualified presumption of safety (QPS) list similar to that used for microorganisms.	Please refer to the response to comment 98.
291	Katharina Julia Brenner (Personal Capacity)	Detailing Operational Limits and Key Parameters (Page 20, Lines 553-555): Comment: The document should provide clear guidance on defining and monitoring critical operational parameters such as temperature, pH, pressure, and reaction times. It should include specific acceptable ranges and the impact of deviations on product safety and quality. This will	This responsibility lies with the Food Business Operator to determine and monitor critical operational parameters for their product's production. The Panel notes the recommendations but considers that a

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		ensure that the production process is controlled effectively, maintaining the consistency and safety of the novel food.	detailed expansion of the section referred to goes beyond the scope of this Guidance.
323	EuropaBio	583 – 586: 'In cases when food enzymes of microbial origin are used as processing aids for the production of a novel food, the processes and operational conditions in place for the inactivation/removal of these enzymes are to be provided and the presence or absence of these enzymes in the novel food has to be demonstrated experimentally along with their enzymatic activity, if present (EFSA CEP Panel, 2021).' Rather than emphasising the requirement for inactivation, the applicant should demonstrate that the enzyme is inactivated or has no technological function in the final food. 591 - 593: 'Food enzymes used in the production of novel food should preferably have been already assessed with a positive outcome by the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (EFSA CEP Panel).' It is disproportionate to require that for a novel food produced biocatalytically, two approvals are needed, while for a novel food produced by a microorganism (i.e. whole-cell biocatalysis), only one is needed. We suggest that both options be equally permitted. It should be sufficient for an applicant to describe the enzyme as part of the production process, this should be sufficient. Food enzymes used in Novel Foods may have already been assessed, and if not, should be assessed, according to relevant Food Enzymes guidance.	Please refer to the response to comments 49, 156, and 259 in relation to scientific requirements for food enzymes used in the production of novel foods, in order to establish the safety of the novel food.
531	FoodchainID	Section 2.2 and 2.3 are unclear. It would be clearer if section 2.2 and 2.3 are merged, and requirements for each NF categories listed separately, such as made for the identity section.	Section 2.2 contains considerations for specific production process steps, whereas section 2.3 contains considerations applied to specific food categories. Please refer to the response to comment 19.
543	Bonumose, Inc.	We recommend that when enzymatic processing aids are used, demonstration of enzymatic activity in the novel food not be required if it can be demonstrated that the enzyme is not present in the novel food. If there is no enzyme present, there can be no activity and so the testing would be redundant. Moreover, certain enzymatic activity tests require protein to be present in the	Please refer to the response to comment 49.

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		sample. If there is no protein present, the activity cannot be measured.	
552	Novonesis (merger of former Novozymes and Chr. Hansen)	page 19-20, lines 593-597: Section 2.2., lines 583-597, describe the 'cases where food enzymes of microbial origin are used as processing aids for the production of a novel food'. Lines 593-597 describes that 'In case the food enzymes have not been assessed or the risk assessment is still in progress, additional data on the microorganisms used to produce the food enzymes could be requested to establish the safety of the novel food, in line with the scientific criteria outlined in relevant EFSA guidance documents (EFSA FEEDAP Panel, 2018; EFSA, 2021e,)'. The scientific criteria for safety assessment of food enzymes, incl. the microorganisms used to produce them, are outlined in the guidance document, 'Scientific Guidance for the submission of dossiers on Food Enzymes', EFSA CEP Panel (2021), available online at https://doi.org/10.2903/j.efsa.2021.6851. This guidance document is referenced in the draft NF guidance as 'EFSA CEP Panel (2021)' (see e.g. in line 586). Consequently, being the appropriate and relevant EFSA guidance document, it should be referenced in lines 596-597, instead of current reference: 'EFSA FEEDAP Panel (2018)' (line 596) which is concerning requirements for enzymes used as additives in animal feed, and reference: 'EFSA, 2021e', which is already referenced in the 'EFSA CEP Panel (2021)' and is therefore redundant. In conclusion, we suggest rephrasing current lines 596-597 from: 'the scientific criteria outlined in relevant EFSA guidance documents (EFSA FEEDAP Panel, 2018; EFSA, 2021e,). The assessment of the novel food will be without prejudice to the safety assessment of the' To, suggested new lines 596-597: 'the scientific criteria outlined in relevant EFSA guidance documents (EFSA CEP Panel, 2021). The assessment of the novel food will be without prejudice to the safety assessment of the'	A reference to EFSA CEP Panel (2021) has been included in section 2.2 in relation to scientific requirements for food enzymes used in the production of novel foods, in order to establish the safety of the novel food. The text has been revised to provide further clarity.
586	AseBio - Spanish Bioindustry Association,	1. Line: 583 – 586 'In cases when food enzymes of microbial origin are used as processing aids for the production of a novel food, the processes and operational conditions in place for the inactivation/removal of these enzymes are to be provided and the presence or absence of these enzymes in the novel food has	Please refer to the response to comments 49, 156 and 259 in relation to scientific requirements for food enzymes used in the production of

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		to be demonstrated experimentally along with their enzymatic activity, if present (EFSA CEP Panel, 2021).` Rather than emphasising the requirement for inactivation, the applicant should demonstrate that the enzyme is inactivated or has no technological function in the final food. 2. Line: 591 - 593 `Food enzymes used in the production of novel food should preferably have been already assessed with a positive outcome by the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (EFSA CEP Panel).` It is disproportionate to require that for a novel food produced bio-catalytically, two approvals are needed, while for a novel food produced by a microorganism (i.e. whole-cell biocatalysis), only one is needed. We suggest that both options be equally permitted. It should be sufficient for an applicant to describe the enzyme as part of the production process, this should be sufficient. Food enzymes used in Novel Foods may have already been assessed, and if not, should be assessed, according to relevant Food Enzymes guidance.	novel foods, in order to establish the safety of the novel food.
608	Cellular Agriculture Europe	Lines 583 - 586: We would suggest that 3 batches are required to demonstrate the absence or presence of enzymes, similarly to what is recommended in the Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA, 2018). Lines 593 - 596: We would appreciate it if EFSA could be more specific on the possible required data. In addition, what about data requirements for recombinant proteins used in the production process that are not enzymes (e.g. growth factors)	Please refer to the response to comments 49, 98, 156 and 259 in relation to scientific requirements for food enzymes and growth factors of microbial origin used in the production of novel foods, in order to establish the safety of the novel food.
668	Atova Regulatory Consulting SL	(Line 583-586, page 19) Please can EFSA clarify ow many batches of novel food should be analysed for enzyme activity? We propose three batches. (Line 593-596, page 19) Please can EFSA comment on the use of other recombinant proteins used in the production process that are not enzymes (e.g. recombinant growth factors used in cell-cultured meat/seafood production)? Should applicants perform a complete assessment of those proteins? What guidance should be followed? Will the approach mentioned in this section of the guidance for food enzymes be applicable? (Line 594, page 19) Food enzyme producers may not be willing to disclose their proprietary data on the enzyme	Please refer to the response to comments 49, 98, 156 and 259 in relation to scientific requirements for food enzymes and growth factors of microbial origin used in the production of novel foods, in order to establish the safety of the novel food.

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		production strain. Ultimately it is the responsibility of the FBO to comply with Regulation (EC) No 1332/2008 once the Union list of food enzymes is published. For ongoing food enzyme applications, would a letter form the enzyme applicant confirming their relationship and linking to their application suffice?	
700	FoodDrinkEurope	[Lines 583 - 586] If enzymes are used, potentially to remove DNA, does this text mean to say that these enzymes need to be removed/inactivated? If the enzymes are approved, do they need to be removed or inactivated? Is this different from enzymes used in traditional foods?	Please refer to the response to comment 49.

Table 19: 2.3 Considerations for specific novel food categories

Comment number	Commentor	Comments	EFSA NDA Panel responses
19	Undisclosed (Personal Capacity)	Lines 599-637 This section could have sub-headings for the different types of novel foods or a summary table might be useful	The Panel does not agree with the proposal.
99	Undisclosed (Personal Capacity)	Sterility and Pathogen Control in Cultured Meat (Lines 622ff, page 20) Comment: Recommendations for sterility should recognise the potential use of co-cultures in cultured meat. The use of the term 'modifications' could be clarified to avoid confusion with genetic modifications, which are not typically involved in cell culture for food products.	The text has been revised to provide further clarity in relation to the scientific requirements for novel foods consisting of, isolated from, or produced from cell cultures or tissue cultures.
157	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 599-637 This section could have sub-headings for the different types of novel foods, or a summary table Lines 612 - 614 - This information should be considered confidential to the production process. Providing a general description of the technique along with demonstration that no microbial cells are present in the novel food should be satisfactory for regulators to assess the safety of the novel food. - Do you expect specific details / controls for techniques to remove / inactivate microbial cells ? What do you mean by downstream process ? Lines 630-632 'The genetic stability of the cells throughout the production (e.g., karyotypes, whole-genome sequencing) is to be	1. Please refer to the response to comment 19. 2. Please kindly note that, for production processes employing microorganisms, the detailed description of the techniques used to remove/inactivate microbial cells during downstream processing (i.e., recovery, purification and concentration steps after fermentation) is a requirement set by

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		demonstrated, by comparison of the starting material and the cells at the end of the production process.` In this sentence, it is stipulated that genetic stability should be assessed by whole-genome sequencing. However, some mutations will happen, and there is currently no guidance what a `sufficient level of genetic stability` would be in terms of WGS data. Therefore, also the requirement for genetic stability should be proportionate to the potential safety risks. Therefore, the suggestion here would be to adapt the sentence: 'The genetic stability of the cells throughout the production (e.g., karyotypes, whole-genome sequencing) is to be demonstrated by comparison of the starting material and the cells at the end of the production process, focussing on the characteristics that are relevant for the safety of the product (e.g. stability/reproducibility of product formation, impact on traits of potential safety concern).`	EFSA FEEDAP Panel (2018). Moreover, as stated in section 2, the processes employed to produce the novel food, including key parameters and operational limits, should be thoroughly and completely described. Regarding confidentiality aspects, please refer to the response to comment 141. The Panel considers that no change to the Guidance is needed. 3. The text has been revised to provide further clarity in relation to scientific requirements (genetic stability of cell lines) for novel foods consisting of, isolated from or produced from cell cultures or tissue cultures.
205	EU Specialty Food Ingredients	Lines 612-614: We do not see the need to describe the techniques used in detail including time, temperature and kinetics. Instead, giving a brief description of the technique (mentioning ranges for important parameters) together with CoAs proving that no microbial cells of the production organisms and other substances of concern (e.g., secondary metabolites) are present in the novel food, should be sufficient to assess the safety of the novel food in this matter. This information should be considered confidential to the production process. Lines 630-632: In this sentence, it is stipulated that genetic stability should be assessed by whole-genome sequencing. However, some mutations will happen, and there is currently no guidance what a 'sufficient level of genetic stability' would be in terms of WGS data. Therefore, also the requirement for genetic stability should be proportionate to the potential safety risks. The sentence should be further edited to remove '(e.g. karyotypes, whole-genome sequencing)' and should be amended accordingly: 'The genetic stability of the cells throughout the production is to be demonstrated by	Please refer to the response to comments 141 and 157.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		comparison of the starting material and the cells at the end of the production process, focussing on the characteristics that are relevant for the safety of the product (e.g. stability/reproducibility of product formation, impact on traits of potential safety concern).`	
251	The Good Food Institute Europe	1. Line 619-620 For foods consisting of, isolated from, or produced from cell culture or tissue culture, information is to be provided on the type of cells used as source (e.g., primary cells or established cell lines). Comment: EFSA should note that the term 'cell culture' or 'tissue culture' has been applied to any plant, animal, fungal, algal, microbe cultivation earlier in this guidance document (e.g. line 252). As such, this section could be perceived as applying to microbial, fungal, and plant cell cultures as well as cells derived from animals. EFSA should consider adding clarifying statements. 2. Line 630-632 The genetic stability of the cells throughout the production (e.g., karyotypes, whole-genome sequencing) is to be demonstrated, by comparison of the starting material and the cells at the end of the production process. Comment: As per above, if EFSA means to include for example microbes under the definition of 'cell culture', this section may be problematic as genetic compositions of microbes could be changed due to random mutations that naturally occur. In this situation EFSA should clarify the extent of genetic change that would represent an issue for risk assessment purposes. 3. Line 632-634: Also changes of the morphology, markers of differentiation and other phenotypic features of the cells at the start and at the end of the production process should be investigated and described. Comment: EFSA should clarify what the acceptable levels of changes to morphology are during cultivation and define what actionable steps are included in the definition of 'investigated'. 4. Line 634-637: Information on the compliance with Good Cell Culture Practices should be provided, as well as on the compliance with applicable relevant standards, such as those outlined in the EMA Guidance document on the derivation and characterisation of cell substrates used for production of biotechnological/biological products. Comment:	1. The information applies to the foods covered under sections 1.2. and 1.5. The text has been revised to provide further clarity. 2. Please refer to the response to comment 157. 3. The Panel acknowledges that the acceptable levels of changes to cell morphology during cultivation can vary on a case-by-case basis. Therefore, it is up to the applicant to determine and demonstrate the requested information. This investigation should be comprehensive and detailed, ensuring that any significant changes are documented and justified in the context of the specific production process. The Panel notes the recommendations but considers that a detailed expansion of the section referred to goes beyond the scope of this Guidance. 4. Please kindly note that it is the responsibility of the applicants to follow 'applicable relevant standards' for good cell practices, such as those issued by EMA or OECD, and document the degree of compliance, in order to establish the safety of the novel food. The Panel considers that

Comment number	Commentor	Comments	EFSA NDA Panel responses
		While references to compliance with Good Cell Culture Practice and EMA guidance documents are welcome cross-references, it is important that EFSA qualifies these by noting that this may not be necessary in all cases. Many of the requirements outlined in the EMA guidance are not applicable to cells used for the production of food, and it is therefore the case that full adherence or compliance with these guidance provisions would neither be possible nor appropriate.	no change to the Guidance is needed.
260	VTT, Technical Research Centre of Finland	2.3 Considerations for specific novel food categories Page 20, Lines 616- 618: 'The applicant should investigate, and report whether the specific production conditions of the novel food (e.g., due to processing aids or component of the media) may trigger the formation of toxic compounds by microorganisms' Content: This sentence is suggested to be more specific on how to investigate the formation of toxic compounds. Should the applicant analyse toxicity of end-product in the range of processing conditions? We suggest that this advising text should be more specific.	This evaluation will be conducted on a case-by-case basis, taking into account the metabolic capacity of the specific microorganism, along with the input materials and the production process used. According to Section 2, the potential formation of processing contaminants should be assessed based on the applied processes, and a description of the parameters that could lead to the formation of specific processing contaminants should be provided. Additionally, for substances produced by microbial fermentation, it is essential to investigate the presence of undesirable metabolites, as outlined in Section 3. The Panel considers that no change to the Guidance is needed.
269	Dwayne Holmes (Personal Capacity)	Page 20, Line 622 – While 'absence of pathogens' would be important to document, 'overall sterility' may not be appropriate for cultured meat and seafood production processes. In addition to the potential for using co-cultures (including beneficial microorganisms), having sterile products may be problematic from a safety standpoint. It is possible that inoculation with benign microorganisms could be part of a production step to introduce competitors to prevent pathogenic microorganisms. Page 20, Line 625 - 626 - Use of the term	Please refer to the response to comment 99 in relation to scientific requirements for novel foods consisting of, isolated from, or produced from cell cultures or tissue cultures. Please kindly note that it is the responsibility of the applicants to follow 'applicable relevant standards' for good cell practices, such as those

Comment number	Commentor	Comments	EFSA NDA Panel responses
		'modifications' in this section may cause confusion as that is usually associated with genetic modification, which is generally not performed/does not happen during cell isolation or differentiation but may occur during immortalisation or reprogramming, however all were mentioned together in the same list. Perhaps it would be better to use phrasing such as 'physical changes to cells (e.g. chemical, genetic, etc.)' or 'alterations' in place of 'changes. Page 21, Line 634 - 637 – Since the book referenced for Good Cell Practices (30) is a non-open access source, it might be useful to indicate other valid guidance (e.g. ISO, etc.). Furthermore, as many of requirements outlined in the EMA guidance are not applicable to cells used to produce food it makes full adherence or compliance inappropriate. Reference to compliance with EMA guidance documents (and similarly Good Cell Practices) should be qualified by a statement saying, 'only where relevant.' Finally, as cell lines and methods of cell culture for food production are identified and best practices emerge, it might be useful to produce and manage a list of approved lines or procedures similar to the qualified presumption of safety (QPS) list used for microorganisms.	issued by EMA or OECD, and document the degree of compliance, in order to establish the safety of the novel food. Please kindly note that EFSA's QPS approach for safety assessment is intended for microbial taxonomic units. The Panel notes the recommendation on the QPS list for cell lines and cell culture methods but considers that it goes beyond the scope of this Guidance.
292	Katharina Julia Brenner (Personal Capacity)	Clarity on 'Significant Degree' (Line 232, page 8) Comment: The phrase 'significant degree' is vague and could be interpreted variably. It would be beneficial to define this term more precisely, possibly with quantifiable criteria or by providing specific examples to guide evaluators and applicants.	This is a risk management decision. Therefore, the Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.
324	EuropaBio	612 - 613: Instead of describing the techniques used in detail, including time, temperature and kinetics, we suggest giving a brief description of the technique mentioning ranges for important parameters. This, together with CoAs proving that no microbial cells of the production organisms and other substances of concern (e.g., secondary metabolites) are present in the novel food, should be sufficient to assess the safety of the novel food in this matter. 630 - 632: The requirement for genetic stability should be proportional to safety risk. The sentence should be further edited to remove '(e.g. karyotypes, whole-genome sequencing)' and should be	Please refer to the response to comments 141 and 157.

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		amended accordingly: 'The genetic stability of the cells throughout the production is to be demonstrated by comparison of the starting material and the cells at the end of the production process, focusing on the characteristics that are relevant for the safety of the product (e.g. stability/reproducibility of product formation, impact on traits of potential safety concern).'	
532	FoodchainID	Section 2.2 and 2.3 are unclear. It would be clearer if section 2.2 and 2.3 are merged, and requirements for each NF categories listed separately, such as made for the identity section.	Please refer to the response to comment 531.
544	Bonumose, Inc.	We request some clarity on how the description of a novel food derived from a processed plant material such as maltodextrin should be identified. Some of the requested information in Section 2.3 does not seem relevant for highly-processed food ingredients that are already widely used in the industry. For example, 'Information on substances used in the manufacturing process, e.g., identity and purity of the extraction solvents, ratio of extraction solvent to the material, reagents, additives, residues remaining in the final product and any special precautions (e.g., protection from light and controlled temperature)' could contain proprietary information for the supplier of the maltodextrin. The safety of the maltodextrin could be evaluated from the SDS and specifications. Given the highly processed nature of this material and its wide prevalence in the food supply, these processing details are unlikely to influence the novel food.	The Panel acknowledges that aspects of production processes can vary on a case-by-case basis. Therefore, it is up to the applicant to determine and demonstrate the requested information. This investigation should be comprehensive and detailed. Additionally, please refer to the response to comment 155 regarding raw materials. The Panel notes the recommendations but considers that a detailed expansion of the section referred to goes beyond the scope of this Guidance.
553	Novonesis (merger of former Novozymes and Chr. Hansen)	page 20, lines 612-614: We do not see the need to describe the techniques used in detail including time, temperature and kinetics. Instead, giving a brief description of the technique mentioning ranges for important parameters, together with CoAs proving that no microbial cells of the production organisms and other substances of concern (e.g., secondary metabolites) are present in the novel food, should be sufficient to assess the safety of the novel food in this matter.	Please refer to the response to comment 141.
562	International Probiotic	Lines 599-637 2.3 Considerations for Specific Novel Food Categories. IPAEU: This section would benefit from improved	Please refer to the response to comment 19.

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	Association - Europe (IPA Europe)	classification, into smaller, more focused subsections, to enhance clarity and readability.	
587	AseBio - Spanish Bioindustry Association,	1. Line: 612 - 613 Instead of describing the techniques used in detail, including time, temperature and kinetics, we suggest giving a brief description of the technique mentioning ranges for important parameters. This, together with CoAs proving that no microbial cells of the production organisms and other substances of concern (e.g., secondary metabolites) are present in the novel food, should be sufficient to assess the safety of the novel food in this matter. 2. Line: 630 - 632 The requirement for genetic stability should be proportional to safety risk. The sentence should be further edited to remove '(e.g. karyotypes, whole-genome sequencing)' and should be amended accordingly: 'The genetic stability of the cells throughout the production is to be demonstrated by comparison of the starting material and the cells at the end of the production process, focusing on the characteristics that are relevant for the safety of the product (e.g. stability/reproducibility of product formation, impact on traits of potential safety concern).'	1. Please refer to the response to comment 157 in relation to the scientific requirements for novel foods consisting of, isolated from, or produced from cell cultures or tissue cultures (genetic stability of cell lines) and for production processes employing microorganisms (techniques used to remove/inactivate microbial cells during downstream processing). 2. While the focus on safety is essential, it is important to note that identity aspects are also relevant to the risk assessment of novel foods. The demonstration of genetic stability not only addresses safety concerns but also helps ensure the consistency and identity of the product throughout the production process. Therefore, the Panel considers that no change to the Guidance is needed.
609	Cellular Agriculture Europe	1. Lines 599 - 637: This section could have subheadings for the different types of novel foods or a summary table might be useful. 2. Lines 634 - 637: We suggest that the reference to compliance with Good Cell Culture Practice and EMA guidance documents is qualified by a statement saying only 'where relevant'. Many of the requirements outlined in the EMA guidance are not applicable to cells used for the production of food and full adherence or compliance is not appropriate.	1. Please refer to the response to comment 19. 2. Please refer to the response to comment 251.
669	Atova Regulatory Consulting SL	(Line 633-637, page 21) We request that the reference to compliance with Good Cell Culture Practice and EMA guidance documents is qualified by a statement saying only where	Please refer to the response to comment 251.

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		relevant. Many of the requirements outlined in the EMA guidance are not applicable to cells used for the production of food and full adherence or compliance is not appropriate.	

Table 20: 2.4 Additional considerations

Comment number	Commentor	Comments	EFSA NDA Panel responses
52	Specialised Nutrition Europe (SNE)	Page 21 Line 642-643: variability of starting materials Companies have agreements with suppliers on specifications of starting materials. Does it mean that the applicant for the novel food needs to provide analytical data of all starting material or only the agreed specification on that starting material? The variability of starting materials is already safeguarded by the agreed specification with the supplier of the raw material. If the raw material falls outside the agreed specification, it will not be used. Therefore we see no need to increase the requirements of the current guidance with regards to this topic.	Please refer to the response to comment 155.
158	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Lines 642-644 Specifications are established between suppliers and purchasers for raw materials. Raw material variability is limited by those specifications as material that is out-of-specification will not be accepted nor used. These increased requirements do not add value to the safety of the novel food. 'Any change' or 'any significant change that may impact safety'? We would prefer the latter. EFSA would most likely prefer the latter as 'any change' would lead to a flood notifications for minor changes. 2. This is similar to Lines 644-647 where 'significant changes' is the term used. ' Lines 644-647 'Moreover, as stipulated in Article 25 (a) of Regulation (EU) 2283/2015, significant changes occurring after the risk assessment and or after the eventual authorisation of the novel food that might impact its safety must be immediately notified to the EC.' The addition of significant is crucial because it would be meaningless and	1. Please refer to the response to comment 155. 2. Please refer to the response to comment 155.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		disproportionate to report any and all changes [and to have a (better) basis for applying the Minor Strain Change policy].	
188	Istituto zooprofilattico sperimentale delle venezie	It is important to clarify if only changes affecting safety should be notified or all changes regarding production process, composition...	Please refer to the response to comment 155.
206	EU Specialty Food Ingredients	Lines 642-643: Companies have agreements with suppliers on specifications of starting materials. Does it mean that the applicant for the novel food needs to provide analytical data of all starting material or only the agreed specification on that starting material? The variability of starting materials is already safeguarded by the agreed specification with the supplier of the raw material. If the raw material falls outside the agreed specification, it will not be used. These increased requirements do not add value to the safety of the novel food. Lines 643-644: 'Any change' or 'any significant change that may impact safety'? We would prefer the latter. EFSA would most likely prefer the latter as 'any change' would lead to a flood notifications for minor changes. This is similar to Lines 644-647 where 'significant changes' is the term used. Lines 644-647: The addition of significant is crucial because it would be meaningless and disproportionate to report any and all changes.	Please refer to the response to comments 52 and 155.
325	EuropaBio	1. 639 - 642: Further clarification is needed as to what exactly is covered in this section. 644 – 647: It would be disproportionate to require disclosure of any and all changes. 2. Accordingly, the sentence should be revised to include significant before changes: 'Moreover, as stipulated in Article 25 (a) of Regulation (EU) 2283/2015, significant changes occurring after the risk assessment and or after the eventual authorisation of the novel food that might impact its safety must be immediately notified to the EC.'	1. The text has been revised to provide further clarity. 2. Please refer to the response to comment 185.
545	Bonumose, Inc.	We request reconsideration of the requirement that 'Any changes to the production process that might occur during the risk assessment must be duly notified to EFSA by the applicant. Moreover, as stipulated in Article 25 (a) of Regulation (EU) 2283/2015, changes occurring after the risk assessment and or after the eventual authorisation of the novel food that might	Please refer to the response to comment 155.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		impact its safety must be immediately notified to the EC.' It is not clear what types of changes require this notification, and it is not feasible for any new production process to be held eternally constant. For example, should an unexpected event occur, there may be a need for process adjustments that would maintain the integrity and safety of the final production. It is highly likely that applicants for a novel food authorisation are using a process that they will continue to optimise as they prepare for and enter the commercial market. If every single processing change, even those that do not affect the final product, requires reporting and compositional analysis of 5 independent batches of finished product, the time required for EFSA's review and the cost of such analyses would prevent the applicant from ever optimising the process. Should the applicant have the resources to provide all of this information to EFSA, this additional cost would need to be transferred to the consumer. Moreover, if EFSA requires immediate notification of any processing change, that notification would not be able to be accompanied by the requested compositional analysis due to the time needed to collect samples and facilitate testing. We recommend that notification of changes be limited to those that alter the final novel food product.	
554	Novonesis (merger of former Novozymes and Chr. Hansen)	page 21, lines 639-642: Could you please clarify how and to which extent EFSA qualifies 'different processes'? E.g., would a NF available in powder and liquid form be considered different processes and would require to be covered into the application for instance?	Please refer to the response to comment 325.
588	AseBio - Spanish Bioindustry Association,	1. Line: 639 - 642 Further clarification is needed as to what exactly is covered in this section. 2. Line: 644 – 647 It would be disproportionate to require disclosure of any and all changes. Accordingly, the sentence should be revised to include significant before changes: 'Moreover, as stipulated in Article 25 (a) of Regulation (EU) 2283/2015, significant changes occurring after the risk assessment and or after the eventual authorisation of the novel food that might impact its safety must be immediately notified	1. Please refer to the response to comment 325. 2. Please refer to the response to comment 158.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		to the EC.' This also provides a better basis for applying the Minor Strain Change Policy.	
647	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 645. 'Regulation (EU) 2283/2015': It should say 'Regulation (EU) 2015/2283'.	The text has been revised in line with the comment.
670	Atova Regulatory Consulting SL	(Line 639-642, page 21) It is responsibility of food business operators to market novel foods according to the specifications set in the Union List of novel food and to produce that novel food in compliance with the relevant food hygiene legislation. Providing a HACCP plan should be adequate.	Please refer to the response to comments 689 and 325.

Table 21: 3 Compositional data

Comment number	Commentor	Comments	EFSA NDA Panel responses
119	Medfiles Ltd	1. Comment P21 L662: Medfiles proposes to add to the list the CEN methods and the methods complying with the EU performance criteria (e.g. (EC) No 333/2007, (EU) 2017/644, SANTE 11312/2021 v2 etc). It should be noted that these methods are used for official control of contaminants and residues instead of AOAC, ISO methods in the EU. In addition, CONTAM Panel recommends using methods complying with the EU performance criteria and not standard methods. It is also good to understand that the standard methods such as AOAC, ISO, CEN are not necessarily state of the art because the standardisation takes for so long i.e. they are 'old fashion' and not necessarily sensitive enough to detect low concentrations reliably. In addition, the methods evaluated by the EURL FA could also be permitted to be used for novel foods, where applicable. Finally, it is also noted that methods proposed by the applicants for food improvement agents (e.g. food additives) should also be allowed to be used for novel foods,	1. The examples mentioned in the Guidance, including AOAC and ISO methods, are indicative. Other validated analytical methods can also be acceptable. It is the applicant's responsibility to select the most appropriate and up-to-date method(s) for analysing their novel food. Recommendations from the commentor have been integrated in the Guidance among the examples provided, the text has been revised. 2. Both LOD and LOQ are essential, especially when investigating the presence of substances of potential safety concern. Their relevance and use depend on the nature and purpose of the analytical methods

		where appropriate. This because, these methods have been assessed by EFSA within the dossier evaluation. 2. P22 L665: Medfiles sees that a LOD is irrelevant as it is not reliable and risk assessment would be made based on LOQ. Thus, we would appreciate if only a LOQ is required. In addition, it should be noted by EFSA that the laboratories do not necessarily determine a LOD/LOQ which are as low as technically achievable for the methods, because this is expensive. Often laboratories report a LOD/LOQ which have been tailored to be suitable from the viewpoint of statutory maximum levels. Also, for this reason a LOQ is far more relevant than LOD. In addition, previously a LOQ were required for toxicologically relevant substances which makes sense. Please reconsider adding that LOQ is required for toxicologically relevant substances only. It doesn't make sense that e.g. for safe substances LOQ (or LOD !!) is required. Please note too that a LOD or LOQ is not necessarily determined at all but it is rather stated that a LOQ is the lowest concentration point in the calibration curve.	employed. Applicants are welcome to provide a scientific rationale if they believe a specific parameter is not necessary for their submission. The text has been revised to accommodate all cases.
308	Food Safety & Nutrition Consultancy	Following lines 254-256: if the composition of the novel food is not essentially different from existing foods then the prior approach of 'substantial equivalence' should be re-introduced. It is not needed to re-invent the wheel. Rather EFSA should make use of existing data. Such would allow a fast(er) track towards authorisation. Hence if the composition is qualitatively comparable to existing foods and grossly also quantitatively please unlock the door (again) for substantial equivalence. This is a real opportunity for EFSA and for innovation. [this comment towards re-introducing substantial equivalence can also deserve a place elsewhere: by preference as a separate chapter]	Please refer to the response to comment 306.
342	Jeremy Coller Foundation	1. Line 682-683, page 22 - Is there a preference on the format of the data provided? 2. Line 737, page 24 - Would animal cell culture fall into these categories also? 3. Line 815, page 26 - Do the five batches need to be consistent across all tests? Line 881-883, page 28 – Who ultimately decides what the alternative product is comparable	1. Data should be provided in a readable and searchable format. Additional practical information regarding data submission will be detailed in the Administrative Guidance on novel foods. 2. The text has been revised to provide further clarity.

		to/is replacing as this will be indicative of the minimum nutrient requirements?	3. It has been clarified in the Guidance (section 3.1.2) that the analyses should preferably be performed on the same group of batches that have been independently produced (preferably with independent batches of raw materials), to obtain a comprehensive picture of their composition. The text has been revised to provide further clarity. The applicant makes a substantiated proposal regarding the alternative product's comparability and replacement, which is then assessed and ultimately decided by the Panel. Please refer to section 6.2 and section 9.2.2 for additional information on the replacement of food(s) in the diet.

Table 22: 3.1 General requirements

Comment number	Commentor	Comments	EFSA NDA Panel responses
701	FoodDrinkEurope	1. [Lines 661-674] Better distinction could be done in the text between laboratory accreditation and method accreditation. We would suggest starting the section with laboratories accreditation and then methods accreditation, validation, and description, with a ranking from the best (accredited, recognised and validated method) to the least recommended. 2. [Line 665] The current limits of detection and quantification may evolve, therefore we think the qualifier 'current' (reflecting the state at the time of the dossier application) should be mentioned 3. [Lines 677 and 683 - 686] Clarity is required on the requirements related to batch analysis and production process do	1. The Panel notes the recommendations but considers that a detailed expansion of the section referred to goes beyond the scope of this Guidance. 2. Limits of detection (LOD) and limits of quantification (LOQ) can indeed change over time. Therefore, it is essential to provide the current LOD/LOQ values for the methods used in the dossier at the time of

Comment number	Commentor	Comments	EFSA NDA Panel responses
		they need 5 additional non-consecutive batches or one is only needed to show substantial equivalence? Should the five non-consecutive batches cover the process variability? This could be problematic for companies. Thus we ask that it is explicitly indicated that pilot scale batches could be submitted providing no major changes will be implemented when scaling up to industrial scale. In general, this new requirement seems not proportional for the safety of the novel food. Our interpretation of this new requirement is that FBOs would need to provide a lot of additional data from additional batches at different levels of process parameters and explain the reasons. This means enormous amount of testing per process parameter. The extra safety this would bring is not understandable since FBOs would always need to produce within established specifications for the novel food. The variability of the process parameters is based upon experience, know-how and quality systems.	application. Please refer also to the response to comment 119. 3. As specified in the Guidance (section 3.1.2), the analytical information should be provided on at least five representative batches of the novel food that have been independently produced (preferably with independent batches of raw materials), unless a different number of batches is explicitly requested in this Guidance. It is expected that the analysed batches are produced either at an industrial production scale or at one representative of it. Representativeness shall be justified. The text has been revised (section 3.1.2) to provide further clarity.

Table 23: 3.1.1 Analytical methods

Comment number	Commentor	Comments	EFSA NDA Panel responses
20	Undisclosed (Personal Capacity)	Line 674 There is often not both LOD and LOQ. So suggest changing to LOD and/or LOQ	The text has been revised in line with the comment.
69	Nutraveris - A FoodchainID company	o Many accredited laboratories use analytical method for a food matrix beyond the scope of accreditation/standardization. The draft guideline states 'it should be treated as in-house method (the same applies in cases that standard methods are modified)'. We foresee extended issues with some well-known laboratories not willing to share their internal method or the modification of the standard method, as most of the standard methods are adapted by the laboratories. Moreover, novel food are innovative products, which do not enter systematically in	The applicant can provide a justification for using a non-official method for the analysis of certain parameters and for selecting a laboratory not accredited for this method. If in-house methods are employed, the analytical protocols should be fully described, and the results of the corresponding method

Comment number	Commentor	Comments	EFSA NDA Panel responses
		the scope of accreditation. In many cases, it is not possible to obtain a validated method with a validate certification.	validation procedures must be provided. If an analytical method is used for a food matrix beyond the scope of accreditation or standardisation, it should be treated as an in-house method, and the same applies when standard methods are modified. If analyses are not performed in accredited laboratories, a justification should be included. It remains the applicant's responsibility to conduct the analysis and gather all required documentation, including method validation data. The Panel considers that no change to the Guidance is needed, apart the one linked to comment 20.
293	Katharina Julia Brenner (Personal Capacity)	1. Specification of Analytical Methods and Their Validation (Page 21, Lines 661-665): Comment: The guidance highlights the use of validated methods, preferably internationally recognised. However, it could be improved by specifying that the selection of analytical methods must be justified based on the nature of the analyte, the complexity of the food matrix, and the detection limits required. Furthermore, the document should emphasise the necessity of calculating and justifying the sample size (n) upfront using appropriate statistical methods to ensure the significance of the analytical results. This would help in achieving reproducible and reliable data, critical for regulatory assessments. 2. Good Scientific and Statistical Practices in Analytical Methodology (Page 21, Lines 666-674): Comment: While the document requires detailed reporting of the analytical methods used, including LOD and LOQ, it should also mandate the inclusion of a statistical analysis plan that outlines how analytical variability and uncertainty are to be handled. This should cover statistical techniques for data validation, method comparison, and the handling of outliers, ensuring that the	1. It is the applicant's responsibility to select the most appropriate and up-to-date method(s) for analysing their novel food. Regarding sampling, the Panel notes the recommendations but considers that a detailed expansion of the section referred to goes beyond the scope of this Guidance. 2. The elements described in the comment align with general accreditation requirements. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		analytical methods employed are robust, scientifically sound, and yield data that are both accurate and precise.	
469	Undisclosed (Personal Capacity)	If an analytical method is used for a food matrix beyond the scope of accreditation / standardisation, it should be treated as in-house method. If in-house methods are employed, the analytical protocols implemented should be fully described, and the results of the respective method validation procedures should be provided. For novel foods the food matrix is often beyond the scope of accreditation/standardisation as it is new, therefore in-house methods needs to be employed. However we often encounter that labs are not willing to share their methods and also are not aware of this procedure by EFSA. Is this something that could be discussed with the laboratories, otherwise the request is not realistic.	Please refer to the response to comment 69.
610	Cellular Agriculture Europe	Lines 661 - 674: We invite EFSA to better distinguish laboratory accreditation from method accreditation in the text. We would suggest starting the section with laboratories accreditation and then methods accreditation, validation, and description Line 665: We propose the following wording (proposed added words are highlighted in bold): 'The current limits of detection (LOD) and/or qualification (LOQ) should be mentioned'. There is often not both LOD and LOQ. In addition, LOD and LOQ may evolve, thus we should state current at time of the dossier application.	Please refer to the response to comments 20 and 701.
648	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Lines 664-665. 'The respective methods of analysis should be described alongside their references': Methods and their validations are proprietary information for the labs and therefore there is strong resistance from labs to share this information with the applicant. What would be EFSA advice in these cases? 2. Line 666. 'information on the matrix accreditation': Are there any specific accreditation standards/certificates EFSA is referring to?	1. Please refer to the response to comment 69. 2. Matrix accreditation of a method in food analysis refers to the process of validating and accrediting an analytical method for use with specific types of food matrices. It ensures that the method is reliable and accurate for detecting or quantifying substances within the particular food matrix being analysed. This type of accreditation confirms that the method performs well for the food products in

Comment number	Commentor	Comments	EFSA NDA Panel responses
			question, considering factors like matrix effects, which can impact the accuracy and precision of the analysis. Specific methods can be accredited by recognised standardisation bodies or validated through recognised protocols. The Panel considers that no change to the Guidance is needed.
671	Atova Regulatory Consulting SL	1. (Line 664, page 21) Are limits of detection and quantification required for all parameters analysed or only for substances of concern (as in the current novel food guidance)? Please clarify. Also, some laboratories either the LOD or the LOQ for a method. Is providing just the LOQ acceptable in cases where the LOD is not provided? 2. (Line 668, page 22) For internal methods or modifications of internationally recognised methods (i.e. use in a food matrix beyond the scope of the internationally recognised method), some laboratories refuse to share the complete method description and validation results. When these methods are accredited by a national accreditation body, the principle of the method (e.g., HPLC, chromatography) and the method accreditation should be sufficient to demonstrate the method suitability without compromising the intellectual property of the laboratories. Moreover, it is not uncommon for the main laboratory to subcontract some analyses to a second laboratory (rereferred by EFSA as 'multisite studies'), adding complexity to the ability to disclose this information. We suggest EFSA to consider the principle of the method and the accreditation by a national accreditation body as an alternative to providing a complete method description and results of the method validation for internal methods. We also suggest EFSA to describe in more detail the data required as results of the method validation.	1. Please refer to the response to comments 20 and 69. 2. Please refer to the response to comment 648. The Panel notes the recommendation regarding further details on method validation but considers that providing such details goes beyond the scope of this Guidance.

Table 24: 3.1.2 Addressing compositional variability

Comment number	Commentor	Comments	EFSA NDA Panel responses
6	Analyze & Realize GmbH	line 678-679 only if applicable; see our comment on 2.4. This requirement cannot be reasonably met for all types of novel foods (e.g., botanicals with a limited supply or derived from commodity, large-scale agricultural raw materials).	Regarding 'independent batches of raw materials,' it should be noted that incorporating this requirement allows the food business operators as well as the risk assessors to investigate potential compositional variability due to this factor. The Panel acknowledges, however, that this can be challenging in certain cases. The text has been revised in line with the comment (i.e., with preferably independent batches of raw materials).
21	Undisclosed (Personal Capacity)	Lines 677-678 The analytical information should be provided on at least five representative batches of the novel food that have been independently produced This is often problematic for new companies and we would suggest replacing five with 'at least three representative batches' or adding 'unless specifically justified' after the existing text Also consideration should be given that in some cases continuous culture might be the nature of the process and so defined batches might actually be replaced by times in the cycle etc.	The number of batches was selected by the Panel based on their extensive experience, ensuring meaningful specifications, and investigating variability, particularly regarding critical parameters for compositional identity and safety. Acknowledging potential variability from raw materials and production cycles, the Panel mandates this requirement to establish robust specifications. Analysing five batches should not pose an undue burden for FBOs. For continuous production processes, additional reasoning can be provided for the selected batches. Testing 'at least five representative batches' is crucial for ensuring product safety and quality, as it helps establish reliable specifications that safeguard consumer health. Moreover, please refer to the response to comment 6.

Comment number	Commentor	Comments	EFSA NDA Panel responses
53	Specialised Nutrition Europe (SNE)	Page 22 Line 683-686: 'whole variability spectrum of the production process parameters' This new requirement is unclear for us, and it seems not proportional for the safety of the novel food. Our interpretation of this new requirement is that we need to provide a lot of additional data from additional batches at different levels of process parameters and explain the reasons. This means enormous amount of testing per process parameter. We do not understand the extra safety this would bring since we would always need to produce within established specifications for the novel food. The variability of the process parameters is based upon experience, know-how and quality systems.	The intention is to focus on the process parameters considered relevant for the identity, the hazard identification, and safety of the final product. This approach ensures the safety and consistency of the novel food while recognising the practical aspects of production.
74	Bene Meat Technologies A.S.	line 681: please specify in the text what types of ' harmful substances' are referred to. Reasoning: there is a missing definition of harmful substances and it is not clear if this refers to any potentially harmful substance or to those which are harmful in the food industry/prohibited to use.	The text has been revised to provide further clarity. The word 'harmful' has been replaced by 'hazardous'.
87	BaseClear	In lines 677-678, it is mentioned that 'Analytical information should be provided on at least five representative batches of the novel food that have been independently produced.' It should be clarified whether the requirement for 'five representative batches' applies solely to compositional variability analysis or if it extends to other analyses such as viable cells test, presence of DNA, toxicity test, MIC, and antimicrobial production analysis.	Please refer to the response to comment 701.
123	Medfiles Ltd	Comment P22 L682: Please clarify what is meant by 'such data'. Does it mean that data from five batches need to be generated when there are several production processes?	Indeed, when several production processes are proposed, such data should be provided for each process. If not provided, the applicant must offer a scientific rationale explaining why the data provided is representative and sufficiently supports the assessment of the novel food.
159	Synpa, French association of specialty food	1. Lines 676-690 Among the five batches that need to be characterised, can laboratory or pilot industrial batches be tested? If yes, what is the maximum number that would be	1. Please refer to the response to comment 701.

Comment number	Commentor	Comments	EFSA NDA Panel responses
	ingredients manufacturers and distributors	allowed? For novel food derived from natural sources, the need to assess variability depending on seasonality/geography can be an obstacle to innovation (might need 5 years of sourcing to produce five batches). 2. Lines 677-678 'The analytical information should be provided on at least five representative batches of the novel food that have been independently produced' This is often problematic for companies, please explicitly indicate that pilot scale batches could be submitted providing no major changes will be implemented when scaling up to industrial scale. 3. Lines 677-686 Many types of production processes, including fermentation processes, include a large number of variables and parameters. For fermentation processes this can include e.g. pH, oxygen, temperature(s) throughout, variability of concentration of all fermentation substances used, etc. Therefore, to cover the whole variability spectrum of the production process parameters would require a large amount of analyses. We note that the novel food production has to comply with certain specifications, no matter the production process batch. As the safety considerations of these specifications are already assessed by EFSA, we consider that the variability of production process parameters is already sufficiently addressed. 4. Lines 683 - 684 Novel foods are mainly coming from natural raw materials meaning that there is already a batch-to-batch variability in data presented to EFSA. Is this variability sufficient for EFSA? If not, adding variability of the process will be really difficult / impossible to manage. In fact, in that case, applicant should use one same batch of raw material with different process parameters to evaluate the process variability. In addition the applicant is supposed to manage/control the production process in order to avoid huge variabilities in the final product.	2. Please refer to the response to comments 6 and 701. 3. Please kindly note that the ability of the food business operator to produce the novel food in a consistent and reproducible manner should be demonstrated as the basis for hazard identification and eventually for the establishment of the specifications of the novel food. Please refer to section 2.4 for additional considerations on the consistency in production methods and variability in the supplying starting materials, which should be covered by the analytical data provided. The Panel considers that no change to the Guidance is needed. 4. Please refer to the response to comments 53 and 701.
207	EU Specialty Food Ingredients	Lines 683-686: This new requirement is unclear for us, and it seems not proportional for the safety of the novel food. Our interpretation of this new requirement is that we need to provide a lot of additional data from additional batches at	Please refer to the response to comments 53 and 159.

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		different levels of process parameters and explain the reasons. From our perspective, in many types of production, e.g. fermentation processes, there are too many parameters that would have to be taken into account to cover this request, e.g. pH, oxygen, temperature at different steps, variability of concentration of all of the fermentation substances used etc… This is exceeding a pharma validation, which is rarely conducted in such detail for most pharmaceutical products due to the potential risk of going out of specifications. Practically, key operating parameters and ranges are established, but not all potential variations are systematically tested, especially not in every possible combination. An enormous amount of production campaigns and analyses would be necessary to cover the whole variability spectrum of the production process parameters. We note that the novel food production has to comply with certain specifications, no matter the production process batch. As the safety considerations of these specifications are already assessed by EFSA, we consider that the variability of production process parameters is already sufficiently addressed. The variability of the process parameters is based upon experience, know-how and quality systems. Moreover, novel food applications are generic in nature (with time-limited data protection in some cases only), so different producers may have different process parameters. In view of this workload not only for the applicant to generate the data but also for EFSA to review the information provided we do not believe that the gain in knowledge justifies the additional workload. We understand that EFSA wants to get insights into potential risks associated with the specific processes, but we believe that these can be better addressed by specific individual requests during review (where necessary) instead of reviewing huge amounts of (largely irrelevant) data. We propose that applicants shortly discuss process development and justify specification of the Novel Food according to the process. Especially if some production parameters are key to e.g. prevent a process impurity (control of pH, temperature, …), or to remove some impurities via e.g. crystallisation (solvent mix).	

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		Please note that such examples are potentially already addressed in the HACCP required in section 2.1 of the Guidance.	
252	The Good Food Institute Europe	Line 677-678 The analytical information should be provided on at least five representative batches of the novel food that have been independently produced Comment: In line with international regulators (including the FDA), EFSA could consider replacing the need for 'five representative batches' with 'at least three representative batches' or enabling the testing of a lower number of batches if this is supported by scientific arguments. Equally, EFSA should define 'independent batches', as some production processes - particularly for cultivated meat products - may draw on continuous culture that limit the ability to define 'independent' batches for analysis.	Please refer to the response to comment 701.
294	Katharina Julia Brenner (Personal Capacity)	1. Justification and Calculation of Sample Size (Page 22, Lines 675-683): Comment: The guidance advises on addressing compositional variability by analysing multiple batches, but it lacks detailed instructions on how to calculate and justify the appropriate sample size for these analyses. To ensure statistical significance, the guidance should specify that the sample size (n) must be decided and calculated upfront based on good scientific and statistical practices. This includes providing a methodology for determining n, such as power analysis or hypothesis testing frameworks, which would help in obtaining meaningful and statistically significant results. 2. Systematic Approach to Handling Compositional Variability (Page 22, Lines 683-685): Comment: While the section mentions the need to explore the variability of potentially harmful substances, it does not provide a clear systematic approach or criteria for when additional batches are necessary. Guidelines should be included on how to assess and handle different sources of variability (e.g., raw material variability, seasonal effects, process parameters) and their impact on the composition of the novel food. These guidelines should also detail how to document and interpret the findings in a scientifically rigorous manner.	1. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance. 2. The Panel notes the recommendation but considers that outlining a systematic approach or further criteria goes beyond the scope of this Guidance, considering the heterogeneity among novel foods.

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326	EuropaBio	683 - 686: Many types of production processes, including fermentation processes, include a large number of variables and parameters. For fermentation processes this can include e.g. pH, oxygen, temperature(s) throughout, variability of concentration of all fermentation substances used, etc. Therefore, to cover the whole variability spectrum of the production process parameters would require a large amount of analyses. We note that the novel food production has to comply with certain specifications, no matter the production process batch. As the safety considerations of these specifications are already assessed by EFSA, we consider that the variability of production process parameters is already sufficiently addressed.	Please refer to the response to comments 53 and 159.
555	Novonesis (merger of former Novozymes and Chr. Hansen)	page 22, lines 683-686: From our perspective, in many types of production, e.g. fermentation processes, there are too many parameters that would have to be taken into account to cover this request, e.g. pH, oxygen, temperature at different steps, variability of concentration of all of the fermentation substances used etc.. An enormous amount of production campaigns and analyses would be necessary to cover the whole variability spectrum of the production process parameters. The novel food subject of an application has to be inside certain specifications, no matter the production process parameters of that specific batch. Since the specifications are already assessed by EFSA regarding safety, we see EFSAs concerns regarding the variability of production process parameters already addresses sufficiently.	Please refer to the response to comments 53 and 159.
589	AseBio - Spanish Bioindustry Association,	Line: 683 - 686 Many types of production processes, including fermentation processes, include a large number of variables and parameters. For fermentation processes this can include e.g. pH, oxygen, temperature(s) throughout, variability of concentration of all fermentation substances used, etc. Therefore, to cover the whole variability spectrum of the production process parameters would require a large amount of analyses. We note that the novel food production has to comply with certain specifications, no matter the production process batch. As the safety considerations of these specifications are	Please refer to the response to comments 53 and 159.

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		already assessed by EFSA, we consider that the variability of production process parameters is already sufficiently addressed.	
611	Cellular Agriculture Europe	1. Lines 677 - 678: The analytical information should be provided on at least five representative batches of the novel food that have been independently produced' This is often problematic for new companies and we would suggest replacing five with 'at least three representative batches' or adding 'unless specifically justified' after the existing text or suggest the same wording used for stability 'Testing of a lower number of batches is to be duly supported by scientific arguments.' (816-817) Also consideration should be given that in some cases continuous culture might be the nature of the process and so defined batches might actually be replaced by times in the cycle etc. Indeed, the definition of 'independent batches' is an issue, especially for continuous processes. We would therefore suggest adapting the wording and recommendation accordingly. 2. Lines 682 - 683: 'When are proposed, such data should be provided for each process', does EFSA need 5 additional non-consecutive batches or one is only needed to show substantial equivalence? We would welcome clarity on the requirements related to batch analysis and production process.	1. Please refer to the response to comment 701. 2. Please refer to the response to comment 123.
649	Pen & Tec Consulting S.L.U. (trading as Argenta®)	1. Lines 678-679. 'independently produced (i.e., with independent batches of raw materials)': For novel foods that are still at pilot scale (e.g. startups), purchasing five batches of each raw material may not be feasible. Will EFSA accept exceptions to this request? 2. Lines 683-685. 'Moreover, compositional data should also cover the whole variability spectrum of the production process parameters (e.g., highest and lowest amount of solvents used, range of temperatures applied)': Do EFSA expect five batches for each extreme of the spectrum to be covered?	1. Please refer to the response to comment 701. 2. Please refer to the response to comments 53 and 159.
672	Atova Regulatory Consulting SL	1. (Line 677-678, page 22) 'The analytical information should 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)' For continuous	1. Please refer to the response to comment 701. 2. Please refer to the response to comment 701.

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		production processes (e.g., where there is a constant flow of medium (made from large volumes of raw materials) through the bioreactor and from which multiple batches can be produced from one production run), what does EFSA consider independently produced batches? Collection of samples at different timepoints? We recommend that EFSA provides a suitable definition with enough flexibility to consider continuous processes and specifies what is appropriate for continuous vs. fed batch processes. As defined in Directive 2004/10/EC: 'Batch means a specific quantity or lot of a test item or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such'. 2. (Line 678-679, page 22) EFSA indicates that batches used to analysed compositional variability should be manufactured using independent batches of raw materials as a well. However, this poses considerable challenges from both practical and economic standpoints. While novel food manufacturers are responsible for implementing HACCP and complying with food hygiene legislation, ultimately it is the raw material manufacturer's responsibility to comply with their product specifications. EFSA is already requesting information for all input materials (section 2.1 and Annex B) used in the manufacturing including their specifications and/or certificate of analysis, and we consider that this should be sufficient evidence. 3. (Line 679-680, page 22) Regarding the sentence 'The examined batches should be sampled in a manner adequate to address potential compositional variations (e.g., seasonal) of the raw materials'. Does EFSA mean that the batches should be prepared taking into consideration the variability of raw materials? Otherwise, could EFSA clarify the adequate novel food sampling procedure to address compositional variations of the raw materials and include examples? 4. (Line 684, page 22) 'Compositional data should also cover the whole variability spectrum of the production process parameters (e.g., highest and lowest amount of solvents used,	3. Indeed, the batches should be prepared with consideration of potential variability in the raw materials. For example, if a plant used as a raw material has composition variations depending on the season, this should be taken into account when selecting the batches for analysis. This approach helps in investigating compositional variability and setting more representative specification limits. The Panel notes the recommendation but considers that providing additional information on sampling procedures goes beyond the scope of this Guidance. 4. The applicant can provide scientific justifications for the selection of novel food batches analysed, in line with the requirements specified in the Guidance.

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		range of temperatures applied)`. Atova suggests focusing the testing around the `worst-case scenario` rather than covering the whole variability spectrum of the production process parameters. E.g. rather than covering the highest and lowest amount of solvents used, from a safety perspective, we are inclined to argue that covering the highest amount of solvent in the production process represents the `worst-case scenario`, as it would account for the highest risk for carry-over of potential impurities.	

Table 25: 3.1.3 Sampling practices

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54	Specialised Nutrition Europe (SNE)	Page 22 Line 692-696 This paragraph is new in the guidance, and it requests additional in-depth details about a sampling plan and its rationale. Sampling plans are regarded as part of the routine work within a food production location and are under the control of local authorities. It is covered under the applicable EU requirements for having a HACCP/quality system in place in a food production location. Our suggestion is to delete this paragraph or rewrite this paragraph so that less details have to be submitted by the applicant, more in line with the current guidance.	The Panel does not agree with the proposal.
100	Undisclosed (Personal Capacity)	Sample Size (n) considerations (691ff, page 22) Comments: it is advised to set high academic standards for the sample size calculation. It is advised to calculate the needed sample size upfront, when deciding on the specific study design of the novel food testing and analyses. This is important, as only with a sufficient sample size, reliable and significant results can be obtained. This section could furthermore benefit from a more robust explanation of the statistical basis for determining sample sizes and intervals, particularly for novel foods with expected high variability. This would help ensure that sampling practices are representative and statistically sound.	The Panel notes the recommendation but considers that providing additional information on sampling procedures goes beyond the scope of this Guidance.

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208	EU Specialty Food Ingredients	Lines 692-696: This paragraph is new in the guidance, and it requests additional in-depth details about a sampling plan and its rationale. Sampling plans are regarded as part of the routine work within a food production location and are under the control of local authorities. It is covered under the applicable EU requirements for having a HACCP/quality system in place in a food production location. Our suggestion is to delete this paragraph or rewrite this paragraph so that less details have to be submitted by the applicant, more in line with the current guidance.	The Panel notes the recommendation but considers that providing additional information on sampling procedures goes beyond the scope of this Guidance.
276	Ministry of Regional Affairs and Agriculture	Line 692- would it be possible to refer to a document(s) that explain the principles of representative sampling? Line 694- would it be possible to give examples of sampling protocols?	Please refer to the response to comments 100 and 208.
295	Katharina Julia Brenner (Personal Capacity)	1. Determination and Justification of Sample Size (Page 22, Lines 691-693): Comment: The document advises on the use of representative sampling methods but lacks specific guidelines on how to determine the appropriate sample size. It is crucial to calculate and justify the sample size upfront, based on good scientific and statistical practices, to ensure that the results are statistically significant and representative of varied production conditions. This should include a detailed explanation of the statistical methods used to calculate sample size and the factors considered in these calculations. 2. Application of Good Statistical Practices (Page 22, Lines 691-696): Comment: While the document mentions representative sampling, it does not explicitly address the incorporation of good statistical practices in the sampling plan. Emphasising the importance of statistically validated sampling techniques would strengthen the reliability of the results. The guidance should provide examples of such practices or references to standard statistical methodologies that can be applied to ensure the robustness of the sampling process.	1. Please refer to the response to comment 54. 2. Please refer to the response to comments 100 and 208.
471	Undisclosed (Personal Capacity)	Principles of representative sampling should be applied (e.g., sample size, containers, conditions), and the rationale on why the employed sampling plan is considered representative should	Please refer to the response to comments 54, 100 and 208.

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		be provided. The guidance would benefit from a more detailed explanation of what a representative sampling plan entails.	
556	Novonesis (merger of former Novozymes and Chr. Hansen)	page 22, lines 692-694: Sampling plans can be quite comprehensive; therefore, we would like to ask EFSA to confirm that provision of the general principles/parameters are sufficient to avoid unnecessary large amounts of data being provided and reviewed. If EFSA insists on detailed information, it should be stated in the guidance that such data would be kept confidential.	Please refer to the response to comments 54, 100 and 208.
702	FoodDrinkEurope	1. [Lines 692 - 696] This paragraph is new in the guidance, and it requests additional in-depth details about a sampling plan and its rationale. Sampling plans are regarded as part of the routine work within a food production location and are under the control of local authorities. It is covered under the applicable EU requirements for having a HACCP/quality system in place in a food production location. Our suggestion is to delete this paragraph or rewrite this paragraph so that less details have to be submitted by the applicant, more in line with the current guidance. 2. [Lines 723 - 731] We note that this requirement comes from the opinion of EFSA Scientific Committee (2021). Nevertheless, we think it should refer to the guidance and not be spelled out here, in case the parameters would be updated in the future rendering this requirement on the Guidance for NF obsolete. 3. [Lines 735 - 736] 'Therefore, if the manufacturing process does not include any step that may lead to the presence of small particles (e.g., spray-drying, micronisation, encapsulation, filtration)' This does not recognise these are standard food processes across the whole food industry and they should only be relevant where the ingredients are from mineral or inert insoluble form only.	1. Please refer to the response to comments 54, 100 and 208. 2. The Panel does not agree with the proposal. Please refer to General Principle 2 of the Guidance. 3. The references to specific food processes have been removed. The EFSA NDA Panel will evaluate the nature of each novel food and its manufacturing process on a case-by-case basis. They will determine whether the potential presence of small particles, including nanoparticles, needs to be addressed, in cases in which the applicant has not provided relevant evidence. The text has been revised to provide further clarity.

Table 26: 3.1.4 Compositional analytes

Comment number	Commentor	Comments	EFSA NDA Panel responses
22	Undisclosed (Personal Capacity)	1. Lines 706-709 'For novel foods meeting the specific considerations regarding novel protein sources (section 9.3), protein content should be quantified both using the 6.25 nitrogen-to-protein conversion factor and the sum of the anhydrous amino acids, to investigate a potential over- or under-estimation of the protein content.' Please add references to the specific test methods you require here. In some cases rather than total nitrogen methods actual protein measurement is required. So this section could be tightened up with specific references to avoid confusion. 2. Lines 735-736 'Therefore, if the manufacturing process does not include any step that may lead to the presence of small particles (e.g., spray-drying, micronisation, encapsulation, filtration)' This is a catch all that is unnecessary and does not recognise that these are standard food processes across the whole food industry and they should only be relevant where the ingredients are from mineral or inert insoluble form only.	The text has been revised to provide further clarity. The Panel notes the recommendation but considers that listing specific methods goes beyond the scope of this Guidance. 2. Please refer to the response to comment 702.
70	Nutraveris - A FoodchainID company	1. o For complex mixture from natural origin, it is often not possible to assess solubility and/or dissolution rate for every component of the mixture. Assessing the particle size distribution by SEM in such complex ingredient is also particularly difficult and sometimes impossible. Moreover, the proposed nano-specific risk assessment is not feasible for complex ingredients. Are you considering updating the guidance to provide a feasible approach for this type of ingredient? 2. o Some categories of novel food are excluded of nano-specific assessment. Would oils from botanicals or algae be exempted of nano assessment, if oils are obtained by pressure or solvent extraction, without use of excipients which may create nanoparticles? Similarly, for botanicals preparations, for which an history of consumption exist for the raw material, and for which the manufacturing process does not include any steps which may change the size of particles, can the nano assessment be avoided, based on the history of consumption of the raw material?	1. According to the Guidance from the EFSA Scientific Committee (2021a), several appraisal routes are available to address concerns related to small particles in novel foods. While some methods, such as solubility or dissolution rate assessments, may be resource-intensive, they can be considered. In the Guidance from the EFSA Scientific Committee (2021a), it is acknowledged that certain types of materials can be particularly complex, and alternative approaches, such as comparing the novel food with similar products, are suggested. Additionally, it should be noted that it is not necessary to assess every component individually; instead, the focus could be on those components

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			that are less soluble or dissolve more slowly. 2. The NDA Panel, in consultation with the cross-cutting Working Group on Nanomaterials, evaluated several novel food categories that could potentially be exempted from a nano-specific risk assessment. However, at this time, no additional categories are considered suitable for such an exemption. The Panel will continue to assess on a case-by-case basis whether a novel food requires further in-depth analysis of the potential presence of a significant fraction of small particles, including nanoparticles.
75	Bene Meat Technologies A.S.	line 710: specify that characterisation of specific proteins and peptides relates only to those that are not commonly used in the food industry.	The Panel does not agree with the proposal. The need to characterise specific proteins and peptides should be evaluated on a case-by-case basis, depending on the characteristics and context of the novel food. The Panel considers that no change to the Guidance is needed.
101	Undisclosed (Personal Capacity)	1. Nutritional and Toxicological Considerations (Lines 697ff., page 23) Comment: It is suggested to incorporate structural alerts for toxicological assessments, especially for substances obtained through synthetic routes. The guidelines on nutrient analysis could be expanded based on the novel food's nature, considering potential differences in nutrient profiles between cultured and conventional meat as discussed in the Humbird analysis. 2. Compositional Analytes (Line 697, Page 22) Comment: The section could be improved by providing clear guidelines on	1. Reference to structural alerts is already made in section 8 of the Guidance. The Panel considers that no change to the Guidance is needed. 2. It is the responsibility of the applicant to select valid or standardised methods to generate and provide the required data and ensure compliance with the specifications. The Panel notes the

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		selecting appropriate analytical methods for different types of novel foods, particularly those derived from new production processes. Recommendations on when and how to apply these methods could help ensure the accurate assessment of food safety.	recommendation but considers that it goes beyond the scope of this Guidance.
109	Food Fermentation Europe	Lines 721 to 731 page 23 introduce a new requirement for all novel foods that do not meet the definition of engineered nanomaterial (as defined in Regulation (EU) 2015/2283 article 3.2(f)) to demonstrate the absence of a fraction of nano-scale particles, or alternatively that this fraction of nano-scale particles is covered by the conventional risk assessment using appraisal routes given in the EFSA Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles ('Guidance on Particle – TR'). This requirement is understandable for chemical substances, products of mineral origin and polymers, for which Section 1.1 of the draft guidance requires information on 'particle size, shape and distribution if particles are present in the final product' (line 392, page 13). However, this new provision presents a significant new and disproportionate requirement to be applied across the board to all other categories of novel foods of biological origin distinguished in the draft guidance that are not intentionally produced at the nano-scale and do not meet the definition of engineered nanomaterial. Indeed Section 1 of the document does not require any information on particle size, shape and distribution for foods consisting of, isolated from or produced from microorganisms (Section 1.2), from plants, macroscopic fungi and algae (Section 1.3), from animals (Section 1.4), or from cell culture or tissue culture derived from previous categories (Section 1.5). As a matter of fact, the draft guidance acknowledges that 'some categories of novel foods do not require a priori a nano-specific risk assessment, e.g., (i) microorganisms (e.g., bacteria, yeasts, fungi), (ii) unmodified proteins (including enzymes) and amino acids, (iii) whole foods (e.g., seeds, fruits, insects).' (lines 732-735 pages 23-24). However the draft guidance places a burden of proof on the	The NDA Panel, in consultation with the cross-cutting Working Group on Nanomaterials, evaluated several novel food categories that could potentially be exempted from a nano-specific risk assessment. However, at this time, no additional categories are considered suitable for such an exemption. The Panel will continue to assess on a case-by-case basis whether a novel food requires further in-depth analysis of the potential presence of a significant fraction of small particles, including nanoparticles. According to the Guidance from the EFSA Scientific Committee (2021a), several appraisal routes are available to address concerns related to small particles in novel foods. While some methods, such as solubility or dissolution rate assessments, may be resource-intensive, they can be considered. References to specific food processes, which are commonly used, have been removed. The Panel and the Working Group on Novel Foods will consider the nature of the novel food and its manufacturing

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		applicant to document that 'the manufacturing process does not include any step that may lead to the presence of small particles (e.g., spray-drying, micronisation, encapsulation, filtration)' (lines 735-736, page 24). The view of Food Fermentation Europe is that this broad new requirement to demonstrate the absence of a fraction of nano-scale particles, or alternatively that this fraction of nano-scale particles is covered by the conventional risk assessment as per the Guidance on Particle – TR, places an unreasonable and unnecessary additional burden on applicants to conduct potentially significant additional and costly analysis for novel foods of biological origin. The draft guidance itself acknowledges that this requirement is not needed for a number of novel food categories, but the exemption carved out by the document is too narrow to avoid unnecessary additional testing for many applicants. Indeed we note that the manufacturing processes cited as examples of processes disqualifying novel foods from the exemption from the need to conduct a specific nano-scale assessment (due to the potential generation of small particles) are standard processes across the whole food industry, and that many novel food manufacturing processes will include at least a filtration step and possibly spray-drying as well. We note that the Guidance on Particle – TR provides an exemption from the small particle assessment for highly soluble foods, but products such as proteins may not be highly soluble and would therefore be fully subject to the additional small particle assessment. Based on the foregoing, Food Fermentation Europe respectfully requests that the draft guidance be revised to only require this small particle assessment for novel foods of biological origin that do not meet the definition of engineered nanomaterial when there is reason to believe that a fraction of small particles in the specific novel foods of interest may cause a particular safety concern.	process on a case-by-case basis to determine whether the potential presence of small particles, including nanoparticles, needs to be addressed.
124	Medfiles Ltd	Comment: P23L732: Thank you for a good clarification when small particle testing is required and when not.	The Panel appreciates the recognition of EFSA's ongoing efforts
160	Synpa, French association of	1. Line 700 Please clarify what is meant by 'microbial indicators'.	1. The text has been revised to provide further clarity.

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	specialty food ingredients manufacturers and distributors	2. Line 721 : Nanocharacterisation If production process contains spray-drying, micronisation, encapsulation, filtration steps, demonstration of absence of small particles will be expected- If the NF is in powdered format obtained following a spray-drying step, demonstration of absence of small particles will be expected? On how many batches, the demonstration of absence of nanoparticles is expected?‘ 3. Line 732 What about microalgae and product derived from microalgae? 4. Line 734 In general, avoiding unnecessary testing is welcome. Can EFSA explain the rationale why amino acids are mentioned, and not e.g. other micronutrients or natural polymers, that could also be exempted from systematic testing if the production process does not indicate an intentional manufacturing at the nano state? 5. Lines 735-736 ‘Therefore, if the manufacturing process does not include any step that may lead to the presence of small particles (e.g., spray-drying, micronisation, encapsulation, filtration)‘ This does not recognise these are standard food processes across the whole food industry and they should only be relevant where the ingredients are from mineral or inert insoluble form only.	2. Please refer to the response to comments 701 and 702. 3. Please refer to section 1.2 for the definition of microorganisms intentionally used in the food chain, including microalgae. Section 3.1.4 has been clarified to include microalgae as an example of a microorganism for which a nano-specific risk assessment might be waived. 4. Please note that a nano-specific risk assessment is not required for microorganisms used as novel foods (such as active agents and biomasses) if the manufacturing process does not include any steps that could result in the presence of small particles. 5. Please refer to the response to comment 702.
209	EU Specialty Food Ingredients	1. Lines 698-700: We kindly ask EFSA to clarify what ‘microbial indicators‘ are. 2. Lines 732-734: In general, avoiding unnecessary testing is welcome. Can EFSA explain the rationale why amino acids are mentioned, and not e.g. other micronutrients or natural polymers, that could also be exempted from systematic testing if the production process does not indicate an intentional manufacturing at the nano state?	1. Please refer to the response to comment 160. 2. Please refer to the response to comment 109.
229	Planet A Foods GmbH	- ll. 732-739: If a novel food is the product of an extraction step from microorganism, is the process considered an exemption from the characterisation/demonstration of absence of small particles as well?	Please note that a nano-specific risk assessment is not required for microorganisms used as novel foods (such as active agents and biomasses) if the manufacturing process does not include any steps that could result in the presence of

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			small particles. The Panel considers that no change to the Guidance is needed.
253	The Good Food Institute Europe	1. Line 703 - 705: For…substances produced by microbial fermentation, the presence of undesirable metabolites should be investigated;' Comment: EFSA should clarify the definition of 'undesirable metabolites' and specify whether this refers exclusively to mycotoxins and microcystins, or is broader in scope. 2. Line 732-733 Considering their nature and in order to avoid unnecessary testing, some categories of novel foods do not require a priori a nano-specific risk assessment, e.g., (i) microorganisms. Comment: Based on the language used in this section, any microorganism that is processed (spray-drying, filtrations) will need to go through the nanomaterial risk assessment. EFSA should clarify whether there is any exemption to the nanomaterial risk assessment if these substances show dissolution or solubility as per the guidance document on nanomaterials.	1. The text has been revised to provide further clarity in relation to the presence of metabolites of safety concern. 2. Please refer to the response to comments 109 and 229.
270	Dwayne Holmes (Personal Capacity)	1. Pages 23-24, Line 697 - Section '3.1.4 Compositional analytes' - To use structural alerts for substances obtained by chemical synthesis. This reference could be mentioned here: EFSA Scientific Committee (2019). 2. Pages 23-24, Line 733-38 Clarity on exemption from analysis for small particles for cultured meat and seafood (a 'whole food') which may have limited potential due to small scale/early step filtration. 3. Pages 23-24, Line 735-736 - These production processes are used extensively in the food industry for non-novel foods. To make this clearer, we suggest including examples from recent novel food submissions to help applicants when the small particle guidelines apply.	1. Please refer to the response to comment 101. 2. Please refer to the response to comments 109 and 229. 3. Please refer to the response to comment 702.
327	EuropaBio	1. 703-705: The definition of 'undesirable metabolites' is vague and, by experience, can lead to extensive requirements compared to other jurisdictions. 2. 713-716: Proposal to delete this sentence, as it is clear that there is no need to characterise proteins for foods not containing nor derived from proteins.	1. Please refer to the response to comment 253. 2. The Panel does not agree with the proposal.

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533	FoodchainID	In case the novel food is manufactured by different producers with consistency in production method. Do the analysed batches have to come from different producer?	
590	AseBio - Spanish Bioindustry Association,	1. Line:703-705 The definition of 'undesirable metabolites' is vague and, by experience, can lead to extensive requirements compared to other jurisdictions. 2. Line: 713-716 Proposal to delete this sentence, as it is clear that there is no need to characterise proteins for foods not containing nor derived from proteins.	1. Please refer to the response to comment 253. 2. Please refer to the response to comment 327.
612	Cellular Agriculture Europe	1. Lines 706 - 709: 'For novel foods meeting the specific considerations regarding novel protein sources (section 9.3), protein content should be quantified both using the 6.25 nitrogen-to-protein conversion factor and the sum of the anhydrous amino acids, to investigate a potential over- or under-estimation of the protein content.' We suggest that EFSA adds references to the specific test methods required here. In some cases, rather than total nitrogen methods actual protein measurement is required. So this section could be tightened up with specific references to avoid confusion. 2. Lines 723 - 731: We suggest that the guidance clarifies the size of the fraction of small particles (% in mass? In number?) and that the solubility and dissolution rate must be assessed in water. The guidance is referring to the EFSA Scientific Committee Guidance (2021) but what if the latter is updated in the coming years? Technically speaking, it is very challenging to analyse for the presence of nanoparticles when using digestive fluids (containing salts and enzymes) as recommended by EFSA SC, and pH-adjusted water is often preferred in literature 3. Lines 735 - 736: 'Therefore, if the manufacturing process does not include any step that may lead to the presence of small particles (e.g., spray-drying, micronisation, encapsulation, filtration)' In our view, this statement does not recognise that these are standard food processes across the whole food industry and they should only be relevant where the ingredients are from mineral or inert insoluble form only.	1. Please refer to the response to comment 22. 2. The Panel acknowledges the concerns expressed but considers that expanding this section goes beyond the scope of this Guidance. 3. Please refer to the response to comment 702.
650	Pen & Tec Consulting	1. Lines 698-700. 'Information on the identity and the quantity of impurities or by-products, residues and chemical and	1. The Panel notes the recommendation but considers that it

Comment number	Commentor	Comments	EFSA NDA Panel responses
	S.L.U. (trading as Argenta®)	microbiological contaminants should be provided (e.g., heavy metals, mycotoxins, PCBs/dioxins, pesticides, microbial indicators and pathogens.': Could EFSA be more specific about the pathogens and microbial indicators as well as heavy metals and other contaminants such as PCB, dioxins or PAH for which information is expected to be always provided? 2. Line 718. 'Novel Food Regulation (EU) 2015/2283': Inconsistent reference to the regulation. 3. Line 739. '(as defined in the Guidance by the EFSA Scientific Committee (2021a)).': For consistency, suggest amending to '(as defined in EFSA Scientific Committee, 2021a).'	goes beyond the scope of this Guidance. 2. The Panel acknowledges the comment. 3. The text has been revised in line with the comment.
673	Atova Regulatory Consulting SL	(Line 735-736, page 24) 'Therefore, if the manufacturing process does not include any step that may lead to the presence of small particles (e.g., spray-drying, micronisation, encapsulation, filtration)'. These production processes are widely employed in the food industry for non-novel foods. Soluble protein-derived ingredients should be exempt. To make this clearer, we suggest including examples from recent novel food submissions to help applicants understand when the small particle guidelines apply.	Please refer to the response to comment 702.

Table 27: 3.2 Single substances and simple mixtures

Comment number	Commentor	Comments	EFSA NDA Panel responses
55	Specialised Nutrition Europe (SNE)	1. Page 24 line 740 and 748 The concept of simple vs complex mixture/whole food is understood but associated definitions remain quite vague for practical implementation. Potentially a cut-off should be defined on number/type of constituents to allow to state 'simple mixture'. Potential conflicting interpretation for well standardised & characterised protein hydrolysates that would by default fall under complex mixtures. 2. Page 25 line 780 These references could be best complemented by reference to actual regulatory texts where those substance of concern are also listed (ex 1334/2008,	1. The Panel notes the recommendation but considers that establishing such cut-offs goes beyond the scope of this Guidance. Protein hydrolysates fall under the definition of complex mixtures. 2. As outlined in the Guidance, the list of tools provided is a non-exhaustive one. The Panel considers

Comment number	Commentor	Comments	EFSA NDA Panel responses
		natural compounds within REACh etc..) as the listed tools will only give a fraction of the substances present in such novel botanicals	that no change to the Guidance is needed.

Table 28: 3.3 Complex mixtures and whole foods

Comment number	Commentor	Comments	EFSA NDA Panel responses
23	Undisclosed (Personal Capacity)	1. Line 762 'antinutrients' are not defined until the toxicology section 9.2.1 2. Lines 1422-1427. This definition ideally needs to be moved to Section 3.3 or at least cross referred to in Section 3.3 so the labs know specifically what to consider for analysis.	The text has been revised in line with the comment. An explanatory footnote has been added when the term is first mentioned.
56	Specialised Nutrition Europe (SNE)	Page 24 line 740 and 748 The concept of simple vs complex mixture/whole food is understood but associated definitions remain quite vague for practical implementation. Potentially a cut-off should be defined on number/type of constituents to allow to state 'simple mixture'. Potential conflicting interpretation for well standardised & characterised protein hydrolysates that would by default fall under complex mixtures. Page 25 line 780 These references could be best complemented by reference to actual regulatory texts where those substance of concern are also listed (ex 1334/2008, natural compounds within REACh etc..) as the listed tools will only give a fraction of the substances present in such novel botanicals	Please refer to the response to comment 55.
125	Medfiles Ltd	1. Comment: P25 L792-794: This sentence is very complicated to understand. Please revise it. Medfiles proposes (provided that this is meant): 'For viable or non-viable microorganisms as novel foods, the concentration of viable cells (e.g., by viable plate count) or non-viable cells (e.g., by flow cytometry or dry weight. In case of cell wall/membrane integrity, use flow cytometry; in absence of cell wall/membrane integrity, use dry weight) in the novel food should be reported.' 2. P25 L795-797: Medfiles notes the need for a comparative compositional analysis. Can EFSA add examples here, how this should be done, please. Moreover, can	1. The text has been revised to provide further clarity in relation to the concentration of viable cells and non-viable cells in active agents and biomasses, respectively. 2. It is the responsibility of the applicant to select valid or standardised methods to generate and provide the required data and

Comment number	Commentor	Comments	EFSA NDA Panel responses
		methods like different fingerprinting techniques and omics techniques (e.g. metabolomics, proteomics, lipidomics) be used for the comparative analyses. Medfiles notes that these state of art methods are used e.g. in US GRAS assessments. In addition, can EFSA acknowledge here that these methods, which are not typically conduced in accredited laboratories but in research-laboratories are accepted by EFSA.	ensure compliance with the specifications. Please also refer to the response to comments 432 and 69.
161	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Line 762 'antinutrients' are not defined until the toxicology section 9.2.1 2. Lines 1422-1427. This definition needs to be moved to Section 3.3 or at least cross referred to in Section 3.3. 3. Lines 792 - 798 How to evaluate non-viable cells in an extract?	1. Please refer to the response to comment 23. 2. Please refer to the response to comment 23. 3. Please refer to the response to comment 149.
271	Dwayne Holmes (Personal Capacity)	Page 25, Line 775-776 – 'Particular attention should be given to the possible presence of genotoxic and/or carcinogenic substances.' - This reference could be mentioned here: EFSA Scientific Committee (2019).	The proposed reference is cited elsewhere in the Guidance. The Panel considers that no change to the Guidance is needed.
296	Katharina Julia Brenner (Personal Capacity)	1. Characterization of Complex Mixtures (Page 24, Lines 750-762): Comment: The document outlines the need for qualitative and quantitative characterisations of main constituents of complex mixtures and whole foods. However, it could be improved by specifying more detailed methods for how to perform these analyses, particularly when dealing with mixtures where not all constituents can be fully characterised. Suggestions for advanced analytical techniques suitable for complex mixtures would be beneficial. 2. Consideration of Genotoxic and Carcinogenic Substances (Page 24, Lines 763-776): Comment: There's an emphasis on identifying toxic and allergenic substances, yet the guidance on how to test for and report these substances is vague. Detailed protocols for testing genotoxic and carcinogenic substances, including recommended limits and detection methods, should be included to ensure comprehensive safety evaluations.	The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.
328	EuropaBio	1. 749: Include microorganisms and microbial biomass 2. 767-768: Proposal to amend sentence to include 'comprehensive' i.e. '…a comprehensive literature search (e.g.	1. The text has been revised to provide further clarity.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		based on EFSA, 2010)‘ The systematic review, which is provided as the reference, is a very heavy procedure, and should not be required in all cases. The guidance mentions elsewhere ‘comprehensive‘, which should give more flexibility to the way the literature search is carried out. 3. 787: The reference is outdated in particular as category 1 and 2 products are concerned. Replace the reference by e.g. references to EFSA FEEDAP Panel (2018) and EFSA CEP Panel (2021), or make a reference to Annex A in this draft guidance	2. The text has been revised in line with the comment. 3. It should be noted that section 3.3 refers to scientific requirements for the compositional characterisation of the novel food, while scientific requirements for the taxonomic and hazard identification of microorganisms used as novel foods or in the production of novel foods are listed in section 1.2 and Appendix A, according to relevant EFSA guidance documents (EFSA FEEDAP Panel, 2018; EFSA, 2021e). Scientific requirements for compositional analysis of microorganisms intentionally used in the food chain are not addressed by EFSA FEEDAP Panel (2018) or EFSA CEP (2021), but by EFSA GMO Panel (2011), which also defines the GMM categories for the purpose of the risk assessment. The Panel considers that no change to the Guidance is needed.
557	Novonesis (merger of former Novozymes and Chr. Hansen)	page 25, lines 795-798: We would like to mention that the comparative approach may not adequately address the unique risks associated with the novel food itself. Additionally, determining an appropriate comparator can be subjective and context-dependent because comparing novel foods to existing ones can be challenging due to variations in composition, processing methods, and biological effects. For foods with no existing counterparts, the comparative approach becomes ineffective as it may not address unique risks associated with novel ingredients or production methods. We propose to indicate more clearly that a comparison with a conventional food is optional and not mandatory, since it is not always possible.	The text has been revised to provide further clarity regarding the comparative approach.

Comment number	Commentor	Comments	EFSA NDA Panel responses
591	AseBio - Spanish Bioindustry Association,	1. Line: 749 Include microorganisms and microbial biomass 2. Line: 767-768 Proposal to amend sentence to include 'comprehensive' i.e. '…a comprehensive literature search (e.g. based on EFSA, 2010)' The systematic review, which is provided as the reference, is a very heavy procedure, and should not be required in all cases. The guidance mentions elsewhere 'comprehensive', which should give more flexibility to the way the literature search is carried out. 3. Line: 787 The reference is outdated in particular as category 1 and 2 products are concerned. Replace the reference by e.g. references to EFSA FEEDAP Panel (2018) and EFSA CEP Panel (2021), or make a reference to Annex A in this draft guidance	1. Please refer to the response to comment 328. 2. Please refer to the response to comment 328. 3. Please refer to the response to comment 328.
613	Cellular Agriculture Europe	1. Line 762: 'antinutrients' are not defined until the toxicology section 9.2.1 2. Lines 1422-1427. This definition ideally needs to be moved to Section 3.3 or at least cross referred to in Section 3.3 so the labs know specifically what to consider for analysis. In addition, we would also point out that many antinutrients are in grains and legumes. There are growth factors derived from plants. In which case, would they automatically be ruled out because of presumed risk of antinutrient activity?	1. Please refer to the response to comment 23. 2. Please refer to the response to comment 23. The Panel notes the rest of the comment but considers that a detailed expansion of this section goes beyond the scope of this Guidance.
651	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Lines 754-755. 'The amount of unidentified components should be indicated and should be as low as possible.': Should this be understood to mean that anything that can technically be identified should be identified? To what length should the applicant go to minimise the amount of unidentified components? What is considered a reasonably low amount of unidentified components?	The compositional analysis should be as detailed as possible and reasonable. Emphasis must be placed on substances that may pose safety concerns as well as on compositional aspects related to the identity of the novel food. The amount of unidentified components should be minimised as much as possible. The extent of sufficient analysis is linked to the novel food itself and should be considered on a case-by-case basis. The Panel considers that no change to the Guidance is needed.

Comment number	Commentor	Comments	EFSA NDA Panel responses
674	Atova Regulatory Consulting SL	1. (Line 762, page 24) Where it refers to antinutrients, we suggest that a reference to Section 9.2.1 is made where antinutrients are discussed further. 2. (Line 774-775, page 25) 'Any substances of concern derived from starting materials (e.g. plants, algae, fungi) should be classified according to their chemical structure.' Please provide clarification on what is means to classify according to chemical structure. 3. (Line 792-794, page 25) Please confirm number of batches to be analysed for viable and non-viable cells.	1. Please refer to the response to comment 23. 2. The text has been revised to provide further clarity. 3. Please refer to the response to comment 666 and 701.
703	FoodDrinkEurope	1. [Line 755] The guidance should mention what 'as low as possible' can mean in terms of quantifiable values with some examples in brackets 2. [Line 762] There is a need to provide a definition of 'antinutrients' in the text.	1. Please refer to the response to comment 651. 2. Please refer to the response to comment 23.

Table 29: 3.4 Stability

Comment number	Commentor	Comments	EFSA NDA Panel responses
24	Undisclosed (Personal Capacity)	Lines 799-829 It would be useful to add here that dossiers can be submitted with ongoing shelf-life stability studies, such that the data accumulates as the scientific evaluation proceeds and the shelf life is always only what the latest timepoint demonstrates. This is a practical consideration as companies cannot wait 2 years before submitting a dossier, so a compromise case-by-case approach has always been applied	It is the responsibility of the applicant to timely prepare and present their data, including those produced through the stability studies which shall cover at least the end of the proposed shelf life. It should be noted that complete stability results are essential for setting specifications and investigating respective compliance. The Panel considers that no change to the Guidance is needed.
110	Food Fermentation Europe	1. Lines 799 to 829 page 26 discuss stability testing requirements. Real-time stability studies can take more than 2 years to complete, and most Small and Medium Enterprises cannot wait two years before submitting their dossier. Therefore	1. Please refer to the response to comment 24. 2. Stability testing under accelerated conditions may be used as an

Comment number	Commentor	Comments	EFSA NDA Panel responses
		Food Fermentation Europe respectfully requests that this section of the guidance document explicitly confirm that novel food dossiers can be submitted with ongoing shelf-life stability studies and can be considered complete and pass the suitability check phase of the EFSA review process without having complete stability studies, provided of course that such studies have been duly pre-notified to EFSA and results are provided in accordance with Regulation (EU) 2019/1381 before the end of the EFSA risk assessment phase. 2. Lines 824 to 825 page 26 also indicate that accelerated conditions can be used for stability testing. Food Fermentation Europe respectfully requests that the draft guidance more clearly and explicitly state that accelerated testing conditions are valid and accepted methods to demonstrate the stability of novel foods under the relevant intended conditions of storage.	alternative to real-time stability testing, as already mentioned in the Guidance. The applicant has to ensure that the extrapolation of the results from accelerated conditions to intended conditions of storage is duly evidenced. Otherwise, additional studies might be requested. It is up to the applicant to select real-time or accelerated stability testing, and all the methodology has to be valid and documented. The text has been revised to provide further clarity.
126	Medfiles Ltd	Comment: P25 L800: Why the need to state a self-life is not included in this section? Please consider adding it.	The text has been revised in line with the comment.
162	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Lines 799-829 We would recommend adding here that dossiers can be submitted with ongoing shelf-life stability studies, such that the data accumulates as the scientific evaluation proceeds and the shelf life is always only what the latest timepoint demonstrates. This is a practical consideration as companies cannot wait 2 years before submitting a dossier, so a compromise case-by-case approach could be considered. 2. Lines 814-818 For products with a long shelf life, production of five batches for stability – especially if this excludes pilot scale batches – is onerous and would lead to a lot of waste, which is not environmentally friendly. Novel products may not be placed on the market without pre-approval, which is a lengthy process, thus these batches would need to be scrapped. Accelerated shelf-life testing such as at higher temperatures is not suitable for viable microorganisms. The length of time to perform full shelf-life testing for five batches is extensive, particularly as notification of the study is required thus results from the preliminary investigative work cannot be included in support of the application. Suggest that full results for fewer batches be submitted at the time of application together with available data	1. Please refer to the response to comment 24. 2. The Panel considers that no change to the Guidance is needed. 3. Yes, please refer to the response to comment 110. Please note that at least five batches are to be tested with the same methodological approach.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		on additional batches under investigation. Subsequent data can be provided for the additional batches under the stability study as available during the risk assessment process Refer Guidance on identity and characterisation of feed additive https://doi.org/10.2903/j.efsa.2017.5023 ‘ 3. Lines 814-821 For stability testing, can all five batches be tested only in accelerated conditions? If not, what is a maximum number of batches that can be tested in accelerated conditions? Can submission of the application be done with only the first timepoint of stability ? whilst the other while be submitted during application assessment.‘	
189	Istituto zooprofilattico sperimentale delle venezie	The need to investigate stability is an issue for those willing to submit application for shelf stable product as shelf life study would be very long lasting. There is the risk that applicant reduce shelf life to shorten the study period. This is in contrast with strategies to reduce food waste.	Please refer to the response to comments 24 and 162.
210	EU Specialty Food Ingredients	1. Lines 814-818: For products with a long shelf life, production of five batches for stability – especially if this excludes pilot scale batches – is onerous and would lead to a lot of waste, which is not environmentally friendly. Novel products may not be placed on the market without pre-approval, which is a lengthy process, thus these batches would need to be scrapped. Accelerated shelf-life testing such as at higher temperatures is not suitable for viable microorganisms. The length of time to perform full shelf-life testing for five batches is extensive, particularly as notification of the study is required thus results from the preliminary investigative work cannot be included in support of the application. We suggest that full results for fewer batches be submitted at the time of application together with available data on additional batches under investigation. Subsequent data can be provided for the additional batches under the stability study as available during the risk assessment process. Please refer to the Guidance on identity and characterisation of feed additive (https://doi.org/10.2903/j.efsa.2017.5023). 2. Lines 824-827: Could you please clarify whether you mean accelerated condition approaches could be uses as long as chemical parameters are also monitored or that they can only be	1. Please refer to the response to comments 110 and 162. 2. The text has been revised to provide further clarity.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		used to monitor chemical parameters and not e.g. microbial parameters?	
254	The Good Food Institute Europe	Line 799-892: The monitoring period of the stability test has to cover at least the end of the proposed shelf life. Where there is a potential concern about the protein in the novel food, appropriate protein digestibility studies should be performed as part of the weight of evidence approach for the assessment of the nutritional, toxicological and allergenic properties (e.g., EFSA GMO Panel, 2017, 1096 2021, 2022) Comment: EFSA should clarify here whether safety dossiers can be submitted with ongoing shelf-life stability studies, providing the applicant provides sufficient data as part of this process. EFSA should provide greater clarity - potentially through explicit examples - of the digestibility studies and methods required to meet the definition of 'appropriate'. This could also include reference to specific sections of the EFSA GMFF guidance.	Please refer to the response to comments 24 and 318.
297	Katharina Julia Brenner (Personal Capacity)	1. Comprehensive Stability Testing Protocols (Page 25, Lines 803-813): Comment: The document mentions the importance of stability testing under intended storage conditions and potentially accelerated conditions. However, it lacks specific protocols for these tests, especially regarding the selection of representative batches and the rationale for testing frequencies at intermediate intervals. Providing a detailed protocol for both normal and accelerated conditions, including specific parameters to monitor based on the nature of the novel food, would enhance the reliability of the stability data. 2. Justification for Selected Parameters and Batches (Page 25, Lines 814-825): Comment: While the guidance suggests monitoring stability with at least five independently produced batches, there's no clear justification provided for choosing fewer batches in certain cases. A section elaborating on acceptable scientific arguments that could justify such variations would help applicants ensure compliance and maintain the integrity of their stability studies.	1. The Panel notes the recommendation but considers that the provision of testing protocols goes beyond the scope of this Guidance. 2. The stability testing has to be provided on at least five representative batches of the novel food that have been independently produced. The testing of a lower number of batches should be justified with scientific arguments, which must be provided by the applicant. The Panel acknowledges this recommendation but considers that providing such a list is not feasible due to the variability among novel foods and the different proposed conditions of storage and use.
390	Vaclav Bazata (Personal Capacity)	please, see abstract	No further feedback can be provided because the comment is unclear.

Comment number	Commentor	Comments	EFSA NDA Panel responses
438	Food Supplements Europe	Lines 814-817 While there may be justification for requesting analytical data for at least five representative and independently produced batches of the novel food (lines 577-579), this may be less so for asking also stability data to be presented on five batches, given the long duration of stability studies. The guidance should leave more flexibility as not for all novel foods, degradation products are formed, or breakdown occurs over shelf life. Although it is specified that testing of a lower number of batches is to be duly supported by scientific arguments, can the guidance elaborate on the nature of the scientific arguments that would be acceptable in this context?	Please refer to the response to comments 110, 162, and 297.
534	FoodchainID	In which cases would stability studies conducted in accelerated conditions be extrapolated and be considered as sufficient? Could EFSA illustrate it as an example?	Please refer to the response to comment 110.
563	International Probiotic Association - Europe (IPA Europe)	Lines 814 to 829 IPAEU: to accelerated shelf-life testing such as at higher temperatures is not suitable for viable microorganisms. Completing full shelf-life testing for 5 batches of non-commercial product is time intensive, e.g., taking into account the generally long shelf lives of lyophilised microorganisms and the requirement for notification of the stability study prior to beginning tests on product to be used in support of an application. To address this we propose that full results for fewer batches be submitted at the time of application – for example 3 batches are required for other regulated products. Alternatively, available data on additional batches under investigation can be provided post application validation and/or as available during the risk assessment process.	Please refer to the responses to comments 110 and 162.
614	Cellular Agriculture Europe	1. Lines 799 - 829: It would be useful to add here that dossiers can be submitted with ongoing shelf-life stability studies as long as the applicant can show they are underway and provide data. The data accumulates as the scientific evaluation proceeds and the shelf life is always only what the latest time point demonstrates. This is a practical consideration as companies cannot wait two years before submitting a dossier, so a compromise case-by-case approach has always been applied.	Please refer to the responses to comments 24, 110 and 162.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		2. Line 825: In our view, the Guidance could state more clearly and explicitly that 'accelerated conditions' are accepted as an alternative.	
675	Atova Regulatory Consulting SL	1. (Line 799-829, page 25-26) It is not feasible for an applicant to wait until stability studies are completed to submit their dossier. As such, we suggest that EFSA includes a statement saying that a dossier can be submitted with ongoing stability studies as long as the applicant can show they are underway and provide data. 2. (Line 824-825, page 26) 'Although it is advisable to submit stability testing studies under intended conditions of storage, accelerated conditions may be used as an alternative' Accelerated stability testing saves time and costs and would be very convenient in most novel food applications. Does EFSA accept accelerated stability studies for any type of product? Otherwise, could EFSA clarify when only accelerated stability studies are accepted to evidence the stability of a novel food? 3. (Line 827-828, page 26) Could EFSA kindly offer clarification on the requirements for extrapolating results from accelerated conditions to intended storage conditions? What methodologies would meet the criteria for sufficient evidence? For instance, would it be deemed acceptable to use the Arrhenius equation to calculate extrapolation to room temperature?	1. Please refer to the response to comment 24. 2. Please refer to the response to comment 110. 3. Please refer to the response to comment 110.
704	FoodDrinkEurope	1. [Line 814] We would welcome in the text a statement indicating the clear acceptance of 'accelerated shelf life' studies. If the novel food has a defined 2-year shelf life, it would be extremely difficult for a food business operator to wait 2 years before submitting a NF dossier (while waiting the results of the shelf-life study). It must be clearer that 'accelerated conditions' are accepted as alternative in the guidance document 2. [Lines 833-842] This is not practical when the NF is to be used in multiple food applications. We find the requirement to 'investigate what happens to relevant components of the novel food' too vague. The guidance should propose a strategy (e.g. a decision tree) to prioritise this assessment from a food category standpoint, processing conditions and measured outcomes.	1. Please refer to the response to comment 24. 2. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance. 3. Please refer to the response to comment 701.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		3. [Line 876] Same comment as above (line 665 on Compositional Data)	

Table 30: 3.4.1 Impact of processing on the novel food in the proposed-for-use matrices

Comment number	Commentor	Comments	EFSA NDA Panel responses
25	Undisclosed (Personal Capacity)	Lines 830-842 See above comment in Section 3.4 about ongoing studies and submission	Please refer to the response to comment 24.
41	Intertek	How many batches of the novel food should be tested per food matrix? Presumably not five novel food batches per matrix?	The Panel would like to emphasise that the number of batches to be tested for this purpose is intentionally not specified in the Guidance to provide flexibility, considering the heterogeneity, different scenarios, and specific needs related to this aspect. Therefore, the number of batches to be tested is up to the applicant, but it should be sufficient to allow for meaningful statistical analysis, typically at least three batches. Scientific justification for their decision should be provided. The Panel considers that no change to the Guidance is needed.
163	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Lines 830-844 Impact of food processing : For assessment of food processing impact, how many batches of the NF must be tested? 2. Lines 830-844 In general, it should be recognised that this section is not relevant if the novel food is an ingredient already authorised as food for the same applications but produced by a new manufacturing process. We would also like to underline that, in case the novel food is an ingredient intended to be added in different types of finished foods, it may be difficult, if	1. Please refer to the response to comment 41. 2. The Panel does not agree with the comment. Food ingredients produced through different processes may vary, for example, in their profiles of processing contaminants or precursor compounds. Regarding the matrices to be tested, the Guidance already

Comment number	Commentor	Comments	EFSA NDA Panel responses
		not possible, to investigate in all types of matrices taking into account extremes. 3. Lines 831-842 As written, the required testing in final food products is borderline limitless. The novel food manufacturer would not only have to test their own ingredient, but also test ALL potential processed foods may change in presence of that ingredient. For that, establish proper testing methods would need to be established (including validation of those methods) for many different matrices. Additionally, the novel food manufacturer may or may not be aware of all different possible applications where the final food product producer is using the novel food.	specifies that 'at least the extremes of the possible processing conditions' should be considered by the applicant. 3. Please refer to the response to point 2 of this comment.
190	Istituto zooprofilattico sperimentale delle venezie	It is important to consider processing effect on safety. However who is responsible for additional processing? I the applicant sell powder with approved intended use, he cannot have control on how the purchaser (processing powder into different products) acts. The processor should consider risk arising from this processing within is food safety management system. To date all the burden is on Novel food producer and nothing on businesses buying these for further processing. Also in this case it is hard to enforce this rules (from a competent authority point of view).	Investigating the impact of additional processing on the novel food when used as ingredient, as well as the occurrence of e.g., processing contaminants due to the presence of the novel food in the intended-for-use matrices is the responsibility of the applicant. The Panel considers that no change to the Guidance is needed.
211	EU Specialty Food Ingredients	1. Lines 830-844: We would suggest to indicate that this section is not relevant for applications concerning ingredients, which are alternatives to already authorised novel foods, but produced by a new manufacturing process, provided that their use in intended in the same food categories. 2. Lines 833-842: This is not practical when the NF is to be used in multiple food applications. The novel food manufacturer would not only have to test their own ingredient, but also test all potential processed foods may change in presence of that ingredient. For that, establish proper testing methods would need to be established (including validation of those methods) for many different matrices. Additionally, the novel food manufacturer may or may not be aware of all different possible applications where the final food product producer is using the novel food. The guidance should propose a strategy (decision	1. Please refer to the response to comment 163. 2. Please refer to the response to comment 704.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		tree?) to prioritise this assessment from a food category standpoint, processing conditions and measured outcomes (what means 'it should be investigated what happens to relevant components of the novel food', this is too vague).	
298	Katharina Julia Brenner (Personal Capacity)	1. Analysis of Processing Impact on Novel Food Components (Page 26, Lines 830-836): Comment: The guidance outlines the need to investigate the impact of processing on the novel food when used as an ingredient. However, it lacks specific protocols or methodologies on how to conduct these investigations effectively. The guidance should include standardised testing methods or frameworks that address the changes in the chemical, physical, and nutritional properties of novel foods under different processing conditions, including extreme conditions such as high temperatures or varying pH levels . 2. Investigation of Interactions and Contaminants (Page 26, Lines 836-840): Comment: The document mentions the need to study interactions with other food constituents and the formation of processing contaminants but does not provide details on how to identify and quantify these interactions and contaminants. Detailed guidelines on analytical methods and acceptable limits for processing-induced contaminants should be added to ensure food safety and compliance with regulatory standards . 3. Use of Model Systems in Processing Studies (Page 26, Lines 832-835): Comment: While model systems are suggested for studying the effects of processing, there is no clarification on the selection criteria or validation of these systems. The guidance should specify the characteristics of model systems that make them suitable for simulating actual food matrix conditions and processing methods. This would help ensure that the data generated are relevant and reliable for risk assessment purposes .	1. The Panel notes the recommendation but considers that provision of testing protocols goes beyond the scope of this Guidance. 2. The Panel notes the recommendation but considers that provision of detailed guidance on the analytical methods and acceptable limits goes beyond the scope of this Guidance. 3. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.
546	Bonumose, Inc.	Novel foods, by their definition are those that are new to the food supply. Therefore, it may be unknown or unpredictable how an ingredient may be used. If it is a versatile ingredient, it could be used in many different matrices and applications. It would not be possible for an ingredient manufacturer to provide	The uses of novel foods are specified and legally binding, ensuring that safety is assessed based on the proposed uses and use levels. Therefore, stability and safety

Comment number	Commentor	Comments	EFSA NDA Panel responses
		stability testing on every possible food application. Manufacturers have no interest in putting a product on the market that would risk consumer health and so it is in their interest to conduct their own testing to ensure that the stability of their food product is upheld and there are not any deleterious matrix interactions with a new ingredient. However, to require these companies to disclose such proprietary information is not feasible.	evaluations are conducted within these defined conditions. It is the applicant's responsibility to assess the behaviour of a novel food when used as an ingredient in the intended matrices. The Panel considers that no change to the Guidance is needed.
615	Cellular Agriculture Europe	See above comment in Section 3.4 about ongoing studies and submission	Please refer to the response to comment 24.
652	Pen & Tec Consulting S.L.U. (trading as Argenta®)	1. Lines 832-833. 'the impact on the novel food of this processing is to be investigated': How many batches of the novel food shall be tested when investigating impact of processing? 2. Lines 840-842. 'The use of proper comparators (e.g., the product manufactured with the same process/recipe without containing the novel food as ingredient) is necessary.': Should this be understood that investigating by conducting a literature search for possible impact of processing is not an option?	1. Please refer to the response to comment 41. 2. A literature search can be utilised to investigate and help determine the appropriate testing parameters.

Table 31: 4 Specifications

Comment number	Commentor	Comments	EFSA NDA Panel responses
9	Undisclosed (Personal Capacity)	846-856 Suggest swapping the order of the first two paragraphs. The order should match the order on specifications in the EFSA Opinions and the Union List.	The Panel does not agree with the proposal. The first paragraph explains the concept of specifications, while the second addresses their purpose from a risk management perspective.
40	Intertek	Lines 884 to 885 - does this mean that novel specifications are never required for parameters for which there are EU regulatory limits? For example, does this mean that novel food specifications are not required for contaminants that have limits specified in Regulation (EU) 2023/915?	Specifications can still be proposed for such parameters, although they are generally not needed. Any proposed specifications must not exceed the established legal limits,

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			such as those specified in Regulation (EU) 2023/915 for contaminants.
92	Undisclosed (Personal Capacity)	1. Lack of Detailed Methodological Specifications (Page 27, Line 845-875) Comment: The section specifies the parameters for chemical, physicochemical, nutritional, and microbiological characteristics but lacks explicit mention of the methodological standards to be used for testing these parameters. To enhance the scientific accuracy and reproducibility of results, it would be beneficial to reference standard methodologies such as those from ISO or the AOAC. Each parameter should have an associated validated method that specifies conditions such as LOD (Limit of Detection) and LOQ (Limit of Quantification). 2. Vague Descriptions of Microbial Strains (Page 27, Line 854-855) Comment: The document mentions using microbial strains without specifying the requirement for characterisation and preservation of these strains. It should include requirements for strain deposit in a recognised culture collection and details on the genetic stability and phenotypic traits of the strains over successive generations, which are crucial for maintaining consistency in safety assessments. 3. Insufficient Explanation for Stability Markers (Page 27, Line 867-869) Comment: Stability markers such as lipid oxidation or microbial hygiene indicators are mentioned without sufficient guidelines on how these should be quantified or their relevance to safety and quality. The document should include specific stability study protocols, indicating the conditions under which these markers are to be tested and the criteria for interpreting these results for food safety evaluations. 4. Ambiguities in Setting Specification Limits (Page 28, Line 871-874) Comment: While minimum and maximum specification limits are mentioned, the document does not sufficiently detail how these limits are derived. It should incorporate guidelines on the use of statistical analysis and risk assessment models to set these limits, especially for contaminants and nutrients critical to health. 5. Non-disclosure of Analytical Techniques (Page 28, Line 875) Comment: The section mentions analytical techniques without	1. Please refer to section 3.1 for information on the general requirements regarding analytical methods, compositional variability, sampling practices, and compositional analyses for characterising the novel food. It is the applicant's responsibility to select a valid or standardised methodology to provide the required data. The Panel considers that no change to the Guidance is needed. 2. Please note that the scientific requirements for the taxonomic and hazard identification of active agents, biomasses, and production strains are outlined in section 1.2 and Appendix A, in accordance with relevant EFSA guidance documents (EFSA FEEDAP Panel, 2018; EFSA, 2021e). It is the responsibility of the applicant or food business operator to select a valid or standardised methodology to provide the required data and ensure compliance with the specifications. Furthermore, as stated in Article 25(a) of Regulation (EU) 2283/2015, any changes that occur after the authorisation of the novel food that may impact its safety must be immediately reported to the European Commission. The Panel considers that no change to the Guidance is needed.

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		detailing the specific types or conditions under which these techniques are validated for novel foods. Adding references to specific types of equipment, calibration procedures, and validation studies would improve the reproducibility of results and compliance with regulatory standards.	3. Please refer to section 3.1 for general requirements related to analytical methods, compositional variability, sampling practices, and compositional analyses for characterising the novel food. Additionally, section 3.4 outlines the scientific requirements for assessing the stability of the novel food. It is the applicant's responsibility to select a valid and standardised methodology to provide the required data. The Panel considers that no change to the Guidance is needed. 4. The Panel notes the recommendation but considers that expanding the section goes beyond the scope of this Guidance. 5. Please refer to section 3.1 for general requirements related to analytical methods, compositional variability, sampling practices, and compositional analyses for characterising the novel food. The Panel considers that no change to the Guidance is needed.
108	Food Fermentation Europe	Lines 886 to 891 page 28 introduce a new requirement to assess the fraction of small particles in accordance with the recommendations set in the Guidance on Particle – TR even in conventional materials that do not meet the definition of engineered nanomaterials, and to consider the characterisation of the fraction of small particles when setting the specifications for the novel food product. As already discussed in our previous comments in Section 3, Food Fermentation Europe considers that this broad new requirement to demonstrate the absence of a fraction of nano-scale particles, or alternatively that this fraction of nano-scale particles is covered by the conventional	Please refer to the response to comment 109.

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		risk assessment as per the Guidance on Particle – TR, places an unreasonable and unnecessary additional burden on applicants to conduct potentially significant additional and costly analysis for novel foods of biological origin. The draft guidance itself acknowledges that this requirement is not needed for a number of novel food categories (lines 732-735 pages 23-24), but the exemption carved out by the document (lines 735-736, page 24) is too narrow to avoid unnecessary additional testing for many applicants. Based on the foregoing, Food Fermentation Europe respectfully requests that the draft guidance be revised to only require this small particle assessment for novel foods of biological origin that do not meet the definition of engineered nanomaterial when there is reason to believe that a fraction of small particles in the specific novel food of interest may cause a particular safety concern that would require specific consideration in establishing the specifications for the novel food product.	
142	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Lines 846-856 Suggest swapping the order of the first two paragraphs. The order should match the order on specifications in the EFSA Opinions and the Union List. 2. Lines 881-885 It is unclear why specifications that have EU regulatory limits would not be listed in the novel food specifications. Providing the listing would ensure compliance with the regulatory limits. 3. Lines 884-885 Some example of not mandatory EU regulatory limits would useful (are we talking contaminants limits such as pesticides residues, or any other type of specifications)?	1. Please refer to the response to comment 9. 2. Please refer to the response to comment 40. 3. Please refer to the response to comment 40.
186	Istituto zooprofilattico sperimentale delle venezie	Also in this case my doubt is about the sustainability of a system with a product based legislation. Also specifications are derived according to the current system, not according to ALOP, FSO etc but according to specific and few laboratory results. It is also unclear if they are to be intended as Process hygiene criteria of food safety criteria.	The Panel acknowledges the concerns expressed. In the EU, novel food specifications are developed based on current regulatory requirements and specific laboratory results. Specifications are intended to ensure the safety and identity of the novel food. Risk managers have the authority to amend these

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			specifications, including enlarging or narrowing them, regardless of the respective EFSA output. Depending on their nature, these specifications may serve as process hygiene criteria and/or food safety criteria.
195	EU Specialty Food Ingredients	Lines 881-885: We do not understand why the EU regulatory limits potentially applicable to the novel food should not be listed in the specifications. If there are EU regulatory limits, it's important to ensure compliance with those limits and thus include in the specifications.	Please refer to the response to comment 40.
285	Katharina Julia Brenner (Personal Capacity)	Lack of Specific Analytical Methods (Page 27, Lines 845-857): Comment: The document outlines the specifications for chemical, physicochemical, nutritional, and microbiological parameters but does not specify the analytical methods to be used. To improve reproducibility and accuracy, the guidance should include specific recommended methods such as HPLC for chemical assays or PCR for detecting specific microorganisms. This ensures that data from different laboratories are comparable and reliable. Inconsistency in Setting Specification Limits (Page 27, Lines 857-869): Comment: While the document discusses the importance of setting specification limits, it lacks a detailed explanation on how these limits should be established based on scientific data. The guidance should provide a framework for setting these limits, possibly including statistical methods for data analysis and risk assessment models to ensure that the limits are both safe and practical. Ambiguity in Handling Batch Variability (Page 27, Lines 857-869): Comment: The section mentions using batch-to-batch analysis data to support specification limits but does not address how to handle significant variability between batches. Guidelines on acceptable variability ranges and how to adjust specifications based on batch analysis would provide clearer direction for ensuring consistent quality of the novel food. Inadequate Consideration of Novel Food Stability (Page 27, Lines 867-869): Comment: Stability is briefly mentioned; however, detailed protocols for stability testing under both	Please refer to the response to comment 92.

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		normal and accelerated conditions are lacking. The document should specify standard stability testing protocols, including recommended conditions and time points, to adequately assess the shelf life and safety of the novel food over time. Insufficient Guidelines on Contaminant Limits (Page 27, Lines 865-869): Comment: There is a mention of testing for contaminants such as heavy metals and mycotoxins, but no specific limits or testing frequencies are provided. The guidance should include maximum allowable limits for common contaminants and specify the frequency of testing, especially for novel foods prone to contamination. Clarity on Compliance with Union List of Novel Foods (Lines 850-852, page 27): Comment: The document indicates that risk managers will decide on the inclusion and updating of the Union list based on the specification parameters provided. It would be beneficial to outline what specific aspects of the specifications are critical for these decisions, such as threshold levels for contaminants or critical nutrients, to aid applicants in preparing their submissions.	
434	Food Supplements Europe	Lines 849- 856 The specifications should not only serve as a tool for risk managers but also for the risk assessor because these are the (sole) criteria that will determine whether the food as placed on the market by any food business operator (and not only the applicant) complies with the authorisation. All data requests should therefore be in function of assessing whether a novel food is safe when placed on the market in accordance with these criteria.	There is no disagreement that specifications are an important tool for ensuring the safety of a novel food once it is on the market. However, this aspect pertains more to compliance and risk management rather than risk assessment. The specifications are used to determine whether the food, as placed on the market by any food business operator (and not just the applicant), adheres to the authorisation requirements. Regarding risk assessment, to anticipate the exposure to substances of possible safety concern from the novel food, the maximum amount of these substances expected to occur in the novel food, such as the maximum

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			limit set in the specifications, is to be considered.
541	Bonumose, Inc.	We recommend a reinstatement of 'substantial equivalence' (Regulation (EC) No. 258/97) for the approval of novel foods. The safety of a novel food is entirely dependent upon the characteristics of the final food product. If a final food product produced by an alternative method meets the same specifications as when that product is produced by the existing method, the product produced via the alternative method would not alter the way in which it is metabolised by the consumer. Because the products and their safety assessments would be identical, granting 'substantial equivalence' to that produced by the alternative method would reduce administrative burdens on EFSA and industry barriers to innovation. Reinstatement of 'substantial equivalence' would be an important step towards addressing the public need for innovative technologies that can reduce cost and increase availability of healthy foods.	Please refer to the response to comment 306.
596	Cellular Agriculture Europe	Lines 846 - 856: We suggest swapping the order of the first two paragraphs. The order should match the order on specifications in the EFSA Opinions and the Union List. Lines 884 - 885: 'If EU regulatory limits are applicable for the novel food, then they do not have to be necessarily listed in the specifications' Can EFSA add examples?	Please refer to the response to comments 9 and 40.
640	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 861. 'proximate analytes (protein, lipids, carbohydrates, ash, and moisture),': Should this include dietary fibre?	Total carbohydrates include all carbohydrate types present in the food, such as sugars, starches, and dietary fibre. Depending on the type of novel food, dietary fibre may be listed separately in the specifications to provide a detailed breakdown of its content.

Table 32: 5 History of use of the novel food and/or of its source

Comment number	Commentor	Comments	EFSA NDA Panel responses
348	GAIKER	Interested in knowing the EFSA's compliance with the FDA's dossiers of General Recognised as Safe (GRAS) in order to expedite the authorisation of alternative proteins in EU	The Panel wishes to highlight that the scope of this Guidance is to assist applicants with the scientific requirements in preparing novel food applications. Thus, it is outside of the scope of this Guidance to indicate EFSA's compliance with the FDA's dossier.

Table 33: 5.2 History of use of the novel food

Comment number	Commentor	Comments	EFSA NDA Panel responses
102	Undisclosed (Personal Capacity)	Insufficient Historical Consumption Data (Page 28, Line 900-903) Comment: The section lacks detailed historical consumption data for novel foods used outside the EU. To improve scientific substantiation, it should include quantitative data on consumption patterns, frequency, and serving sizes, similar to traditional food assessments. Including comprehensive dietary intake data would provide a clearer risk assessment basis. Vague Description of Non-Food Uses (Page 28, Line 901-902) Comment: The document mentions non-food uses of the novel food but does not detail how this information impacts safety assessments. Clarifying how historical non-food uses can inform toxicological safety for food use would enhance the document's rigor. Examples from industrial or medicinal uses could provide insights into potential toxicities. Lack of Systematic Review for Safety Outcomes (Page 29, Line 906-911) Comment: While the need for a comprehensive literature review is noted, the section does not specify the systematic review methodology to be used. Detailing the process, including specific databases, search terms, inclusion	The Panel acknowledges the comment. Examples of consumption data for the novel food have been included in the Guidance. Additionally, information about non-food uses may indicate potential safety concerns that could warrant further investigation in toxicological studies. The EFSA Guidance 2010 on systematic reviews, referenced in this section, provides specific instructions on conducting systematic reviews, including details on databases and search terms. Examples of how to handle and prepare the novel food have also been added to the Guidance. The Panel would like to emphasise that the purpose of this Guidance is to provide instructions to applicants on the information

Comment number	Commentor	Comments	EFSA NDA Panel responses
		and exclusion criteria, and the method for quality assessment of studies, would strengthen the reliability of the safety assessment. d)Incomplete Data on Handling and Preparation (Page 29, Line 904-905) Comment: The section should expand on the historical handling and preparation methods of the novel food to assess its safety and stability. Information on traditional cooking methods, storage conditions, and any known processing contaminants should be included to provide a complete safety profile. General Lack of Cross-References to Toxicological Data (Page 29, Line 900-911) Comment: The document fails to cross-reference historical use data with existing toxicological and allergenicity data. Establishing a link between historical use and scientific safety data could aid in identifying potential risks and safe consumption levels more effectively.	required in a dossier. Generally, the Panel cannot provide rationales for all requested information or pre-determine how this information will be utilised or its impact on the overall assessment.
230	Planet A Foods GmbH	- ll. 914 f: (e.g. other varieties or subspecies or related species of the same genus or family). → Add 'or on foods with highly similar chemical composition (for Novel Foods as drop-in replacements for existing foodstuffs with highly similar or identical composition	The text has been revised in line with the comment.
676	Atova Regulatory Consulting SL	(Line 910, page 28) 'Where applicable, the published literature should be reviewed by taking into account systematic review principles (EFSA, 2010)'. Please provide examples on when it's applicable to follow systematic literature review principles	The citation of EFSA (2010) is intended to guide applicants on how to perform a systematic review of publications when applicable. It is ultimately up to the applicant to decide whether to review publications based on their nature and scope. Therefore, the Panel considers that no change to the Guidance is needed.

Table 34: 6 Proposed uses and use levels and anticipated intake of the novel food

Comment number	Commentor	Comments	EFSA NDA Panel responses
93	Undisclosed (Personal Capacity)	Lack of Specific Intake Scenarios (Page 29, Line 920-923) Comment: The section describes the need for estimates of novel food intake by the EU population based on proposed uses and use levels, yet it lacks detailed intake scenarios considering different consumer habits and regional dietary preferences. To improve the robustness of the dietary exposure assessment, it should include varied consumption patterns reflecting the diversity of the EU population, as well as specific scenarios for high-risk groups such as infants or individuals with certain health conditions. Insufficient Details on Use Levels (Page 30, Line 946-948) Comment: The document specifies the intended uses of the novel food but does not adequately detail the maximum allowable use levels for different food categories. It is critical to provide a detailed breakdown of these levels in a tabulated format, including specific concentration limits per food category to ensure clarity for risk assessors and compliance with safety margins.	To perform intake scenarios for the intended uses of the novel food, the Guidance refers to the EFSA FAIM and DietEx tools. These exposure tools use individual consumption data from the EFSA Comprehensive Food Consumption Database, collected through dietary surveys across various EU countries. They provide estimates (mean and 95th percentile) for different population groups, including infants, children, adolescents, and adults. Therefore, the Panel does not see the need to revise the Guidance. It is the responsibility of applicants to specify the intended uses and maximum levels for the novel food. As stated in the Guidance, applicants should consider appropriate margins of exposure, or 'uncertainty factors,' as suggested by the EFSA Scientific Committee (2012a) when proposing uses and use levels. Therefore, the Panel considers that no change to the Guidance is needed.
143	Synpa, French association of specialty food ingredients manufacturers and distributors	General comment : In this section there appears to be nowhere for the applicant to specify labelling requirements: what name is proposed on the ingredient label.	Under section 6.6, the applicant is required to specify any precautions, restrictions on use, and specific population groups that should avoid consuming the novel food. It is the responsibility of Risk Managers to impose any necessary labelling restrictions when authorising the novel food. Therefore, the Panel

Comment number	Commentor	Comments	EFSA NDA Panel responses
			considers that no change to the Guidance is needed.
187	Istituto zooprofilattico sperimentale delle venezie	This point is very complex and its application very problematic even according to the previous guidelines. No consumption data exists fo specific novel food ingredients. The scenarios that have to be considered for the definition of anticipated intake and consequently for the setting of maximum use levels are not worst case scenarios but instead they are non-realistic scenarios. In the case of edible insects powders, for example, intended to be added to bakery products, pasta and so on, the need to simulate a scenario in which consumers ALWAYS eat bakery product containing the maximum allowed amount of powder, leads to a big overestimation of exposure. To solve this issue most applicants reduce the proposed maximum use levels with several consequences. This impairs the role (if any) that some product can have on sustainability, nutrition and so on making use of novel food ingredient more a marketing choice and not a real contribution to diet variability. I think that several product already on the market would have not been approved if they had to undergone this kind of approval procedure. On the other hand for certain product the choice of country consumption data should not be causal but based on worst case scenarios (highest consumer).	The common approach to estimating the anticipated daily intake of novel foods involves using maximum proposed uses and use levels, along with actual chronic food consumption data. These consumption data are collected by EFSA through national dietary surveys across the European Union. When evaluating the safety of the intended uses and use levels of a novel food, the Panel considers worst-case exposure scenarios, including the highest 95th percentile intake. Therefore, the Panel considers that no change to the Guidance is needed.
196	EU Specialty Food Ingredients	We would like to take the opportunity to thank EFSA for their efforts to enhance the current guidance and to give more detailed descriptions of the requirements for novel food applications especially in this but also in every other chapter as this enables applicants to submit dossiers in a higher quality.	The Panel appreciates the recognition of EFSA's ongoing efforts.
548	Novonesis (merger of former Novozymes and Chr. Hansen)	page 29, lines 918-927: We would like to take the opportunity to thank EFSA for their efforts to enhance the current guidance and to give more detailed descriptions of the requirements for novel food applications especially in this but also in every other chapter as this enables applicants to submit dossiers in a higher quality.	The Panel appreciates the recognition of EFSA's ongoing efforts.
597	Cellular Agriculture Europe	General comment: in this section we note the absence of specific labelling requirements for applicants: 1. What name is	Please refer to the response to comment 143.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		proposed on the ingredient label 2. What advisory warnings are proposed if any	

Table 35: 6.1 Target population

Comment number	Commentor	Comments	EFSA NDA Panel responses
26	Undisclosed (Personal Capacity)	Lines 916-927 General comment – in this section there appears to be nowhere for the applicant to specify labelling requirements: 1. What name is proposed on the ingredient label 2. What advisory warnings are proposed if any	Please refer to the response to comment 143.
57	Specialised Nutrition Europe (SNE)	Page 29 line 936 The word 'general population' can be exclusive and there might be some target groups that would fall out of the scope. We suggest that it should be phrased in a way that the wording is not restraining from applying for novel food, including in those target groups.	The term 'general population' is widely used within EFSA's scientific assessments to denote the entire population, encompassing individuals of all ages and sexes. This term is intended to represent an average or typical consumer within the EU, allowing for a broad risk assessment approach. The Panel considers that the term 'general population' is appropriate to convey the intent to include the entire population in the assessment of novel foods while still providing the flexibility to focus on specific groups as needed (e.g. infants, children, pregnant and lactating women). Thus, the Panel does not consider it necessary to change the use of the term 'general population' in the guidance.

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127	Medfiles Ltd	Comment: P29L935: This is important information – when it is possible to restrict the consumption of the novel food and when not.	Section 6.1 outlines situations in which the consumption of a novel food can be limited to a specific segment of the target population. For example, when the novel food is proposed for use as a food supplement or in foods tailored for specific groups as defined by Regulation (EU) No 609/2013. The Guidance also clarifies that if the novel food is meant to be included as an ingredient in foods, it can only be targeted at the general population, without the option to restrict it to specific subgroups within the general population. Therefore, the Panel considers that no change to the Guidance is needed.
212	EU Specialty Food Ingredients	Lines 931-934: It should be clearly mentioned that food supplements for adults are one exception with possible labelling of 'should not be consumed by infants, children, and adolescents younger than x years of age'.	The Guidance includes the restriction of the target population to adults as an example when a novel food is intended for use as a food supplement. The decision to implement labelling that restricts the use to a specific group of the population will be made by risk managers. Therefore, the Panel considers that no change to the Guidance is needed.
277	Ministry of Regional Affairs and Agriculture	Line 940- Could foods for infants and young children be included as an example?	The text has been revised, and examples have been added to the Guidance.
439	Food Supplements Europe	Lines 931-934 The statement 'When the novel food is intended to be added as ingredient to foods, or to be consumed as whole food, the proposed target population is the general population including all age groups (i.e. cannot be restricted to subgroups thereof) in accordance with Article 5(6) of Commission	The text has been revised, the legal text from Article 5(6) of Commission Implementing Regulation (EU) 2017/2469 has been included in the Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		Implementing' is not a correct reflection so the legal text which states that 'Where it cannot be excluded that a novel food intended for a particular group of the population would be also consumed by other groups of the population the safety data provided shall also cover those groups.' It would be best to quote the legal article to avoid confusion. In addition, this legal provision does not prevent a novel food to be intended only for a specific group of the population, e.g. where this is specified by appropriate labelling. In such cases, the EFSA opinion should clearly reflect both what would be the safety conclusion for the general population, as well as for the intended population group requested by the applicant, so the risk manager can consider both and implement appropriate risk management measures where appropriate (such as labelling).	
705	FoodDrinkEurope	[Lines 940 - 943] It should be clearly mentioned that food supplements for adults are one exception with possible labelling of 'should not be consumed by infants, children, and adolescents younger than x years of age'.	Please refer to the response to comment 212.

Table 36: 6.2 Proposed uses and use levels

Comment number	Commentor	Comments	EFSA NDA Panel responses
27	Undisclosed (Personal Capacity)	Lines 944-976 Very recent EFSA Opinions no longer even include the actual proposed food uses, based on FAIM categories, which is what the Union List is based on. They simply refer to Dietex categorisation, which do not match the Union List. This leads to ambiguity and it is important to resolve this. EFSA opinions must have in them the actual proposed food categories that will appear in the Union List, even if in an appendix. EFSA should also provide a cross-reference list between FAIM and Dietex Categories and keep this updated. The two categorisation systems will otherwise drift further and further apart and the EFSA opinions will become less identifiable with what is in the Union List and lead to errors	When outlining the intended uses for a novel food, applicants have the option to utilise either the FAIM tool categories or the FoodEx2 categories available in the DietEx tool. The expected daily intake of the novel food will be determined based on the intended uses and maximum use levels, using either the FAIM tool or the DietEx tool. As the DietEx tool offers more detailed food categories compared to the FAIM tool, it allows

Comment number	Commentor	Comments	EFSA NDA Panel responses
		transcribing otherwise. It is obvious that no long-term good will come of this continued mismatch.	for a more precise estimation of the intake of the novel food. The guidance recommends that applicants use broad FoodEx2 categories instead of overly specific ones (for example, 'yogurts' in general rather than specific types of yogurts; 'biscuits' in general rather than specific types of biscuits). This recommendation has been included to facilitate the authorisation process. The anticipated daily intake of the novel food estimated using either the FAIM tool or DietEx tool will be utilised to evaluate the safety of the novel food at the proposed uses and use levels. Therefore, the Panel considers that no change to the Guidance is needed.
58	Specialised Nutrition Europe (SNE)	Page 931 line 987 and 996-998 It is important to note that Foods for Special Medical purposes (FSMPs) are not accurately represented in terms of food consumption patterns in the food surveys. SNE therefore suggest that for FSMPs, a specific clarification note is added that the applicant may deviate from those default scenarios with justifications on intended use.	When a novel food is meant to be incorporated into Foods for Special Medical Purposes (FSMPs), applicants must specify that its conditions of use should align with Regulation (EU) No 609/2013. In this case, applicants should not select the food category FSMP in either the FAIM tool or the DietEx tool. The text has been revised.
231	Planet A Foods GmbH	e) does 'liquid or solid' for fats (depends on temperature) fall under this category (chocolate fondue?)	Bullet point e) addresses situations where the novel food is proposed in various forms (e.g., dried, frozen, powdered). If the novel food is a fat, the applicant should specify its form (liquid or solid). For novel foods intended for use in chocolates, the applicant should detail the intended uses within chocolates using the FAIM

Comment number	Commentor	Comments	EFSA NDA Panel responses
			tool or FoodEx2 categories available in the DietEx tool. The Panel considers that no change to the Guidance is needed.
278	Ministry of Regional Affairs and Agriculture	Line 949-953 Could the food categories of the additive regulation also be considered? Their use would significantly help to carry out the controls in the Member States, as the food categories are also explained in the Commission's guidance document.	The Guidance allows applicants to use food additive categories to specify the intended uses of their novel food. Specifically, the FAIM Tool food categories can be employed to indicate these uses, as outlined in bullet points a) and b) under section 6.2. The Panel considers that no change to the Guidance is needed.
440	Food Supplements Europe	Lines 959-960 The guidance states that the choice of overly specific food categories may cause difficulties for national authorities in the authorisation process of the novel food. Can the guidance provide more explanation as the nature and reasons underlying these difficulties?	As the authorisation process falls outside of EFSA's remit, the Panel considers that references to potential challenges risk managers may face during the authorisation of novel foods are beyond the scope of the Guidance. The text has been revised, with the sentence referred to in this comment being deleted.
616	Cellular Agriculture Europe	Lines 944 - 976: Very recent EFSA Opinions no longer include the actual proposed food uses, based on FAIM categories, which is what the Union List is based on. They simply refer to Dietex categorisation, which does not match the Union List. This leads to ambiguity and it is important to resolve this. EFSA Opinions must have in them the actual proposed food categories that will appear in the Union List, even if in an appendix. We also invite EFSA to provide a cross-reference list between FAIM and Dietex Categories and keep this updated. The two categorisation systems will otherwise drift further and further apart and the EFSA opinions will become less identifiable with what is in the Union List and lead to errors transcribing otherwise. It is obvious that no long-term good will come of this continued mismatch.	Please refer to the response to comment 27.

Comment number	Commentor	Comments	EFSA NDA Panel responses
677	Atova Regulatory Consulting SL	(Line 977, page 31) The intake assessment of a novel food from food supplements should be calculated based on the recommended daily intake of the food supplement, not using Dietex or FAIM tools. Could EFSA please confirm if this approach is correct?	The Panel confirms that the interpretation is accurate. The text has been revised to provide further clarification that food supplements should not be chosen in the FAIM tool or DietEx tool, as well as total diet replacements for weight control and foods for special medical purposes.

Table 37: 6.3 Anticipated intake of the novel food

Comment number	Commentor	Comments	EFSA NDA Panel responses
311	Food Safety & Nutrition Consultancy	Introduce (and allow) also probabilistic intake assessments as such are reflecting more realistic intake scenario's over worst case scenario's.	The use of a deterministic or a probabilistic approach when estimating dietary exposure depends on different factors, including the available data and other information. In many cases, the use of probabilistic models is not needed if a lower-tier assessment (e.g., deterministic approach) already rules out the presence of a health risk. In the novel foods domain, only two values are provided as regard the levels to be used, analytical data from batch-to-batch analysis and maximum levels. Having only two values makes it difficult to apply any simulation as part of the probabilistic approach. Simulating the consumption of the different uses of a particular novel food/ novel food ingredient across the population might be a possibility, but this would imply having certain

Comment number	Commentor	Comments	EFSA NDA Panel responses
			information (e.g., market shares) in order to conduct adequate simulations.
617	Cellular Agriculture Europe	Lines 999 - 1002: We would welcome a listing of the EU countries to be considered from the EFSA Comprehensive Food Consumption Database. There is currently no consolidated data for Europe and the database is listing the food intake from recent and older food surveys, and it is unclear which ones must be selected. In addition, a product can be put in the market of one country and consumed in another one in Europe. There are food surveys from the UK but the UK is no longer part of the EU: does it mean that the UK food surveys must not be considered?	The summary statistics of consumption in the EFSA website are currently organised in such a way that allows the selection of consumption data at different FoodEx levels, either chronic or acute consumption, consumption by gender, and to focus on either the whole population/all days or on consumers only/consuming days only. Together with consumption data from 24 out of the 27 EU countries, dietary surveys are also available for pre-accession countries (Bosnia and Herzegovina, Montenegro, Republic of North Macedonia, Serbia) and United Kingdom. In addition, for some of the 24 EU countries and for certain age classes more than one dietary survey could be available; the most recent surveys can be selected by using the available filter in the EFSA website. When conducting a dietary intake assessment for a specific novel food/novel food ingredient, the most recent dietary surveys from all the available EU countries should be selected, i.e., neither pre-accession countries nor the United Kingdom should be selected. This selection is already implemented in DietEx and FAIM exposure models.
653	Pen & Tec Consulting	Lines 1017-1018. '(e.g. safety of edible kernels of Jatropha curcas L. which would reasonably be consumed as peanuts EFSA	The text has been revised in line with the comment.

Comment number	Commentor	Comments	EFSA NDA Panel responses
	S.L.U. (trading as Argenta®)	NDA Panel, 2022b).`: Suggested edit: (e.g. safety of edible kernels of Jatropha curcas L. which would reasonably be consumed as an alternative to peanuts EFSA NDA Panel, 2022b).	
678	Atova Regulatory Consulting SL	(Line 990-995, page 31) The maximum P95 intake of the novel food is not representative of the average/common consumption of food, and it restricts the maximum proposed uses of novel foods, especially when these contain mineral or vitamins for which dietary reference values are set. It may be more realistic to base the intake of minerals and vitamins from the novel food based on the maximum mean intake of the novel food rather than on the maximum P95 intake of the novel food. Our suggestion is to calculate the maximum intake of minerals and vitamins from the novel food based on the intake calculated from the maximum mean intake of the novel food, and compare these values with dietary reference values, since we consider that the maximum mean is more representative of real consumption patterns than the maximum P95.	The Panel recognises that the maximum P95 intake of a novel food does not reflect the average consumption of the novel food. However, in assessing novel foods, the Panel must also consider the consumption habits of high consumers in the EU population, such as those represented by the P95 percentile. Additionally, the Panel conducts safety assessments of both novel foods and their constituents, including vitamins and minerals. Therefore, the Panel does not evaluate the exposure to vitamins and minerals from novel foods in relation to dietary reference values. Instead the exposure of vitamins and minerals from novel foods is compared against health-based guidance values, such as UL. It is important to note that when assessing the exposure to vitamins and minerals from novel foods, the background diet's contribution must be taken into account (see section 6.4 on combined exposure).
706	FoodDrinkEurope	[Lines 999-1002] We would welcome a listing of the EU countries to be considered from the EFSA Comprehensive Food Consumption Database. There is currently no consolidated data for Europe and the database is listing the food intake from recent and older food surveys, and it is unclear which ones must be selected. In addition, a product can be put in the market of one country and consumed in another one in Europe. For example, there are food surveys from the UK but the UK is no more part of	Please refer to the response to comment 617.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		EU: does it mean that the UK food surveys must not be considered?	

Table 38: 6.4 Combined intake considering other sources of the novel food or its main constituents

Comment number	Commentor	Comments	EFSA NDA Panel responses
128	Medfiles Ltd	P32 L1043: Unclear. Could EFSA clarify what's meant 'section 9 is to be advised', please. Is it meant that 'an advice is to be included 'or what's meant.	The text has been revised to clarify to refer to section 9 for exposure to nutrients and antinutrients.
164	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 1025-1045 What if the novel food induces an over exposure to a specific substance which is already limit? EFSA tools do not take substitutions into account. Lines 1028-1033 This statement raises a question, if there is already a consumption of nutritive X at the high end of the Recommended Daily Intake/Allowance (RDI/RDA), does that mean that any novel food with nutritive X is not permitted as a replacement, smothering all change and innovation? Additionally, current EFSA processes do not consider replacement of existing foods by the novel food and may lead to overestimation of exposure. As the novel food may actually reduce exposure through replacement, we suggest EFSA work to adjust their intake calculations to address replacement of current foods with novel foods.	The Panel acknowledges that novel foods can be added to foods that may partly replace foods that significantly contribute to the intake of specific compounds (e.g. vitamins, minerals) in the diet. When replacement occurs, applicants should consider the potential double accounting which derives from the novel food and the diet. Due to the complexity of this exercise and the variety of novel foods and their intended uses, EFSA Tools available for exposure cannot be modified to account for replacement. However, the Guidance has been updated to include the need to consider the double accounting of compounds.
213	EU Specialty Food Ingredients	Lines 1027-1033: We believe that this is a potential issue when the general background (in particular for a contaminant) is already linked to a dietary intake level close or above the reference value. Considering that the EFSA tools do not consider replacement of existing food by the NF, it may lead to an over exposure (e.g., considerations concerning lycopene in the EFSA	Please refer to the response to comments 164 and 311.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		opinion on the safety of yellow/orange tomato extract as a novel food). For instance, if there is already a consumption of nutrient X at the high end of the Recommended Daily Intake/Allowance (RDI/RDA), does that mean that any novel food with nutrient X is not permitted as a replacement, smothering all change and innovation? Therefore, we would encourage EFSA to better address in their tools the replacement of conventional foods or already marketed NF by the proposed new NF.	
707	FoodDrinkEurope	(Lines 1027–1033) When assessing the combined intake considering other sources of the novel food or its main constituents we believe EFSA should address better in their guidance the fact that the proposed new NF would replace conventional foods or already marketed NF.	Please refer to the response to comment 164. Applicants should also provide considerations on the exposure from already authorised novel foods which are already on the market. The text has been revised to reflect this requirement.
312	Food Safety & Nutrition Consultancy	Introduce (and allow) also probabilistic intake assessments as such are reflecting more realistic intake scenario's over worst case scenario's.	Please refer to the response to comment 311.
429	Solar Foods	The term 'high daily intake' is operationally defined as the 95th percentile, denoting a considerable level of consumption. A more prudent approach would be to consider the 90th percentile, reflecting a still substantial but less extreme consumption level. It's essential to acknowledge that while some consumers may not maintain a balanced diet, their habits shouldn't dictate the consumption standards for all new foods,	The standard practice at EFSA involves using the 95th percentile intake estimates for risk assessments. It is worth noting that in certain domains, higher percentiles, such as the 99th, are also utilised. Therefore, the Panel will follow the existing standards set by EFSA for the safety assessment of novel foods.

Table 39: 6.5 Estimate of exposure to undesirable substances and other substances of possible safety concern

Comment number	Commentor	Comments	EFSA NDA Panel responses
165	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 1048-1050 Toxicology testing would identify and establish safe levels of these impurities. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has guidances (Q3A and Q3B) on qualifying impurities and EFSA should consider the same type of approach for novel foods. Lines 1054-1059 This statement raises a question, if there is already a consumption of nutritive X at the high end of the Recommended Daily Intake/Allowance (RDI/RDA), does that mean that any novel food with nutritive X is not permitted as a replacement, smothering all change and innovation?	It is essential to identify substances of potential concern, whether intentionally or unintentionally present in the novel food, to ensure they are adequately risk assessed. Any concerns identified during this assessment will be highlighted in EFSA's opinion. The evaluation may also include exposure assessments or comparisons with existing food products on the market. The identification of substances that may pose safety concerns (and the subsequent estimation of their exposure) depends on the compositional analyses provided under section 3. Due to the diversity of novel foods, their varying compositions, intended uses, and use levels, it is not feasible to establish a definitive list of substances of potential safety concern along with their safe levels. Please refer also to the response to comment 164.
214	EU Specialty Food Ingredients	Lines 1054-1059: The same comment for section 6.4 applies here. This statement raises a question, if there is already a consumption of nutrient X at the high end of the Recommended Daily Intake/Allowance (RDI/RDA), does that mean that any novel food with nutrient X is not permitted as a replacement, smothering all change and innovation? Lines 1048-1051: Toxicology testing would identify and establish safe levels of these impurities. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	Please refer to the response to comments 164 and 165.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		(ICH) has guidances (Q3A and Q3B) on qualifying impurities and EFSA should consider the same type of approach for novel foods.	
577	Aletheia: il segreto del buon vivere	'Undesirable substances' are defined by European legislation only for feed as 'any substance or product, with the exception of pathogenic agents, present in and/or on the product intended for animal feed which presents a potential danger to human health, animal health or the environment or do not adversely affect livestock production.' In food, these compounds fall into the category of contaminants, defined by EFSA as chemicals not intentionally added to food or feed that may be present in them as a result of the various stages of their production, processing or transport. The substances listed in the commentary to Section 1.2.1 of the Guidance (hormones, antimicrobials, etc.), being intentionally used in the production process of cell-based meat, do not fall into this category.	Please note that in the updated Guidance, the previous section 'Estimate of exposure to undesirable substances' has been renamed to 'Estimate of exposure to substances of safety concern', and examples of such substances are provided. The text has been revised. Please also refer to the response to comment 165.
618	Cellular Agriculture Europe	Lines 1046 - 1062: We would welcome further clarity from EFSA on what exposure would be regarded as acceptable/tolerable in terms of safety for undesirable substances with a background diet already exceeding the health-based guidance values or for which there are no health-based guidance values? Exposure to various environmental contaminants such as heavy metals or mycotoxins are often above HBGV from the background diet or without HBGV (Pb, As, OTA, aflatoxins…).	Applicants should account for the potential double counting of substances of safety concern from the novel food and the background diet, particularly when exposure to these substances from the diet already exceeds health-based guidance values (HBGV). The Guidance has been updated to reflect this. For substances of safety concern without established HBGVs, a case-by-case evaluation will be applied.
708	FoodDrinkEurope	[Line 1060] We would welcome further clarity from EFSA on what exposure would be regarded as acceptable/tolerable in term of safety for undesirable substances with a background diet already exceeding the health-based guidance values or for which there is no health-based guidance values?	Please refer to the response to comment 618.

Table 40: 6.6 Precautions and restrictions of use

Comment number	Commentor	Comments	EFSA NDA Panel responses
28	Undisclosed (Personal Capacity)	Lines 1063-1067 There is no specific mention of precautionary labelling in this section	Applicants are required to specify the precautions and usage restrictions for the novel food. Risk managers will be responsible for implementing labelling related to these precautions and usage restrictions. The Panel considers that no change to the Guidance is needed.

Table 41: 7 Absorption, distribution, metabolism and excretion

Comment number	Commentor	Comments	EFSA NDA Panel responses
94	Undisclosed (Personal Capacity)	Insufficient Specificity on Animal Model Relevance (Page 33, Line, 1083–1085) Comment: The guidance notes that differences in ADME between animals and humans may affect interpretation of animal studies, yet it lacks specific criteria for selecting animal models that best mimic human physiology. Including criteria for model selection based on physiological and metabolic similarities to humans would improve the relevance and reliability of the data . Vague Criteria for Waiving ADME Studies (Page 35, Line, 1112–1113) Comment: The section permits waiving ADME studies under certain conditions but does not provide detailed criteria for these exemptions. Explicitly defining these conditions, such as the presence of extensive existing data demonstrating safety and typical metabolic pathways, would enhance transparency and regulatory compliance . Need for Enhanced Comparative Metabolism Studies (Page 36, Line, 1129–1130) Comment: Although comparative metabolism studies are mentioned, the document does not specify how to ensure comparability between in vitro human systems and animal models. Detailing methodologies to validate that the metabolism in human-derived in vitro systems	The Panel agrees with the comment but considers that providing detailed protocols and a list of animal species is beyond the scope of this Guidance. References to relevant documents and guidance are included in the sections highlighted in the comment and can also be found in existing literature and guidance on chemical risk assessment published by various authorities (e.g., WHO, OECD). The text has been revised accordingly.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		accurately reflects in vivo situations would ensure the relevance and applicability of the results to human health risk assessments . Lack of Discussion on Gut Microbiota Impact (Page 36, Line, 1132–1133) Comment: The impact of gut microbiota on the metabolism of novel foods is only briefly mentioned. Given the significant role of gut microbiota in bioavailability and biotransformation, the guidelines should include specific protocols for studying the interaction between novel foods and gut microbiota, particularly how these interactions might modify the toxicity or nutritional properties of the novel food .	
144	Synpa, French association of specialty food ingredients manufacturers and distributors	It is not clear in which case a specific study is required and in which case only literature is sufficient. Could you please precise ? Can literature data, combined with physicochemical data on the NF be sufficient for ADME Tier 1? If the NF is a concentrate or extract of a raw material considered as food, and if ADME data is available for components of this food in the literature, are ADME in vitro absorption and metabolism specific studies still required? If NF are proteins/peptides, are ADME studies required? Demonstration of protein digestion in the GIT, or peptide absorption must be demonstrated? Is literature data sufficient?	The recommendation to conduct a comprehensive literature search aims to identify ADME data relevant to the novel food, potentially reducing the need for unnecessary animal studies. The updated Guidance now outlines the requirements for ADME data in a more transparent and detailed manner, helping to clarify when such studies are necessary (e.g., for novel foods composed of new single substances) and when they are not (e.g., for novel foods containing substances commonly found in the body or diet, such as amino acids from proteins broken down in the GI tract). The Panel acknowledges the recommendation but notes that due to the heterogeneous nature of novel foods, a comprehensive list is not feasible, and a case-by-case approach remains necessary.
240	The Good Food Institute Europe	Line 1124-1127 Existing models include cell-based systems of various levels of complexity (e.g., MDCK, Caco1125 2, human small intestinal and liver organotypic 3D culture models). Such in vitro models could complement in vivo models to assess	The text has been revised in line with the comment.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		absorption and metabolism, noting the interrelationship between the Tiers. Comment: EFSA should consider removing the term 'could complement' and replacing this with 'could eliminate the need for in vivo models' in line with the reduce, replacement and refinement of animal studies (3R) which is an important risk assessment principle that is supported by EFSA among other international regulatory agencies.	
318	EuropaBio	More specificity about the digestibility studies is needed, as well as consistency about this requirement throughout the document.	The Panel notes the recommendation but considers that provision of detailed protocols goes beyond the scope of this Guidance. For protein digestibility, a reference to existing EFSA guidance documents is made.
343	Jeremy Coller Foundation	Line 1108, page 34 - Supportive of the general principle of reducing and replacing animal studies - is there a database available of recommended studies/laboratories that can carry out these alternative tests? Similarly, this may be useful for all the validated test types specified as essential within the dossier evidence pack to assist businesses with gaining high-quality data and budgeting time/costs in advance of submissions. This should also benefit EFSA in reducing the number of errors in dossiers.	To our knowledge, such a database does not currently exist. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.
514	PETA Science Consortium International e.V.	PETA Science Consortium International e.V. (the Science Consortium) is grateful for the opportunity to comment on the draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283, updating the scientific guidance for the preparation of applications for authorisation of novel foods. The Science Consortium supports measures advising on the scientific information required from the applicant that demonstrates the safety of the novel food and provides the best possible protection for human health while simultaneously meeting the existing commitments and legal requirements to replace and reduce tests on animals. The EU has the opportunity to continue leading the way towards a paradigm shift in regulatory safety testing, and to establish momentum for further developments in this direction. To do so, the	The Panel agrees that information requirements should be based on the best available science, and this is now reflected in the Guidance. The updated Guidance provides a clearer and more comprehensive description of the requirements for ADME and toxicity studies, helping to determine when such studies are necessary and when alternative approaches may be applicable. As emphasised in the Guidance, NAM-based methodologies must be qualified or validated as alternative approaches. The text has been revised.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		following points need to be addressed in the draft guidance: 1. Information requirements must be based on the best available science and therefore must not default to unreliable animal testing, where possible. 2. If information requirements are added which can currently only be fulfilled with testing on animals, flexible language should be introduced to facilitate the development and implementation of fit-for-purpose non-animal methods and their acceptance even without the need to update regulations. 3. While we understand that general rules intended to ensure animal testing is conducted only as a last resort, specific data requirements in the respective Guidance chapters should clearly correspond to best practice in this regard.	

Table 42: 7.1 General considerations

Comment number	Commentor	Comments	EFSA NDA Panel responses
29	Undisclosed (Personal Capacity)	Lines 1093-1096 Please be more specific about the digestibility studies and their methods required, by either direct reference to specific sections of the EFSA GMO guidance and/or listing the actual methods in this section	Please refer to the response to comment 318.
71	Nutraveris - A FoodchainID company	o From the new requirements in the guidance, we understand that this means that TIER II will be required for almost all NF dossiers. - Tier III testing is required for many cases. EFSA should be aware of the cost, difficulty and uncertainties associated with ADME testing in humans. - EFSA indicates that ADME studies may not be needed for some applications. Can EFSA list the type of ingredient which can be exempted of ADME assessment?	Data on ADME have previously been required for certain types of novel foods to conduct a risk assessment. The updated Guidance Document provides a more transparent and detailed description of this requirement, clarifying when extensive ADME studies are necessary (e.g., for novel foods comprising new single substances) versus when they are not (e.g., for novel foods consisting of substances commonly found in the body or diet). The Panel notes the recommendation

Comment number	Commentor	Comments	EFSA NDA Panel responses
			but considers that, due to the heterogeneous nature of novel foods, a comprehensive list of requirements is not feasible; thus, a case-by-case approach remains necessary.
111	Food Fermentation Europe	Lines 1097 to 1106 page 34 again introduce a new requirement to assess the fraction of small particles even in conventional materials that do not meet the definition of engineered nanomaterials, here for the purpose of ensuring that ADME study design suitably covers potential adverse effects of the small particles fraction of the novel food in accordance with the recommendations set in Section 4 of the Guidance on Particle – TR. As already discussed in our previous comments in Sections 3 and 4, Food Fermentation Europe considers that this broad new requirement to demonstrate the absence of a fraction of nano-scale particles, or alternatively that this fraction of nano-scale particles is covered by the conventional risk assessment as per the Guidance on Particle – TR, places an unreasonable and unnecessary additional burden on applicants to conduct potentially significant additional and costly analysis for novel foods of biological origin. The draft guidance itself acknowledges that this requirement is not needed for a number of novel food categories (lines 732-735 pages 23-24), but the exemption carved out by the document (lines 735-736, page 24) is too narrow to avoid unnecessary additional testing for many applicants. Based on the foregoing, Food Fermentation Europe respectfully requests that the draft guidance be revised to only require that ADME study design take into account the fraction of small particles in novel food of biological origin that do not meet the definition of engineered nanomaterial when there is reason to believe that a fraction of small particles in the specific novel foods of interest may cause a particular safety concern that would require specific consideration in the ADME study design.	The section already includes appropriate references to conventional materials containing small particles, including nanoparticles. Please refer to the response to comment 109 and to General Principle 2 of the Guidance.
129	Medfiles Ltd	Comment: P33 L1069: Medfiles welcomes EFSA's non-animal approach taken here. This is now much more in line with ECHA, SCCS etc and 3Rs approach. Comment: P33L1078: Additionally, a comprehensive literature review of existing ADME data on the	The recommendation for conducting a comprehensive literature search aims to identify relevant ADME (absorption, distribution, metabolism,

Comment number	Commentor	Comments	EFSA NDA Panel responses
		novel food or its relevant components should be conducted, and the collected evidence should be critically appraised. Could this be written so that the literature review is not mandatory, e.g., for totally new novel foods or novel proteins where there it is known there is no data in the literature? It is waste of time to do the search with no results and write a report. P34 L1101: Medfiles notes that the guidance deviates from the EFSA small particle guidance. Here the novel food guidance requires to consider nano-scale small particles of < 100 nm, while the small particle guidance defined the nano-scale < 250 nm. Please clarify this difference as this is very confusing. In addition, does this difference imply that in fact for novel foods the small particles < 100 nm should be determined and not < 250 nm? Provided that this is the case, this would differ from the requirements for other EFSA remits where small particles with sizes of < 500 nm/< 250 nm have to be determined. Medfiles would appreciate that there is one guidance and a clear clarification which is the nano-scale to be considered below 100 nm or below 250 nm for novel foods.	and excretion) data for the novel food, potentially eliminating the need for animal studies. While the Panel acknowledges that ADME data may not be available for all novel foods, this approach is intended for scenarios where, for example, the novel food is broken down in the gastrointestinal tract into substances for which ADME data are available. Regarding nanoparticles, the reference to 100 nm pertains solely to the legal definition. As outlined in the Guidance Document, data requirements are detailed in the EFSA TR Guidance of 2021. Please refer to General Principle 2 of the Guidance.
166	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 1082-1084 The extension of responsibility from ingredient to finished good is borderline limitless. For novel foods used as ingredients in a finished product, the final food matrix could be unknown as food product producers may use the additive in new ways not envisioned by the novel food applicant. Clarification to limit testing should be provided.	The applicant should consider potential food matrices, particularly those that could impact the stability and bioavailability of the novel food. However, the Panel agrees that it is not feasible for the applicant to account for all possible food matrices.
215	EU Specialty Food Ingredients	Lines 1082-1084: As stated above for section 3.4.1, the extension of responsibility from ingredient to finished good is borderline limitless. For novel foods used as ingredients in a finished product, the final food matrix could be unknown as food product producers may use the additive in new ways not envisioned by the novel food applicant. Clarification to limit testing should be provided.	Please refer to the response to comment 166.
279	Ministry of Regional	Line 1112-1113- Would it be possible to point out examples based on current practice?	Please refer to the response to comment 71.

Comment number	Commentor	Comments	EFSA NDA Panel responses
	Affairs and Agriculture		
515	PETA Science Consortium International e.V.	Thank you for including in vitro ADME studies under 7.1.1. Tier I ADME testing. To encourage their use and facilitate the transition to non-animal testing, for example by encouraging the use of available in silico methods for food ingredients (ref. 1,2), we recommend adding the following in [brackets] to the introductory chapter. Line 1070 'Data on [or predictions of] absorption, distribution, metabolism and excretion (ADME) in humans and animals are relevant for both nutritional and toxicological assessment of a novel food. ADME studies inform about the extent of absorption of the novel food or its components from the gastrointestinal (GI) tract, their bioavailability, the nature and extent of metabolism and elimination, and the potential of bioaccumulation. Differences in ADME between animals and humans may affect the adequacy and interpretation of experimental animal studies. [Apart from animal experiments and human studies, in vitro ADME studies can predict local internal concentrations with which to compare measured or predicted bioactivity data to better understand systemic and local tissue effects. This information can be used for in vitro to in vivo extrapolation (IVIVE) to translate in vitro bioactivity measurements into in vivo concentrations, dose, or exposure. Physiologically based toxicokinetic (PBTK) models can be used to simulate the concentration-time profile in blood and at the target site.]' References 1. Volarath P, Zang Y (Janet), Kabadi S V. Application of Computational Methods for the Safety Assessment of Food Ingredients BT - Advances in Computational Toxicology: Methodologies and Applications in Regulatory Science. In: Hong H, ed. Springer International Publishing; 2019:233-257. doi:10.1007/978-3-030-16443-0_12 2. Blaauboer BJ, Boobis AR, Bradford B, et al. Considering new methodologies in strategies for safety assessment of foods and food ingredients. Food Chem Toxicol. 2016;91:19-35. doi:https://doi.org/10.1016/j.fct.2016.02.019	The text has been revised to provide further clarity. The description of NAMs has been revised.

Comment number	Commentor	Comments	EFSA NDA Panel responses
592	AseBio - Spanish Bioindustry Association,	More specificity about the digestibility studies is needed, as well as consistency about this requirement throughout the document.	The Panel acknowledges the concern expressed but notes that detailed protocols are beyond the scope of this Guidance. For protein digestibility, a reference to existing EFSA guidance documents is made.
619	Cellular Agriculture Europe	Lines 1093 - 1096: We suggest that EFSA is more specific about the digestibility studies and the methods required, by either direct reference to specific sections of the EFSA GMO guidance and/or listing the actual methods in this section.	Please refer to the response to comment 592.
679	Atova Regulatory Consulting SL	(Lines 1093–1096, page 34) Regarding digestibility studies, we suggest that EFSA provides more clarity, and specifies a list of accepted methods/approaches and provides examples from recent novel food applications as to when and how this was addressed.	Please refer to the response to comment 592.
709	FoodDrinkEurope	[Line 1093] We would welcome further clarity on the digestibility studies that EFSA is referring to	Please refer to the response to comment 592.

Table 43: 7.1.1 Tier I ADME testing

Comment number	Commentor	Comments	EFSA NDA Panel responses
42	Intertek	Line 1135 - please provide references for the example studies (M-ARCOL, SHIME, Triple coculture)	The Panel acknowledges the comment. Numerous publications describe these systems. Examples include these studies: https://doi.org/10.1016/j.apsb.2019.12.001 https://doi.org/10.1126/science.aag2770
168	Synpa, French association of	1. Lines 1138-1139 The ADME section does not discuss inert polymers that have a molecular weight >1000 Da . Per EFSA	1. The Panel agrees that polymers larger than 1000 Da, provided they

Comment number	Commentor	Comments	EFSA NDA Panel responses
	specialty food ingredients manufacturers and distributors	food contact guidance (https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4357), polymers >1000 Da are not absorbed in the GI tract. The novel foods guidance should address these polymers in terms of ADME. Suggest that a statement be added that that the triggers are provided in section 7.1.2. Without that, the reader's first thought after reading would be, ''where are the triggers listed?''. ' 2. Lines 1140-1149 No option for alternative tests to avoid by default animal testing at Tier II?	are not degraded in the gastrointestinal tract, are not absorbed. A clarification has been added to indicate that the triggers are listed in sections 7.2.2 and 7.2.3. The text has been revised in line with the comment. 2. Compared to the 2016 Guidance, the updated Guidance provides a more transparent and detailed description of when in vitro alternatives and specifically human data should be generated. The Panel considers that due to the heterogeneous nature of novel foods, a case-by-case approach is necessary, and providing detailed lists or protocols goes beyond the scope of this Guidance.
217	EU Specialty Food Ingredients	Lines 1138-1139: 1. Section numbering is incorrect as the preceding section was 7.2. 2. The ADME section does not discuss inert polymers that have a molecular weight >1000 Da. Per EFSA food contact materials guidance (https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4357), polymers >1000 Da are not absorbed in the GI tract. The novel foods guidance should address these polymers in terms of ADME. 3. Suggest that a statement be added that that the triggers are provided in section 7.1.2. Without that, the reader's first thought after reading would be, 'where are the triggers listed?'.	Please refer to the response to comment 168.
273	Dwayne Holmes (Personal Capacity)	Page 35, Line 1125-1126 – In the sentence, 'Such in vitro models could complement in vivo models...' the word complement suggests that in vivo models must still be used. If they can be used in place of in vivo models, it might be better written 'Such in vitro models could be used as an alternative to in vivo models...'	The text has been revised in line with the comment.

Comment number	Commentor	Comments	EFSA NDA Panel responses
516	PETA Science Consortium International e.V.	Line 1122 To support the advancement of non-animal methods and innovative scientific methodologies, we suggest adding the following in [brackets]: 'Progress has been made in recent years with the development of human-relevant in vitro models to quantify transport across the intestinal membrane and assess metabolism (OECD, 2021; ICH (draft), 2022)47. Existing models include cell-based systems of various levels of complexity (e.g., MDCK, Caco-2, human small intestinal and liver organotypic 3D culture models). Such in vitro models could complement [or, if they have an equal level of predictivity, replace] in vivo models to assess absorption and metabolism, noting the interrelationship between the Tiers.'	The text has been revised in line with the comment.
535	FoodchainID	Can EFSA clarify if the in vitro data on absorption (human in vitro test system) is required in addition to the literature review (if the literature review provides sufficient evidence of the ADME)? The graph presented in Fig 1 deserve to be clarified (many lines crossing),for better understanding.	The requirement for in vitro data on absorption (human in vitro test systems) in addition to the literature review depends on the representativeness and sufficiency of the available data. Figure 1 is intended solely as an overview of the tiered approach and the interrelationship between tiers, which is described in greater detail in the text. As recommended, the figure legend has been clarified to enhance understanding.
620	Cellular Agriculture Europe	Lines 1125 - 1126: We would suggest modifying in the text 'Such in vitro models could 'substitute' instead of 'complement' in vivo models'. The reduce, replacement and refinement of animal studies (3R) is an important principle that is supported by EFSA among other international agencies, and it is important to let here the possibility that well accepted in vitro studies can replace (and not only 'complement', suggesting that in vivo models are still mandatory), in some cases, in vivo models. Line 1128: 'in vitro comparative metabolism' (e-g- liver, intestines, other target tissues?). We would welcome further clarity on the biotransformation tissues of interest and in vitro. Line 1135: We would welcome further clarity on the following: which ones of	The text has been revised in line with the comment. As emphasised in the Guidance, NAM-based methodologies must be qualified or validated as alternative approaches. The Panel considers that expanding this section in detail goes beyond the scope of this Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		these in vitro studies for which there is no OECD TG are accepted by EFSA . Studies that are not compliant with OECD TG are usually not accepted. In some cases, a better understanding of the safety of a novel food implies to use specific and adapted studies for which there is no OECD TG but there is a risk that such studies would not be accepted by the EFSA NDA Panel.	

Table 44: 7.1.2 Tier II ADME testing

Comment number	Commentor	Comments	EFSA NDA Panel responses
59	Specialised Nutrition Europe (SNE)	Page 36 line 1140 and 1154-1156 Focused on animal testing and contradicts the notion of animal testing reduction/replacement stated earlier in the document. More guidance could be given on alternative routes or cases to generate such data in more human-relevant models. It could be clarified or made more straightforward whether there are options to directly go to Tier 3.	Please refer to the response to comment 168.
300	Katharina Julia Brenner (Personal Capacity)	1. Lack of Detail on Sample Collection for Metabolite Analysis (Page 36, Lines, 1145–1147) Comment: The section specifies that Tier II ADME testing requires both single-dose and repeated-dose studies, yet it lacks detailed guidance on the specific types and timing of sample collection for comprehensive metabolite profiling. It should include protocols for collecting and analysing samples at various time points to effectively capture metabolic changes and identify any metabolites of concern. 2. Vague Guidance on Satellite Groups (Page 36, Lines, 1146–1148) Comment: The guidance suggests using satellite groups from a sub-chronic toxicity study for ADME assessment but does not provide clear criteria on how these groups should be structured or utilised. Specific guidelines on the number of animals, dosing regimen, and the parameters to be monitored would enhance the clarity and utility of the data collected from these groups. 3. Insufficient Details on the Use of OECD TG 417	The Panel notes the recommendation but considers that provision of detailed protocols and explanations on the application of OECD TGs goes beyond the scope of this Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		(Page 36, Lines, 1148–1150) Comment: While the document mentions OECD TG 417 for guidance on Tier II ADME assessment, it should explicitly outline which aspects of this guideline are most relevant to novel food assessments. Inclusion of specific sections from OECD TG 417 that deal with metabolic stability, enzyme induction, and drug-drug interaction potential could be beneficial. 4. Need for Enhanced Methodological Specificity (Page 36, Lines, 1143–1144) Comment: The section mentions evidence for accumulation in the body or formation of metabolites of concern as triggers for Tier II testing but fails to specify the analytical methods or technologies recommended to detect and quantify these parameters. Detailed descriptions of suitable analytical techniques such as LC-MS/MS for metabolite identification and quantification would improve the rigour of the ADME studies.	
517	PETA Science Consortium International e.V.	To facilitate the development, implementation, and use of non-animal assays, it is crucial for regulatory guidance to acknowledge scientifically validated non-animal methods. We recommend including flexible language that allows the use of non-animal methods to include currently validated tests and to-be-validated tests that may not have already been incorporated into guidance or regulation at time of publication. We recommend adding the following in [brackets]: Line 1141 '[The development of PBTK models providing mathematical representations of ADME processes within the body by simulating time-dependent concentrations in blood and target tissues holds promise for the (future) replacement of ADME testing in animals and should be used once established. However, in the absence of equally predictive PBTK data,] the triggers leading to Tier II testing in animals include one or more of the following:'	The text has been revised, adding reference to PBTK modelling. The Panel notes that due to the dependency on further validation, a detailed expansion of the section referred to goes beyond the scope of this Guidance.
536	FoodchainID	Is the absorption of metabolites of the NF a reason to trigger TIER II testing?	This depends on the nature of the metabolite.
621	Cellular Agriculture Europe	Lines 1141 - 1142: Further clarity would be welcome for Tier II testing in animals: does it mean that in silico models are not accepted in Tier II if there are indications that the NF or its	Evidence from in vitro and in silico models are considered under Tier 1, alongside existing data from in vivo

Comment number	Commentor	Comments	EFSA NDA Panel responses
		constituents are absorbed? With the 3R principle, it can be expected that NF guidance would allow the possibility of having alternative (human-based) approaches to animal studies.	studies. Only if the evidence gathered under Tier 1 is insufficient to address ADME will there be a need to proceed to Tier 2 studies.

Table 45: 7.1.3 Tier III ADME testing

Comment number	Commentor	Comments	EFSA NDA Panel responses
622	Cellular Agriculture Europe	Line 1154: Further clarity is needed on any substantial ADME differences between different species, genders and ages. To add genders and ages (to add infants vs adults for example).	The impact of sex and age is addressed through the application of appropriate uncertainty factors for intra- and interspecies variability, as recommended by the Scientific Committee. These factors are considered in the overall assessment. The Panel considers that no change to the Guidance is needed.

Table 46: 7.2 Tiered approach to conduct ADME studies

Comment number	Commentor	Comments	EFSA NDA Panel responses
130	Medfiles Ltd	1. Comment: P34 L112: EFSA writes: The need to conduct ADME studies may be waived provided that duly reasoned scientific arguments are provided (section 8.2.1). Which is this section 8.2.1? It is unclear and it is not possible to comment now. This is very unfortunate. Nevertheless, Medfiles proposes that it would be very good to give examples which kind of elements are needed for waiving ADME studies. To us the waiving should be based on WoE approach and examples of the needed data could be e.g. compositional data, physicochemical data, literature data (in vivo, in vitro, in silico, previous assessments), read-across	1. The text has been revised by removing the incorrect cross-reference. Regarding the need for conducting ADME studies, please refer to the response to comment 71. The requirement to perform a 90-day in vivo study is not solely dependent on whether the substance is absorbed, as it may cause local

Comment number	Commentor	Comments	EFSA NDA Panel responses
		data, in silico data, in vitro data, omics data etc. Now the draft guidance on ADME gives the impression that if novel food is absorbed (which, in generally speaking, food should do in order for human body to biologically function), an in vivo study is (always) needed (satellites in a 90-day study or a separate ADME study). Thank you for considering this. 2. Comment P35 L1128: EFSA proposes to use comparative metabolism of the novel food as described by the PPR opinion. Medfiles agrees that the comparative metabolism is possible to conduct for a single substance (like active substances used in PPPs), however, mixtures, and in particular complex ones, it is probably not feasible (except for selected substances). Medfiles would appreciate if EFSA could elaborate it more how to conduct comparative metabolism studies for simple and complex mixtures. It is also noted that comparative metabolism methods are not validated as stated by PPR. Can EFSA note here something about the validation of these method and if EFSA accept non-validated methods?	effects in the gastrointestinal tract. The need for such studies is determined by the nature of the novel food, as detailed in Section 8. 2. The Panel agrees that there are currently no validated OECD TGs for assessing comparative metabolism; however, these assays have been used for many decades, and relevant references are widely available.
167	Synpa, French association of specialty food ingredients manufacturers and distributors	In this section, sub-sections need to be revised by respectively 7.2.1, 7.2.2 and 7.2.3.	The text has been revised in line with the comment.
216	EU Specialty Food Ingredients	Lines 1112-1113: There is no section 8.2.1 in the document. Need to add that section or revise this statement.	Please refer to the response to comment 130.
272	Dwayne Holmes (Personal Capacity)	1. Page 34, Line 1113 – Section 8.2.1 is indicated in the text, however it is not in the index nor found in the guidance. 2. Page 34-5, Line 1114-1115 – (Including text within Figure 1) It would be useful for EFSA to provide greater clarity in this section, particularly related to absorption of cultured meat and seafood 'or its constituents'(e.g. digested and bioavailable amino acids, fats, etc.). We understand that this would not apply to constituents of cultured meat and seafood where no substances of concern were verified and that after digestion they would be	1. Please refer to the response to comment 130. 2. Please refer to the response to comment 71.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		absorbed. However, as it is stated it may lead to misunderstanding, and it can be concluded that moving to Tier2 is mandatory for instance for the example provided.	
710	FoodDrinkEurope	1. [Line 1118] We would suggest adding in the text 'in silico data 'as well 2. [Line 1126] We would suggest modifying in the text 'Such in vitro models could 'substitute' instead of 'complement' in vivo models '. The reduction, replacement and refinement of animal studies (3R) principle is supported by EFSA. Thus, it is important to let here the possibility that well accepted in vitro studies can replace (and not only 'complement', suggesting that in vivo models are still mandatory), in some cases, in vivo models. 3. [Line 1128] 'in vitro comparative metabolism' (e-g- liver, intestines, other target tissues?) We would welcome further clarity on the biotransformation tissues of interest and in vitro. 4. [Line 1135] Which ones of these in vitro studies for which there is no OECD TG are accepted by EFSA? Studies that are not compliant with OECD TG are usually not accepted. Nevertheless, in some cases, a better understanding of the safety of a novel food implies to use specific and adapted studies for which there is no OECD TG. 5. (Lines, 1141–1142) Further clarity is required for Tier II testing in animals: does it mean that in silico models are not accepted in Tier II if there are indications that the NF or its constituents are absorbed? With the 3R principle, we would expect that the NF guidance would allow the possibility of having alternative (human-based) approaches to animal studies. 6. [Line 1154] Further clarity is required on if any substantial ADME differences between different species, genders and ages.	1. The text has been revised by expanding the reference to in silico. 2. The text has been revised in line with the comment. 3. Please refer to the response to comment 130. 4. Please refer to the response to comment 620. 5. Please refer to the response to comment 621. 6. Please refer to the response to comment 622.

Table 47: 8 Toxicological information

Comment number	Commentor	Comments	EFSA NDA Panel response
65	Nutraveris - A FoodchainID company	1. - EFSA notes the interest to use read-across approach, and new toxicological methods. Can EFSA clarify which kind of tests and the situation where these tests can be accepted? - EFSA ask for rational when the applicant propose a deviation of the tiered approach. However, there is no possibility to obtain a validation of the deviation by EFSA before the submission of the results. This not acceptable for applicant to have to decide what is acceptable or not in place of EFSA. 2. - Line 1320-1323: EFSA notes that studies generally cover the risk assessment of nanoparticles, if precautions and adaptations are implemented according to the nano risk assessment guidance. Can EFSA add in the novel food guidance the adaptations needed for the assessment of nano ingredient?	1. The provision of a comprehensive list of protocols, specific situations, or tests is not feasible due to the vast array of possible scenarios and combinations of available data. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance. 2. Horizontal guidance documents, such as those on nanomaterials, may evolve over time. The Panel aims to avoid frequent revisions of specific guidance documents, such as the Guidance on Novel Foods, in response to changes in horizontal guidance documents. It is essential to consult and carefully consider the applicable horizontal guidance documents in their entirety whenever relevant.
95	Undisclosed (Personal Capacity)	1. Insufficient Guidelines for In Vivo Testing (Page 36, Line, 1178–1180) Comment: The guidance mentions in vivo testing but does not specify which animal models are most appropriate for different types of novel foods. More detailed guidelines could include considerations for choosing relevant species based on the metabolic and physiological similarities to humans, thereby improving the relevance and reliability of the results. 2. Vague Handling of Nanomaterials (Page 36, Line, 1192–1194) Comment: While there is a brief mention of additional requirements for nanomaterials, the document lacks specific protocols for assessing the unique risks associated with nano-scale materials in food. It should detail methodologies for evaluating particle size distribution, surface reactivity, and potential for bioaccumulation, crucial for assessing safety in these cases.	Please refer to the response to comment 65.

Comment number	Commentor	Comments	EFSA NDA Panel response
		3. Lack of Specificity on Read-Across Application (Page 37, Line, 1199–1201) Comment: The document mentions the use of a read-across approach but provides no concrete examples or criteria for its application. Including case studies or specific conditions under which read-across is applicable would help clarify its use in predicting toxicological properties of novel foods. 4. General Approach to Genotoxicity Testing (Page 39, Line, 1234–1236) Comment: The section on genotoxicity testing outlines a general approach but lacks depth on specific tests required for different types of novel foods. Expanding this section to include guidance on selecting appropriate tests based on the chemical structure and expected metabolism of the novel food components would enhance the thoroughness of genotoxic assessments. 5. Insufficient Detail on Human Data Utilization (Page 43, Line, 1368–1370) Comment: The guidance touches on the use of human data but does not specify how this information should be integrated into safety assessments. Detailed instructions on how to incorporate findings from human studies, such as dietary intervention trials or observational studies, into the risk assessment framework would provide a clearer pathway for evaluating human health impacts.	
145	Synpa, French association of specialty food ingredients manufacturers and distributors	Is history of safe use assessment possible, on the model of 'Safety assessment of botanicals and botanical preparations' (EFSA Scientific Committee, 2009), when the novel food is derived from a food source (plant, animal, fungi, algae sources), even when there is an unknown fraction characterised? Food components are usually not characterised up to a 100%. Is 'Presumption of Safety (QPS) approach for the safety assessment of botanicals and botanical preparations (EFSA Scientific Committee, 2014) ' still applicable for risk assessment of novel food derived from plants?	It should be noted that all available information should be thoroughly evaluated, and the approach recommended by the Scientific Committee is a reasonable one. The adequacy of the information to preclude the need for a 90-day study will depend on numerous factors, including the production process, intended uses, usage levels, resulting intake estimates, and other pertinent details.
309	Food Safety & Nutrition Consultancy	In tier 1, animal studies are not compulsory if the compositional data inform so. this further reduces unnecessary animal (and euro and time) us.	In the Guidance it is mentioned that 'All relevant available knowledge on the novel food should be thoroughly

Comment number	Commentor	Comments	EFSA NDA Panel response
			considered to determine the need for toxicity studies, and if so, the corresponding toxicological testing strategy, a thorough description of which, is to be provided.` Therefore, the Panel agrees with the comment but considers that no change to the Guidance is needed.
580	AseBio - Spanish Bioindustry Association,	Line: 1177 – 1179 We support minimising animal testing. However, we note a possible conflict with other jurisdictions (e.g., US, China, Japan, etc.) that require animal testing for novel product approval. If testing is performed for another jurisdiction prior to EU launch, applicants may not have notified EFSA before the animal testing was performed. How will EFSA address this issue of study notification in a novel foods application?	As noted in the comment, animal studies are required not only in other jurisdictions outside the EU but also within the EU. The necessity for animal studies is not to avoid conflicts with other jurisdictions, but because they are generally deemed essential for assessing the toxicity of new compounds, extracts from novel sources, etc. Regarding the registration of animal studies, EFSA is required to adhere to the EU Transparency Regulation, which includes specific rules for the notification of such studies. This requirement applies equally to Novel Food applications.
690	FoodDrinkEurope	1. (Lines 1222–1226) `In cases where the data in the literature raise concerns regarding reproductive – and developmental toxicity, a Tier III extended one generation reproductive toxicity study (EOGRTS), which covers also subchronic toxicity, may be more appropriate. This would be more efficient regarding time and the number of animals needed, as compared to performing a Tier I subchronic toxicity followed by a Tier II reproduction and developmental study.` Is EFSA saying that there's no need to do a full specifically designed sub-chronic study in this case? 2. (Line 1232) Figure 3: can EFSA add computational toxicology in the tier 1 level for genotoxicity? Computational toxicology is	1. A full specifically designed sub-chronic study is not necessary in this case if an OECD TG 443 (Extended One-Generation Reproductive Toxicity Study, EOGRTS) is conducted, provided that available data raise concerns regarding reproductive or developmental toxicity. 2. It should be noted that the present Guidance refers to the EFSA Scientific Committee (2011), which considers the computational approaches

Comment number	Commentor	Comments	EFSA NDA Panel response
		more and more used in combination of in vitro studies to predict if a chemical or a mix of chemicals have a genotoxic potential. 3. [Line 11233] Could EFSA add legend for the full and dotted lines of figure 2.	mentioned in the comment. Therefore, the Panel notes the recommendation but considers that a detailed expansion of the section goes beyond the scope of this Guidance. 3. The text has been revised to provide further clarity.

Table 48: 8.1 General considerations

Comment number	Commentor	Comments	EFSA NDA Panel response
30	Undisclosed (Personal Capacity)	Lines 1160-1205 There is no mention of QPS in this section. Why discuss earlier in guidance without imparting relevance in this section. Where and ingredient is sourced from a QPS microorganism, the relevance and requirement for toxicology studies should be discussed here, as it is with EFSA's food enzymes scientific guidance.	It should be noted that when microorganisms are used as novel foods or in the production of novel foods (production strains) meet the criteria for the QPS approach—namely, (i) unambiguous taxonomic identification as belonging to a species included in the QPS list, (ii) compliance with QPS qualifications, and (iii) no concerns arising from genetic modification for production strains—no toxicity studies are required for the microorganism itself. However, there may still be a need for toxicological studies to address other aspects of the novel food's safety, such as the production process, including the use of raw materials and applied techniques.

Comment number	Commentor	Comments	EFSA NDA Panel response
43	Intertek	Line 1189 - ICH guidelines are mentioned here, but the specific ICH guidelines are not mentioned in the relevant toxicity testing sub-sections (genotoxicity, repeated-dose toxicity etc.), whereas OECD Test Guidelines are mentioned throughout these sections. If ICH guidelines are appropriate to be used, please include the references to ICH guidelines within the toxicity testing sub-sections.	The reference to ICH guidelines has been removed from this section.
112	Food Fermentation Europe	Lines 1192 to 1198 page 37 again introduce a new requirement to assess the fraction of small particles even in conventional materials that do not meet the definition of engineered nanomaterials, here for the purpose of ensuring that toxicology study design suitably covers potential adverse effects of the small particles fraction of the novel food in accordance with the recommendations set in Section 4 of the Guidance on Particle – TR. As already discussed in our previous comments in Sections 3, 4, and 7, Food Fermentation Europe considers that this broad new requirement to demonstrate the absence of a fraction of nano-scale particles, or alternatively that this fraction of nano-scale particles is covered by the conventional risk assessment as per the Guidance on Particle – TR, places an unreasonable and unnecessary additional burden on applicants to conduct potentially significant additional and costly analysis for novel foods of biological origin. The draft guidance itself acknowledges that this requirement is not needed for a number of novel food categories (lines 732-735 pages 23-24), but the exemption carved out by the document (lines 735-736, page 24) is too narrow to avoid unnecessary additional testing for many applicants. Based on the foregoing, Food Fermentation Europe respectfully requests that the draft guidance be revised to only require that toxicology study design take into account the fraction of small particles in novel food of biological origin that do not meet the definition of engineered nanomaterial when there is reason to believe that a fraction of small particles in the specific novel foods of interest may cause a particular safety concern that would require specific consideration in the toxicology study design.	Please refer to the response to comment 109.

Comment number	Commentor	Comments	EFSA NDA Panel response
131	Medfiles Ltd	1. Comment P36 L1163: It is appreciated by Medfiles that prior to conducting toxicological animal studies, such as 90-day study, other data such as compositional data, ADME information and in silico, in vitro and in vivo literature data for toxicologically relevant substances should be considered including data from non-food uses. Does EFSA refer here to one substance-one assessment approach although not explicitly mentioned by EFSA? Regarding the non-food uses, would EFSA also accept safety assessments done by national and international bodies outside of the EU such as US EPA, FDA, OECD, IRAC, UK REACH etc when evaluating the need of the 90-day study or does it put preference on EU-assessments? 2. P37 L1195: Does EFSA refer here to <100 nm or <250 nm size small particles? On P34 L1101: Medfiles noted that the novel food guidance deviates from the EFSA small particle guidance. Here the novel food guidance requires to consider nano-scale small particles of < 100 nm, while the small particle guidance defined the nano-scale < 250 nm.	1. The issue is not about 'accepting' or rejecting assessments conducted by other bodies but rather about evaluating the relevance and representativeness of the studies, including factors such as test material, study population, and doses, to determine their usefulness in demonstrating the safety of the novel food at its proposed uses and use levels. For instance, EFSA does not apply in the context of novel food safety assessment the risk-benefit assessment framework used by EMA or FDA, which often involves well-defined study populations, such as patients, in the pharmaceutical context. The relevance of studies conducted by other bodies must therefore be assessed on a case-by-case basis. 2. Regarding the fraction of small particles, including nanoparticles, the Guidance refers to thresholds specified in the Scientific Committee (2021a). The materials mentioned contain 10% or more of particles (number-based) with at least one dimension smaller than 250 nm. This 10% threshold includes, but is not limited to, nanoparticles.
169	Synpa, French association of specialty food ingredients manufacturer	1. Lines 1161-1206 No reference to alternative tests to animal testing, this should be integrated to fit with general principles of the guidance. 2. Lines 1177-1179 While minimising animal testing is a lofty goal, which we support, there is a possible conflict with other jurisdictions (e.g., US, China, Japan, etc.) that require animal	1. The Panel notes the recommendation but considers that provision of a comprehensive list of protocols, specific situations, or alternative testing methods beyond those already outlined in the ADME

Comment number	Commentor	Comments	EFSA NDA Panel response
	s and distributors	testing for novel product approval. If testing is performed for another jurisdiction prior to EU launch, we would not have notified EFSA before the animal testing was performed. How will EFSA address that issue in a novel foods application? 3. Line 1182 Does that mean that in the case of an extract, if would be more relevant to test the raw material instead of the extract in the toxicological studies ? Testing the raw material instead of the extract id the novel food to be placed on the market seems to be not relevant as the extraction concentrate several component of the raw material and thus change the nutritional profile.	section (e.g., in vitro absorption and metabolism studies) goes beyond the scope of this Guidance. 2. Please refer to the response to comment 580. 3. The use of 'raw materials' in toxicological studies is not requested in the Guidance. Instead, the Guidance specifies that 'concentrates of an appropriate fraction(s) of the novel food may be used to enhance sensitivity.' The Panel considers that no change to the Guidance is needed.
218	EU Specialty Food Ingredients	Lines 1177-1179: It is our understanding that EFSA tries to minimise the need for toxicological studies in order to reduce animal testing, which we fully support, but we see a potential issue, which we would like to explain as an example: after a comprehensive literature review, we are confident that no toxicological studies are necessary for the hazard characterisation of a novel food and submit the application using only literature data in this chapter. For an application for the same product in another jurisdiction, e.g. (e.g., US, China, Japan, etc.), we perform toxicological studies, since they are still considered necessary in any case for this process. During EFSA's safety assessment EFSA disagrees with us and requests toxicological studies to perform the safety assessment. To fulfil EFSA's request, we provide the study results of the studies we performed for the application in another jurisdiction, but the study was not notified to EFSA, since we did not anticipate a need to use the study to support our application in the EU, following the literature review. How would EFSA handle this situation, considering that the intention is to reduce animal studies for the EU?	Please refer to the response to comments 580, 309 and 169.
274	Dwayne Holmes (Personal Capacity)	Pages 36-38, Line 1160-1207 – In this section it should be clearly defined when toxicological studies are not required as per Section 4.1 of the Food Enzyme Guidance. Also including a	It is not feasible to explicitly define when a toxicological study is required due to the multitude of variables and their combinations. These variables

Comment number	Commentor	Comments	EFSA NDA Panel response
		section on the test item and dose-level as this is often an issue for applicants.	include available literature, prior assessments, compositional data, the production process, exposure levels, and existing toxicological and human studies. Food enzymes are less heterogeneous compared to novel foods, leading to more specific requirements. For detailed considerations regarding test material, please refer to the comprehensive paragraph of the Guidance in Section 8.1, 'General Considerations'. In relation to the dosage, please consult the appropriate OECD guidelines.
313	Food Safety & Nutrition Consultancy	In tier 1, animal studies are not compulsory if the compositional data inform so. this further reduces unnecasary animal (and euro and time) us.	Please refer to the response to comment 309.
329	EuropaBio	1177 – 1179 : We support minimising animal testing. However, we note a possible conflict with other jurisdictions (e.g., US, China, Japan, etc.) that require animal testing for novel product approval. If testing is performed for another jurisdiction prior to EU launch, applicants may not have notified EFSA before the animal testing was performed. How will EFSA address this issue of study notification in a novel foods application?	Please refer to the response to comment 580.
518	PETA Science Consortium International e.V.	In line with legal requirements to use scientific methods not entailing the use of live animals when alternatives are available (Directive 2010/63/EU), it should be emphasised to applicants the necessity of first considering non-animal methods and providing robust scientific justification for conducting animal tests. We recommend adding the following in [brackets]: Line 1161 'The purpose of conducting toxicological studies on a novel food is to identify and characterise its potential hazards and to support establishing safe intake levels for humans. [Applicants are reminded that Directive 2010/63/EU, on the protection of animals used for scientific purposes, requires the use of scientifically sound methods not entailing the use of live animals	It should be noted that Directive 2010/63/EU that emphasises that tests on animals should be replaced, reduced or refined (3 Rs), wherever possible has been already included in the General Principles of the Guidance. The proposed tiered approach for ADME & toxicological assessment of novel foods reflects this aspect. The Panel considers that no change to the Guidance is needed.

Comment number	Commentor	Comments	EFSA NDA Panel response
		(Article 4). Applicants must ensure that vertebrate animal testing is only conducted if non-animal methods, which provide adequate reliability and quality of data, are unavailable. The use of animal tests must be robustly scientifically justified.]‘	
537	FoodchainID	The graph presented in Fig 2 deserve to be clarified (many lines crossing),for better understanding.	The graph illustrates the variability in testing strategies, which can differ significantly based on the existing data and the results of generated data.
558	Novonesis (merger of former Novozymes and Chr. Hansen)	page 37, lines 1177-1179: It is our understanding that EFSA tries to minimise the need for toxicological studies in order to reduce animal testing, which we fully support, but we see a potential issue, which we would like to explain as an example: ‘After a comprehensive literature review, we are confident that no toxicological studies are necessary for the hazard characterisation of a novel food and submit the application using only literature data in this chapter. For an application for the same product in another jurisdiction, e.g. a GRAS notification in the USA, we perform toxicological studies, since they are still considered necessary in any case for this process. During EFSA’s safety assessment EFSA disagrees with us and requests toxicological studies to perform the safety assessment. To fulfil EFSA’s request, we provide the study results of the studies we performed for the application in another jurisdiction, but the study was not notified to EFSA, since we did not anticipate a need to use the study to support our application in the EU, following the literature review. How would EFSA handle this situation, considering that the intention is to reduce animal studies for the EU?‘	Please refer to the response to comments 580 and 218.
623	Cellular Agriculture Europe	1. Lines 1160 - 1205: There is no mention of QPS in this section, while it is mentioned earlier in guidance. Where an ingredient is sourced from a QPS microorganism, the relevance and requirement for toxicology studies should be discussed here, as it is with EFSA’s food enzymes scientific guidance. We suggest adding a section on the test item and dose-level as this is often an issue for applicants and reduces the possibility of performing studies on the wrong test item.	1. Please refer to the response to comment 13 in relation to the QPS approach and toxicological requirements on the novel food. Regarding the test item and the dose-level, please refer to the response to comment 274.

Comment number	Commentor	Comments	EFSA NDA Panel response
		2. Line 1174: Suggested addition: 'Available human studies and/or case reports'. We consider that the studies should be provided only when available.	2. The text has been revised in line with the comment.
654	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Lines 1189-1190. 'according to the OECD principles of GLP (Organisation for Economic Co-operation and Development principles of Good Laboratory Practices (OECD, 1998);': Is it the same reference as on line 343? In any case, 'OECD, 1998' is not in the list of references of the draft guidance.	The text has been revised in line by adding the appropriate reference.
680	Atova Regulatory Consulting SL	(Line 1160-1207, page 37-38) There is no mention of the QPS exemption for toxicological studies. We request that this is included. Also, a section that clearly defines when toxicological studies are not required would be highly beneficial as per Section 4.1 of the Food Enzyme Guidance. We also recommend including a section on the test item and dose-level as this is often an issue for applicants and reduces the possibility of performing studies on the wrong test item.	Please refer to the response to comment 13 in relation to the QPS approach and toxicological requirements on the novel food. Please refer to the response to comment 274 regarding the need for toxicological studies. Please refer to Section 8.1, 'General Considerations,' for guidance on the toxicological studies that may be required. Given the diverse categories of novel foods outlined in Regulation 2015/2283 (Article 3), it is not feasible to offer additional recommendations on when toxicological studies might be waived.
711	FoodDrinkEurope	1. [Line 1174] The studies should be provided only when available 2. [Line 1161-1206] There is no reference to alternative tests to animal testing here, this should be integrated to fit with general principles of the guidance.	1. Please refer to the response to comment 623. 2. Please refer to the response to comment 169.

Table 49: 8.2 Tiered approach to conduct toxicological studies

Comment number	Commentor	Comments	EFSA NDA Panel response
31	Undisclosed (Personal Capacity)	Lines 1222-1226 'In cases where the data in the literature raise concerns regarding reproductive – and developmental toxicity, a Tier III extended one generation reproductive toxicity study	Please refer to the response to comment 690 with regard to EOGRTS.

Comment number	Commentor	Comments	EFSA NDA Panel response
		(EOGRTS), which covers also subchronic toxicity, may be more appropriate. This would be more efficient regarding time and the number of animals needed, as compared to performing a Tier I subchronic toxicity followed by a Tier II reproduction and developmental study.` Is EFSA actually saying no need to do a full specifically designed sub-chronic study in this case? For Tier 1 why is there no mention of OECD 422 OECD (2016), Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264264403-en. Where OECD 408 (i.e. 90 day exposure) can actually be combined with a reproductive toxicity screen (OECD 421 OECD (1995), Test No. 421: Reproduction/Developmental Toxicity Screening Test, OECD Publishing, Paris, https://doi.org/10.1787/9789264070967-en)	While the proposal to consider OECD Test Guideline 422 as a Tier-1 study is reasonable when reproductive or developmental toxicity concerns are raised by literature data, it should be noted that OECD TG 422 alone is not adequate to address subchronic toxicity. An OECD TG 422 study may be sufficient as a Tier-1 study only if there are reproductive or developmental toxicity concerns, coupled with scientifically sound justifications for not conducting a subchronic toxicity study. This approach would not be the default; however, the Guidance allows for flexibility provided that robust scientific arguments support the chosen approach.
170	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 1222-1226 In cases where the data in the literature raise concerns regarding reproductive – and developmental toxicity, a Tier III extended one generation reproductive toxicity study (EOGRTS), which covers also subchronic toxicity, may be more appropriate. This would be more efficient regarding time and the number of animals needed, as compared to performing a Tier I subchronic toxicity followed by a Tier II reproduction and developmental study.` Is EFSA saying no need to do a full specifically designed sub-chronic study in this case?	Please refer to the response to comments 690 and 31.
314	Food Safety & Nutrition Consultancy	In tier 1, animal studies are not compulsory if the compositional data inform so. this further reduces unnecessary animal (and euro and time) us.	Please refer to the response to comment 309.
519	PETA Science Consortium International e.V.	1. Line 1220 The recently published ECHA report 'Evaluating results from 55 extended one-generation reproductive toxicity studies under REACH' (ref. 3) exposed several methodological deficiencies, including, for example, a high variability for most measurements, including thyroid hormone measurements, anogenital distance measurements, and follicle counts. This	1. The Panel acknowledges the comment. The Panel considers that no change to the Guidance is needed. 2. The text has been revised to provide further clarity ('in

Comment number	Commentor	Comments	EFSA NDA Panel response
		creates uncertainty as to what extent these measurements contribute to the identification of harmful substances. To future-proof the guidance, please consider adding the following in [brackets]: 'Findings from a Tier I subchronic toxicity study may for instance trigger the need for performing Tier II reproductive and developmental toxicity studies: In cases where the data in the literature raise concerns regarding reproductive – and developmental toxicity, a Tier III extended one generation reproductive toxicity study (EOGRTS), which covers also subchronic toxicity [or other studies, if they are equally or more predictive of human outcomes and use fewer animals] may be more appropriate.' 2. Line 1226 Suggestion to remove the carcinogenicity and chronic study: Decades of research suggest that rodent long-term repeated-dose bioassays lack reproducibility and predictive power for human tumorigenic events (ref. 4–6). The relevance of these animal data to human cancer risk assessment is lacking; there are numerous examples of chemically induced rodent neoplasms that are not considered applicable to human risk (ref. 7–11). Rat and mouse lifetime bioassays lack modern validation and scientific rigor. We strongly recommend eliminating the requirement for rodent cancer bioassays, and instead relying on advanced, relevant non-animal testing methods that better safeguard human health and the environment. Additionally, a recent JRC Technical report shows that most of the histopathological effects are seen after 28 and 90 days compared to 180 days and 365 days (ref. 12). This is also reflected in the proposal of the European Commission to remove the long-term toxicity study from the information requirements under REACH at the latest CASG-IR discussions (https://circabc.europa.eu/ui/group/a0b483a2-4c05-4058-addf-2a4de71b9a98/library/d4d1e1bc-42f2-490e-af4b-187b4f1bcca0/details). Additionally, time extrapolation factors (EFs) can account for differences in exposure duration of experimental studies (ref. 13). We recommend removing the following in quotes: Such cases may require follow-up investigations 'such as mechanistic studies and/or a Tier III	exceptional cases by a Tier III chronic toxicity or carcinogenicity study').

Comment number	Commentor	Comments	EFSA NDA Panel response
		chronic toxicity or carcinogenicity study.‘ And replacing with the following in [brackets]: Such cases may require follow-up investigations [and such decisions about potential follow-up studies should be made on a case-by-case basis and with robust scientific justification. It should be noted that any applicant shall ensure that testing on vertebrate animals is carried out only when non-animal methods are unavailable.] References 3. European Chemicals Agency (ECHA). Evaluating Results from 55 Extended One-Generation Reproductive Toxicity Studies under REACH: Final Report of the EOGRTS Review Project.; 2023. doi:10.2823/92503 4. Cohen SM. The relevance of experimental carcinogenicity studies to human safety. Curr Opin Toxicol. 2017;3:6-11. doi:10.1016/j.cotox.2017.04.002 5. Cohen SM. Human carcinogenic risk evaluation: An alternative approach to the two-year rodent bioassay. Toxicol Sci. 2004;80(2):225-229. doi:10.1093/toxsci/kfh159 6. Gottmann E, Kramer S, Pfahringer B, Helma C. Data quality in predictive toxicology: reproducibility of rodent carcinogenicity experiments. Environ Health Perspect. 2001;109(5):509-514. doi:10.1289/ehp.01109509 7. Steinbach TJ, Maronpot RR, Hardisty JF. Human Relevance of Rodent Leydig Cell Tumors. In: Hamilton & Hardy’s Industrial Toxicology. ; 2015:1189-1196. doi:https://doi.org/10.1002/9781118834015.ch109 8. Knight A, Bailey J, Balcombe J. Animal Carcinogenicity Studies: 1. Poor Human Predictivity. Altern to Lab Anim. 2006;34(1):19-27. doi:10.1177/026119290603400117 9. Foster JR, Tinwell H, Melching-Kollmuss S. A review of species differences in the control of, and response to, chemical-induced thyroid hormone perturbations leading to thyroid cancer. Arch Toxicol. 2021;95(3):807-836. doi:10.1007/s00204-020-02961-6 10. Boobis AR, Cohen SM, Dellarco VL, et al. Classification schemes for carcinogenicity based on hazard identification have become outmoded and serve neither science nor society. Regul Toxicol Pharmacol. 2016;82:158-166. doi:10.1016/j.yrtph.2016.10.014 11. Doe JE, Boobis AR, Cohen SM, et al. A new approach to the classification of carcinogenicity. Arch Toxicol. 2022;96(9):2419-2428. doi:10.1007/s00204-022-03324-z 12. Jennings P,	

Comment number	Commentor	Comments	EFSA NDA Panel response
		Chandrasekaran V, Hardy B, et al. Mechanistic Analysis of Repeated Dose Toxicity Studies.; 2023. doi:doi:10.2760/824535 13. Escher SE, Mangelsdorf I, Hoffmann-Doerr S, et al. Time extrapolation in regulatory risk assessment: The impact of study differences on the extrapolation factors. Regul Toxicol Pharmacol. 2020;112:104584. doi:https://doi.org/10.1016/j.yrtph.2020.104584	
624	Cellular Agriculture Europe	Lines 1221 - 1226: `In cases where the data in the literature raise concerns regarding reproductive – and developmental toxicity, a Tier III extended one generation reproductive toxicity study (EOGRTS), which covers also subchronic toxicity, may be more appropriate. This would be more efficient regarding time and the number of animals needed, as compared to performing a Tier I subchronic toxicity followed by a Tier II reproduction and developmental study.` Shall we understand that there is no need to do a full specifically designed sub-chronic study in this case? For Tier 1 we note the absence of a reference to OECD 422 OECD (2016), Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264264403-en. Where OECD 408 (i.e. 90 day exposure) can actually be combined with a reproductive toxicity screen (OECD 421 OECD (1995), Test No. 421: Reproduction/Developmental Toxicity Screening Test, OECD Publishing, Paris, https://doi.org/10.1787/9789264070967-en.) Lines 1232 - 1233: Figure 2: We suggest that EFSA adds computational toxicology in the tier 1 level for genotoxicity. Computational toxicology is more and more used in combination with in vitro studies to predict if a chemical or a mix of chemicals have a genotoxic potential. We also invite EFSA to add legend for the full and dotted lines of figure 2	Please refer to the responses to comments 690 and 31.

Table 50: 8.3 Genotoxicity

Comment number	Commentor	Comments	EFSA NDA Panel responses
113	Food Fermentation Europe	Lines 1246 to 1248 page 39 again introduce a new requirement to assess the fraction of small particles even in conventional materials that do not meet the definition of engineered nanomaterials, here for the purpose of ensuring that genotoxicity study design suitably covers potential adverse effects of the small particles fraction of the novel food in accordance with the recommendations set in Section 4 of the Guidance on Particle – TR. As already discussed in our previous comments in Sections 3, 4, and 7, Food Fermentation Europe considers that this broad new requirement to demonstrate the absence of a fraction of nano-scale particles, or alternatively that this fraction of nano-scale particles is covered by the conventional risk assessment as per the Guidance on Particle – TR, places an unreasonable and unnecessary additional burden on applicants to conduct potentially significant additional and costly analysis for novel foods of biological origin. The draft guidance itself acknowledges that this requirement is not needed for a number of novel food categories (lines 732-735 pages 23-24), but the exemption carved out by the document (lines 735-736, page 24) is too narrow to avoid unnecessary additional testing for many applicants. Based on the foregoing, Food Fermentation Europe respectfully requests that the draft guidance be revised to only require that genotoxicity study design take into account the fraction of small particles in novel food of biological origin that do not meet the definition of engineered nanomaterial when there is reason to believe that a fraction of small particles in the specific novel foods of interest may have different genotoxic potential.	The Guidance on TR (sections 2.1 and 2.2) specifies that for botanicals and other complex materials of biological origin, the applicant may provide a rationale to demonstrate that an assessment of small particles, including nanoparticles, is either unnecessary or already addressed within the safety assessment process. For example, if these materials contain small particles of natural origin similar to those found in foods considered safe for consumption, the applicant may argue that these particles have a similar fate and hazard profile in the gastrointestinal tract as those naturally present in comparable foods. Therefore, additional assessment may not be required if supported by relevant studies. A scientifically sound justification, supported by available evidence, should be presented. Please refer to the response to comment 109.
132	Medfiles Ltd	1. Comment: P30 L1249: Please note the typo. 2. P30 L1261: For this section, Medfiles would appreciate if the OECD numbers with the titles of the genotox studies were listed similarly to the section above. This would make it easier for the reader. Thank you.	1. The text has been revised in line with the comment. 2. The Panel acknowledges the recommendation but notes that the information in the respective paragraph cannot provide detailed guidance on the specific tests or OECD Test Guidelines (TG) to be

Comment number	Commentor	Comments	EFSA NDA Panel responses
			used, as the in vivo tests required will depend on the findings from the in vitro studies. Applicants should refer to the EFSA guidelines cited in the references for more detailed information.
171	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Line 1234 Are genotoxicity studies Tier 1 studies always required? What could be an example of exemption for genotoxicity testing (botanicals with presumption of safety status)?In the literature, genotoxicity tests are often not compliant with GLP (and OECD guidelines), can they still support the absence of genotoxic concern and thus remove the necessity of conducting Tier 1 studies? 2. Lines 1247-1248 Should also refer to EFSA nano TR Guidance (possible exemptions for nano-specific toxicology/genotoxicity testing). 3. Line 1249 Do you consider an extract of microorganism as non-viable cells novel food ? 4. Line 1249 r missing for 'requested' 5. Lines 1251-1252 We agree that testing the microorganism in in vitro genotoxicity test may not provide valuable information. However, as testing the lysate and/or supernatant may also not provide valuable information on genotoxicity and may in fact lead to false-positive classifications. We suggest that genotoxicity requirements be revisited and revised. There are other ways to determine if genotoxic metabolites are produced, such as evaluation of the microorganism's genome for genes that produce toxic metabolites. This is discussed elsewhere in the document and that section should be referenced here. Testing the supernatant has many limitations, such as: (1) Will the genetic tox assay organisms grow in the supernatant? (2) are the materials in the supernatant homogenous during sample collection from fermentors? (3) The toxic metabolite would need to be identified. (4) There could be a toxic metabolite produced but at such low levels in the supernatant that it does not produce an effect, but upon concentration during production, reach a toxic level. This would be missed. (5) would you need to remove	1. It should be noted that genotoxicity is assessed to address potential safety concerns identified in other parts of the assessment process, such as those related to the production process. As a result, it is not feasible to provide specific examples of exemptions from genotoxicity testing within this Guidance. 2. The text has been revised in line with the comment. 3. Please note that the requirement for genotoxicity testing applies to novel foods consisting of microorganisms (active agents and biomasses, as defined in section 1.2) and depends on the taxonomic classification and hazard identification described in section 1.2 and Appendix A. For both active agents and biomasses, the recommended approach for evaluating genotoxicity is to test both the supernatant and the cell lysate, ensuring that cell/spore lysis is effectively demonstrated. 4. Please refer to the response to comment 132. 5. Please note that this approach has been discussed and agreed upon with the EFSA Scientific Committee

Comment number	Commentor	Comments	EFSA NDA Panel responses
		all water/liquid and reconstitute the supernatant before dosing? (6) the supernatant isn't the final product, and its contents shouldn't be in the final product. Testing the supernatant would not mimic the final novel food product. For the lysate, does EFSA expect the manufacturer to count cells, then lyse them, remove the lysing agent, then add the lysate to in vitro genetox assays? How will the lysating agent be removed to ensure there aren't changes in genotoxicity due to the lysate? Also, cellular contents themselves are toxic as evidenced by tumour lysis syndrome (exhibited by cancer patients). How would one determine if the toxin was produced by the bacteria or just the concentration of internal cellular components?	Working Group on Genotoxicity and is considered the minimum dataset requirement for such novel foods. Section 8.3 has been clarified regarding the number of samples to be tested. However, there is no specific guidance on the protocol for testing the supernatant, cell/spore lysis, or the demonstration of efficient lysis. It is the applicant's responsibility to select a valid or standardised methodology to provide the required data.
219	EU Specialty Food Ingredients	Lines 1247-1248: There should also be a reference to EFSA nano TR Guidance (possible exemptions for nano-specific toxicology/genotoxicity testing). Line 1249: r missing for 'requested'. Lines 1251-1252: 1. We agree that testing the microorganism in in vitro genotoxicity test may not provide valuable information. However, testing the lysate and/or supernatant may also not provide valuable information on genotoxicity and may in fact lead to false-positive classifications. We suggest to revise the genotoxicity requirements. There are other ways to determine if genotoxic metabolites are produced, such as evaluation of the microorganism's genome for genes that produce toxic metabolites. This is discussed elsewhere in the document and that section should be referenced here. 2. Testing the supernatant has many limitations, such as: (1) Will the genetic tox assay organisms grow in the supernatant? (2) Are the materials in the supernatant homogenous during sample collection from fermentors? (3) The toxic metabolite would need to be identified. (4) There could be a toxic metabolite produced but at such low levels in the supernatant that it does not produce an effect, but upon concentration during production, reach a toxic level. This would be missed. (5) Would you need to remove all water/liquid and reconstitute the supernatant before dosing? (6) The supernatant isn't the final product, and its contents shouldn't be in the final product. Testing the supernatant would	Please refer to the response to comment 171.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		not mimic the final novel food product. 3. For the lysate, does EFSA expect the manufacturer to count cells, then lyse them, remove the lysing agent, then add the lysate to in vitro genetox assays? How will the lysating agent be removed to ensure there aren't changes in genotoxicity due to the lysate? Also, cellular contents themselves are toxic as evidenced by tumour lysis syndrome (exhibited by cancer patients). How would one determine if the toxin was produced by the bacteria or just the concentration of internal cellular components?	
232	Planet A Foods GmbH	Clear statement confirming the exemptions of QPS strains for genotoxicity testing should be added	Please refer to the response to comment 13. The text has been revised.
255	The Good Food Institute Europe	Line 1240 - 1241: Specific approaches should be followed based on the characteristics and compositions of the novel food. Comment: EFSA could consider providing specific examples of the format, structure and methodology of the various genotoxicity testing to be completed for various novel production techniques including precision fermentation and cultivated meat.	The Panel acknowledges the necessity of evaluating novel foods derived from the new technologies mentioned. Currently, there is insufficient experience to provide detailed guidance on these categories of novel foods. Therefore, a case-by-case evaluation approach will be applied.
257	Novonesis (merger of former Novozymes and Chr. Hansen)	In line 1249-1252, page 39, it is stated that when the novel food is a microorganism (viable or non-viable cells), the applicant is requested to perform genotoxicity testing depending on the taxonomy and microbiological hazard identification. The recommended approach to evaluate genotoxicity is to test both the supernatant and the cell lysate. Guidance/recommendations on how to prepare the supernatant and the cell lysate (e.g. in Appendix or by literature references) would be considered useful.	Please refer to the response to comment 171.
564	International Probiotic Association - Europe (IPA Europe)	Lines 1249 – 1252 IPAEU: Regarding the aspect of genotoxicity testing, particularly when assessing novel foods consisting of microorganisms (viable or non-viable cells), we wish to express our questions. We welcome further clarification and justification regarding the rationale behind such testing requirements. We suggest that the rationale and suitability of the suggested genotoxic testing of microorganisms be further reviewed and discussed, including the relevance of investigation of the genome	Please refer to the response to comment 171.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		for the possibility of production of genotoxic metabolites (e.g. characterisation of genes of potential concern as per line 443).	
625	Cellular Agriculture Europe	Line 1241: We would welcome an example of the genotox test(s) to be done or not for cultured food and proteins.	Please refer to the response to comment 255.
655	Pen & Tec Consulting S.L.U. (trading as Argenta®)	1. Line 1249. 'the applicant is equested to': Please note a minor typo in 'requested'. 2. Lines 1251-1252. 'The recommended approach to evaluate genotoxicity is to test both the supernatant and the cell lysate': For live microorganisms, is it not required to test genotoxicity of the live strain? For heat-treated microorganisms, is the genotoxicity test of the heat-treated strain needed? Could EFSA specify whether one batch of the supernatant or the lysate is needed for this genotoxicity tests? 3. Line 1252. 'Proof of efficient lysis of the cells/spores must be provided': Could EFSA elaborate on the interpretation of 'efficient lysis': i.e. indicating visual techniques (SEM, etc.) and expected number of visual fields (8-10) to prove lysis efficiency as well as a note indicating that not all strains can be fully lysate and, in this case, the applicant can provide justification of the methods used and a % of lysis efficiency? Does the lysis efficiency test need to be notified as this is part of preliminary data of the genotoxicity testing and could be considered as characterisation of the novel food?	1. Please refer to the response to comment 132. 2. Please refer to the response to comment 171. 3. Please refer to the response to comment 171. Regarding the notification of studies, if cell or spore lysis analysis is included in the study protocol for a genotoxicity study, it would be part of that study. However, if the analysis is conducted independently of the genotoxicity study, it can be considered as part of the product characterisation. In this case, it would not be subject to the study notification obligations.
681	Atova Regulatory Consulting SL	(Line, 1252, page 39) 'Proof of efficient lysis of the cells should be demonstrated'. Please describe the method preferred to prove efficient lysis. Alternatively, we suggest rephrasing: Steps used to achieve efficient lysis of the cells should be described'	Please refer to the response to comment 171.
712	FoodDrinkEurope	1. (Line, 1241) Could EFSA add example of the genotox test(s) to be done or not for cultured food and proteins, as it was done for mixture, nano or microorganism 2. (Line, 1253) Can EFSA add computational approach that would be accepted for genotoxicity testing? Computational toxicology is more and more used in combination of in vitro studies to predict if a chemical or a mix of chemicals have a genotoxic potential 3. (Line, 1254) Can EFSA specify that a bacterial reverse mutation assay is not recommended for nanomaterials?	1. Please refer to the response to comment 255. 2. Please refer to the reference provided in this Guidance on EFSA's genotoxicity approach (EFSA Scientific Committee, 2011). The Panel considers that no change to the Guidance is needed.

Comment number	Commentor	Comments	EFSA NDA Panel responses
			3. With regards to genotoxicity testing of nanomaterials/small particles, Please refer to EFSA Scientific Committee (2021a, b). The text has been revised.

Table 51: 8.3.1 Tier I Genotoxicity testing

Comment number	Commentor	Comments	EFSA NDA Panel responses
172	Synpa, French association of specialty food ingredients manufacturers and distributors	Line 1259 How many samples do you advise to store ?	The Panel acknowledges the request but considers that it goes beyond the scope of this Guidance. Please refer to OECD TG 487 for further details.
520	PETA Science Consortium International e.V.	The in vitro gene mutation test in mammalian cells (OECD TG 476, 2016) is an established method accepted under plant protection product regulation (Commission Communication in the framework of the implementation of Commission Regulation (EU) No 283/2013). We strongly recommend adding this test to the basic battery of in vitro tests. If there is a reason that this method should not be used for testing novel foods, please include the reason why in the text.	The Panel agrees with the comment. However, it should be noted that the genotoxicity testing for novel foods is following the general strategy proposed by the EFSA Scientific Committee in 2011 (where the mammalian mutation test is indicated as possible test to be used). A revision of this strategy is beyond the scope of this guidance.
626	Cellular Agriculture Europe	Lines 1253 - 1254: We suggest that EFSA adds computational approach that would be accepted for genotoxicity testing. Computational toxicology is more and more used in combination of in vitro studies to predict if a chemical or a mix of chemicals have a genotoxic potential Can EFSA specify that a bacterial reverse mutation assay is not recommended for nanomaterials? Ames test is not adapted for nanomaterials.	Please refer to the response to comment 690.
656	Pen & Tec Consulting	Lines 1256-1260. 'In case of positive outcome of the in vitro micronucleus test, the applicant will be requested to further	Please note that in the Guidance, it is recommended to store samples from

Comment number	Commentor	Comments	EFSA NDA Panel responses
	S.L.U. (trading as Argenta®)	investigate whether the novel food induces aneugenicity by performing a kinetochore staining or fluorescence in situ hybridisation (FISH). Therefore, the applicant is advised to store relevant samples for further analysis testing.': Does EFSA expect the same batch to be tested in the in vitro micronucleus test as in the potential kinetochore staining or FISH?	the micronucleus in vitro test to allow for subsequent analysis using kinetochore staining or fluorescent in situ hybridisation on the same samples.

Table 52: 8.3.2 Tier II Genotoxicity testing

Comment number	Commentor	Comments	EFSA NDA Panel responses
521	PETA Science Consortium International e.V.	The in vitro chromosome damage assays gave a high percentage of misleading positive results, often related to cell line choice and confounded by differing methods of estimating cytotoxicity (ref. 14). To better interpret in vitro genotoxicity results, it has been suggested that all available information including in silico and in vitro data should be considered in a holistic weight of evidence approach (ref. 15). Therefore, to reduce animal testing, a thorough assessment of positive in vitro results should be made before proceeding with in vivo tests. This assessment may include evaluation of toxicokinetic and toxicodynamic profiles along with determination of the exposure pathway, and investigations using advanced in vitro and in silico models to clarify the mode/mechanism of action (ref. 1,16,17). We suggest removing the following in quotes: 'In case of positive or ambiguous results for genotoxicity from the Tier I in vitro test battery' And add the following in [brackets]: [If the information referred to in chapter 8.3.1 (Tier I Genotoxicity testing), used together in an integrated weight of evidence assessment, gives rise to a genotoxicity concern,] the follow-up approaches, as well as recommendations on test types, interpretations of results, evidence of target tissue exposure and other issues in testing in vivo the genotoxicity of substances present in food, are described in detail in the Opinions of the Scientific Committee (EFSA Scientific Committee, 2011b; EFSA Scientific Committee, 2017; EFSA Scientific Committee, 2021b).	Please note that in section 8.3.2 on Tier II Genotoxicity Testing, the Guidance refers to the EFSA Scientific Committee documents from 2011, 2017, and 2021. The suggested approach in this guidance considers the integrated approach mentioned in your comment. Specifically, EFSA Scientific Committee (2011) in section 5.1.3 on 'Follow-up of positive results from the basic battery' states: 'If positive results are obtained in the basic battery of in vitro tests, all relevant data should be reviewed before proceeding to the next step. The subsequent actions may include (a) concluding the assessment without further testing, (b) conducting additional in vitro testing, or (c) performing in vivo testing. It may also be determined that the positive in vitro results are not relevant to the in vivo situation, or a decision may be made to complete the

Comment number	Commentor	Comments	EFSA NDA Panel responses
		[However, to clarify positive in vitro results prior to conducting in vivo tests, the results may first be investigated using in silico and advanced in vitro methods.] In addition, where in vivo genotoxicity testing is required, repeated-dose toxicity studies should integrate appropriate genotoxicity tests, where possible, to reduce the number of animals tested. References: 1. Volarath P, Zang Y (Janet), Kabadi S V. Application of Computational Methods for the Safety Assessment of Food Ingredients BT - Advances in Computational Toxicology: Methodologies and Applications in Regulatory Science. In: Hong H, ed. Springer International Publishing; 2019:233-257. doi:10.1007/978-3-030-16443-0_12 14. Fowler P, Smith R, Smith K, et al. Reduction of misleading (‘false‘) positive results in mammalian cell genotoxicity assays. III: Sensitivity of human cell types to known genotoxic agents. Mutat Res Toxicol Environ Mutagen. 2014;767:28-36. doi:https://doi.org/10.1016/j.mrgentox.2014.03.001 15. Kirkland DJ, Aardema M, Banduhn N, et al. In vitro approaches to develop weight of evidence (WoE) and mode of action (MoA) discussions with positive in vitro genotoxicity results. Mutagenesis. 2007;22(3):161-175. doi:10.1093/mutage/gem006 16. Yasui M, Fukuda T, Ukai A, et al. Weight of evidence approach using a TK gene mutation assay with human TK6 cells for follow-up of positive results in Ames tests: a collaborative study by MMS/JEMS. Genes Environ. 2021;43(1):7. doi:10.1186/s41021-021-00179-1 17. Benigni R. In silico assessment of genotoxicity. Combinations of sensitive structural alerts minimise false negative predictions for all genotoxicity endpoints and can single out chemicals for which experimentation can be avoided. Regul Toxicol Pharmacol. 2021;126:105042. doi:https://doi.org/10.1016/j.yrtph.2021.105042	assessment for other reasons‘. Therefore, the Panel notes the recommendation but considers that a detailed expansion of the section goes beyond the scope of this Guidance.

Table 53: 8.3.3 Tier III Genotoxicity testing

Comment number	Commentor	Comments	EFSA NDA Panel responses
60	Specialised Nutrition Europe (SNE)	Page 40 line 1268-1271 Mismatch between text description and the title calling out Genotoxicity testing.	The text has been revised in line with the comment.
522	PETA Science Consortium International e.V.	Rat and mouse lifetime bioassays lack modern validation and scientific rigor. These animal data lack relevance to human cancer risk assessment and there are numerous examples of chemically induced rodent neoplasms that are not considered applicable to human risk. To transparently discuss potential limitations of in vivo carcinogenicity assays and to refer to validated non-animal assays, we recommend adding the following in [brackets]: 'Positive in vitro or in vivo genotoxicity tests could be followed up by carcinogenicity and or reproductive studies only if the mechanism of genotoxicity is clearly identified and if it is not directly DNA reactive. Further guidance on the triggers for these studies and their implementation are outlined in the respective OECD Guidelines (OECD TG 451, 452 or 453). [It is important to recognise that discussions around the relevance of carcinogenicity assays to human health have highlighted instances where chemically induced tumours in rodents may not accurately reflect human risk. This underscores the need for careful interpretation of such test results, bearing in mind the potential discrepancies between effects observed in rodents and human reactions to carcinogenic substances (ref. 4–11). In the realm of carcinogenicity testing, in vitro assays such as the Cellular Transformation Assays (CTAs) emerged as a quicker and cost-effective non-animal alternative to traditional in vivo rodent tests. These assays serve as a critical preliminary step for evaluating the carcinogenic potential of chemicals. However, the effective application of these in vitro tests necessitates the development of robust quantitative in vitro to in vivo extrapolation (QIVIVE) methodologies. Such advancements are essential for accurately translating in vitro observations to dose-related contexts.]' References: 4. Cohen SM. The relevance of experimental carcinogenicity studies to human safety. Curr Opin Toxicol.	The Panel notes the recommendations. The text has been revised.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		2017;3:6-11. doi:10.1016/j.cotox.2017.04.002 5. Cohen SM. Human carcinogenic risk evaluation: An alternative approach to the two-year rodent bioassay. Toxicol Sci. 2004;80(2):225-229. doi:10.1093/toxsci/kfh159 6. Gottmann E, Kramer S, Pfahringer B, Helma C. Data quality in predictive toxicology: reproducibility of rodent carcinogenicity experiments. Environ Health Perspect. 2001;109(5):509-514. doi:10.1289/ehp.01109509 7. Steinbach TJ, Maronpot RR, Hardisty JF. Human Relevance of Rodent Leydig Cell Tumors. In: Hamilton & Hardy's Industrial Toxicology. ; 2015:1189-1196. doi:https://doi.org/10.1002/9781118834015.ch109 8. Knight A, Bailey J, Balcombe J. Animal Carcinogenicity Studies: 1. Poor Human Predictivity. Altern to Lab Anim. 2006;34(1):19-27. doi:10.1177/026119290603400117 9. Foster JR, Tinwell H, Melching-Kollmuss S. A review of species differences in the control of, and response to, chemical-induced thyroid hormone perturbations leading to thyroid cancer. Arch Toxicol. 2021;95(3):807-836. doi:10.1007/s00204-020-02961-6 10. Boobis AR, Cohen SM, Dellarco VL, et al. Classification schemes for carcinogenicity based on hazard identification have become outmoded and serve neither science nor society. Regul Toxicol Pharmacol. 2016;82:158-166. doi:10.1016/j.yrtph.2016.10.014 11. Doe JE, Boobis AR, Cohen SM, et al. A new approach to the classification of carcinogenicity. Arch Toxicol. 2022;96(9):2419-2428. doi:10.1007/s00204-022-03324-z	
627	Cellular Agriculture Europe	Line 1275: Further clarity would be welcome on the sub-acute studies (e.g., 14-day, 28-day), i.e. to add the 28-day as an example as well when it can be done instead of a 14-day tox study	The Guidance clarifies that sub-acute studies may be conducted (not mandatory) to inform the selection of appropriate doses for subsequent sub-chronic studies. If the applicant has sufficient information, such as relevant literature data, and has considered the anticipated human intake at the proposed uses and levels, such a study may not be necessary. In such cases, the complete technical report of the dose

Comment number	Commentor	Comments	EFSA NDA Panel responses
			range-finding study should be submitted. The Panel considers that no change to the Guidance is needed.

Table 54: 8.4 Repeated-dose toxicological studies

Comment number	Commentor	Comments	EFSA NDA Panel response
61	Specialised Nutrition Europe (SNE)	Page 40 line 1272 This part of the guidance is still heavily promoting the use of animal tests which is contradictory to other parts of the guidance where it is encouraged to explore alternatives/more human-relevant approaches.	The Panel acknowledges the comment. To assess the potential toxicity of new substances and other types of novel foods, animal studies remain one of the most suitable models for risk assessment. However, the Guidance Document not only allows for flexibility but also encourages applicants to minimise animal use. This can be achieved by utilising existing literature and incorporating new alternative testing methods, provided that these methods are accompanied by relevant validation or qualification data.
133	Medfiles Ltd	1. P40 L1279: Please note this comment from P11 L329-345 also here: Medfiles welcomes strengthening of the 3R principle throughout the guidance and that a comprehensive/detailed chemical characterisation, literature review for toxicologically (and nutritionally) relevant substances identified in the characterisation and in vitro studies should be conducted prior to any animal studies. Nevertheless, EFSA notes that 'a subchronic study is often needed', which gives the impression that even if the Applicant provided a proper data based on the 3R principles (no its own 90-day study), there is a great chance that 90-day study would be requested anyhow by EFSA. Thus, could EFSA	1. Please refer to the response to comment 117. 2. The Panel acknowledges the comment and considers that no change to the Guidance is needed.

Comment number	Commentor	Comments	EFSA NDA Panel response
		consider it better in its guidance that in fact the 90-day study could be waived and give examples when and based on which data this could be possible. E.g. Medfiles assumes that if the applicant is able to carry out a component-based risk/safety assessment concluding the safety of a novel food, this could be one way to avoid a 90-day study. Similarly, Medfiles assumes that if the Applicant was able to conduct a compositional comparison of the novel food to a food/food ingredient known to be safe e.g. by using omics and/or fingerprinting techniques a 90-day study could be omitted. Hence, could EFSA consider adding this type of guidance in order to waive the 90-day study, and not just to say 'If a subchronic study is not conducted, a well-reasoned justification should be provided.' We also noted that guidance also incorporates better the use of read-across, in silico (QSAR), TTC, omics, (in chemico could be added) and other NAMs as well as use of data on MOAs/mechanisms. In line with 3Rs, Medfiles proposes that the guidance should take more stock about that component-based mixture risk assessment as this could be very relevant in case of simple mixtures. Feedap is using this approach e.g. for botanicals. Much toxicological literature data are already available. In addition, Medfiles notes that TKplate and its use (hopefully also for applicants) is not considered in this guidance. Therefore, Medfiles proposes to add it to the guidance in view that it would become available for all to use. 2. P40 L1279: Medfiles notes that while previously it was directly referred to the OECD TG 408 with parameters from the OECD 407 now many of these parameters are mentioned at a later stage. It would be easier for the reader if already at this stage it is mentioned that OECD 408 with extended parameters may be needed with the respective Section numbers. In addition, in this same context it would be useful to mention that instead of doing Tier I 90-day tox + Tier II (repro/developmental tox), it would be better to conduct EOGRST. Thus, it would be good to move the lines 1221-1225 down close to the 90-day study (and probably shorten the text in 1221-1225).	

Comment number	Commentor	Comments	EFSA NDA Panel response
713	FoodDrinkEurope	1. (Line, 1275) Further clarity is required on the sub-acute studies (e.g., 14-day, 28-day) 2. [Lines 1278-1303 and 1324-1326] Here by default, an animal study (90-day) is requested from Tier 1. Compared with ADME and genotoxicity tierce approaches, where animal testing can be avoided at Tier I, does EFSA mean that this is mandatory for repeated-dose toxicological studies? The mention related to 'well-reasoned justification to be provided' line 1283 should be clarified. For Tier 1, we could mention OECD 422 OECD (2016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test - https://doi.org/10.1787/9789264264403-en). Where OECD 408 (i.e. 90-day exposure) can actually be combined with a reproductive toxicity screen OECD 421(1995 - Reproduction/Developmental Toxicity Screening Test - https://doi.org/10.1787/9789264070967-en). We could also cross-reference to 'Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age' (2017 - EFSA Journal) in this section as well. 3. (Lines, 1328–1343) The following references could also be a consideration to add here, in order to provide further reassurance at Tier 1 for absence of reproductive/developmental concern/provide information for dosing of tier II studies. OECD 422 OECD (2016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test - https://doi.org/10.1787/9789264264403-en). Where OECD 408 (i.e. 90-day exposure) can be combined with a reproductive toxicity screen OECD 421(1995 - Reproduction/Developmental Toxicity Screening Test - https://doi.org/10.1787/9789264070967-en).	1. Please refer to the response to comment 627. 2. Please refer to the response to comment 117. The EFSA Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age is cited elsewhere in the Novel Foods Guidance (section 8.3.2, section 8.5). 3. The Panel considers that no change to the Guidance is needed.

Table 55: 8.4.1 Tier I repeated-dose toxicological studies

Comment number	Commentor	Comments	EFSA NDA Panel responses
32	Undisclosed (Personal Capacity)	1. Lines1307-`1313 'In cases where the data in the literature raise concerns regarding reproductive – and developmental toxicity, a Tier III extended one generation reproductive toxicity study (EOGRTS), which covers also subchronic toxicity, may be more appropriate. This would be more efficient regarding time and the number of animals needed, as compared to performing a Tier I subchronic toxicity followed by a Tier II reproduction and developmental study.' Is EFSA actually saying no need to do a full specifically designed sub-chronic study in this case? For Tier 1 why is their no mention of OECD 422 OECD (2016), Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264264403-en. Where OECD 408 (i.e. 90 day exposure) can actually be combined with a reproductive toxicity screen (OECD 421 OECD (1995), Test No. 421: Reproduction/Developmental Toxicity Screening Test, OECD Publishing, Paris, https://doi.org/10.1787/9789264070967-en.) 2. Lines 1278-1303 Lines 1324-1326 OECD 422 OECD (2016), Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264264403-en. Where OECD 408 (i.e. 90 day exposure) can actually be combined with a reproductive toxicity screen (OECD 421 OECD (1995), Test No. 421: Reproduction/Developmental Toxicity Screening Test, OECD Publishing, Paris, https://doi.org/10.1787/9789264070967-en.) This could be a consideration to add here, in order to provide further reassurance at Tier 1 for absence of reproductive/developmental concern/provide information for dosing of tier II studies etc. Why no cross-reference to Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age - - 2017 - EFSA Journal -	Please refer to the responses to comments 31 and 713.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		Wiley Online Library for infant formula ingredients in this section as well.	
44	Intertek	Lines 1303 to 1304 - a summary table of statistically significant findings is already required to be submitted in Appendix B.3 to the dossier, in accordance with the EFSA Administrative guidance for the preparation of applications on novel foods pursuant to Article 10 of Regulation (EU) 2015/2283. Does the statement here mean that a summary table must be provided within the dossier text, as well as in Appendix B.3?	No duplication is required, provided that the summary table of statistically significant findings is included either within the Toxicology section of the dossier, in an Appendix or in the respective study report.
114	Food Fermentation Europe	Lines 1320 to 1323 page 41 again introduce a new requirement to assess the fraction of small particles even in conventional materials that do not meet the definition of engineered nanomaterials, here for the purpose adapting subchronic toxicity study design to ensure they cover the hazard assessment of small particles of the novel food in accordance with the recommendations set in Section 4 of the Guidance on Particle – TR. As already discussed in our previous comment in Sections 3, 4, and 7, Food Fermentation Europe considers that this broad new requirement to demonstrate the absence of a fraction of nano-scale particles, or alternatively that this fraction of nano-scale particles is covered by the conventional risk assessment as per the Guidance on Particle – TR, places an unreasonable and unnecessary additional burden on applicants to conduct potentially significant additional and costly analysis for novel foods of biological origin. The draft guidance itself acknowledges that this requirement is not needed for a number of novel food categories (lines 732-735 pages 23-24), but the exemption carved out by the document (lines 735-736, page 24) is too narrow to avoid unnecessary additional testing for many applicants. Based on the foregoing, Food Fermentation Europe respectfully requests that the draft guidance be revised to only require that subchronic toxicity design be adapted to take into account the fraction of small particles in novel food of biological origin that do not meet the definition of engineered nanomaterial when there is reason to believe that this fraction of small particles in the specific novel foods of interest may present a different hazard.	Please refer to the responses to comments 109 and 113.

Comment number	Commentor	Comments	EFSA NDA Panel responses
173	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Subacute toxicity Line 1275 Is the 14-day study mandatory now ? Or is it possible, if we already know the dose to be tested thanks to the literature for example, to go directly with the 90-day study ? 2. Subchronic toxicity Line 1278 Where does EFSA stand on 28-day toxicity testing (similar to OECD 407)? Could this test be used for novel food intended to be used in food supplements only, where it is possible to set a restriction of duration use? Could an additional UF of 2 or 10 be acceptable for EFSA? For novel food intended to be used in food supplements, could EFSA accept 28-day toxicity study (if compliant with OECD/ICH and GLP) in lieu of 90-day toxicity study? If it was a regulatory requirement for authorisation in a non-European country (ex: China and Health food regulation) Subchronic toxicity testing is required when NF contains components of unknown toxicity, or with no HBGVs or there is an uncharacterised fraction. Can the TTC approach be used for the components of unknown toxicity or uncharacterised fraction to avoid unnecessary testing?‘ 3. Line 1297 Is the recovery group mandatory ? In which case should we add it ? 4. Line 1303 Are you talking about appendix B ? 5. Lines 1278-1303 and 1324-1326 Here by default, an animal study (90-day) is requested from Tier 1. Compared with ADME and genotoxicity tierce approaches, where animal testing can be avoided at Tier I, does EFSA says this is mandatory for repeated-dose toxicological studies? The mention related to ‘well-reasoned justification to be provided‘ line 1283 should be clarified. For Tier 1, we could mention OECD 422 OECD (2016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test - https://doi.org/10.1787/9789264264403-en). Where OECD 408 (i.e. 90-day exposure) can actually be combined with a reproductive toxicity screen OECD 421(1995 - Reproduction/Developmental Toxicity Screening Test - https://doi.org/10.1787/9789264070967-en) We could also cross-reference to ‘Guidance on the risk assessment of	1. Please refer to the response to comment 627. 2. The Guidance specifies that for Tier I repeated-dose toxicological studies, a 90-day subchronic toxicity study is often required rather than a 28-day study. The responsibility for designing the toxicity testing strategy when preparing a novel food application lies with the applicant. The Panel will evaluate the submitted evidence and may request additional studies if deemed necessary. While the Panel understands the concerns raised, it considers that expanding this section would exceed the scope of the current Guidance. 3. A recovery group can be useful for example in cases where reversibility needs to be assessed. Please refer to the response to comment 32. 4. Please refer to the response to comment 44. 5. Please refer to the response to comments 31 and 713.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		substances present in food intended for infants below 16 weeks of age‘ (2017 - EFSA Journal) in this section as well.	
315	Food Safety & Nutrition Consultancy	In tier 1, animal studies are not compulsory if the compositional data inform so. this further reduces unnecessary animal (and euro and time) us.	Please refer to the response to comment 309.
523	PETA Science Consortium International e.V.	1. Line 1294 This guidance could help reduce animal testing by integrating considerations for testing on vertebrate animals only as a last resort and designing studies to explore multiple parameters or combining studies where feasible. This approach reflects a responsible stance towards animal welfare. Please consider adding the following in [brackets]: ‘The results obtained in the subchronic toxicity study can also provide indications on the need for additional studies on specific effects (section 8.2). [Applicants shall ensure that testing on vertebrate animals is carried out only when non-animal methods are unavailable. If testing on vertebrate animals is robustly scientifically justified, such testing shall be carefully designed, where appropriate, by considering whether several parameters can be assessed within the framework of one study (e.g. kinetic data generation, micronucleus formation, neurotoxicity, immunotoxicity) or whether studies can be combined to the extent permitted by the corresponding test method.]‘ 2. Line 1324 Please consider adding the proposed sentence in [brackets] to ensure the guidance reflects a commitment to comprehensive safety assessments and whilst minimising animal use. ‘When indications of reproductive and/or endocrine effects are identified (from the literature, in vitro, in vivo, and/or human studies), the applicant is advised to include additional endpoints in the 90-day subchronic toxicity study (section 8.4.2.1). [If non-animal methods for assessing these reproductive or endocrine effects are available, they may be used where the mechanistic relevance can be demonstrated.]‘	1. Please refer to the response to comments 518 and 519. 2. The Panel considers that no change to the Guidance is needed.
565	International Probiotic Association - Europe (IPA Europe)	8.4.1.2 Subchronic toxicity Lines 1296-1297 about OECD Method and animal testing. The references to the testing methods are covered in the general principles: line 329 strategy to reduce animal testing , lines 333,334,335 minimisation of animal testing/use of others validated methodologies, line 334	Please refer to the response to comments 117, 139, 306 and 526.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		alternative approaches. When animal testing is required, in some situations, it is possible to combine some OECD methods with others, in order to use less animals (e.g. OECD 408 with OECD 421) for repeated-dose toxicological studies. IPAEU: We would like to draw attention to the method of study outlined by the OECD, wherein we reference the general principles for minimising animal testing. However, while we acknowledge these efforts, we are keen to gain deeper insights into EFSA's strategy concerning alternative testing methods. Specifically, we would greatly appreciate any additional information regarding EFSA's plan to actively engage in the validation and promotion of alternative approaches to traditional animal testing. Your insights on this matter will help our understanding and support of EFSA's initiatives in this domain.	
566	German Federal Institute for Risk Assessment	Lines 1324-1326, page 41 How are other potential adverse effects considered that can be identified from literature or other studies (e.g. adverse impact on human microbiota) and which are usually not addressed by the toxicological studies? Section 8.4.1.2. describes 'when indications of reproductive and/or endocrine effects are identified (from the literature, in vitro, in vivo, and/or human studies), the applicant is advised to include additional endpoints in the 90-day subchronic toxicity study'. Maybe this text part should not be limited to just reproductive and/or endocrine effects, but should also be expanded to 'other adverse effects that can be identified (from the literature, in vitro, in vivo, and/or human studies)', and which might be included as additional endpoints in the toxicity studies.	Please refer to section 7.2.1 with regard to the impact of the novel food on gut microbiota. The Panel considers that no change to the indicated text of the Guidance is needed.
628	Cellular Agriculture Europe	Line 1278: For Tier 1 we note the absence of a reference to OECD 422 OECD (2016), Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264264403-en. Where OECD 408 (i.e. 90 day exposure) can actually be combined with a reproductive toxicity screen (OECD 421 OECD (1995), Test No. 421: Reproduction/Developmental Toxicity Screening Test, OECD Publishing, Paris,	Please refer to the response to comments 31 and 713.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		https://doi.org/10.1787/9789264070967-en.) OECD 422 OECD (2016), Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264264403-en. Where OECD 408 (i.e. 90 day exposure) can actually be combined with a reproductive toxicity screen (OECD 421 OECD (1995), Test No. 421: Reproduction/Developmental Toxicity Screening Test, OECD Publishing, Paris, https://doi.org/10.1787/9789264070967-en.) This could be a consideration to add here, in order to provide further reassurance at Tier 1 for absence of reproductive/developmental concern/provide information for dosing of tier II studies etc. We propose to add a cross-reference to Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age - - 2017 - EFSA Journal - Wiley Online Library for infant formula ingredients in this section as well.	
657	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Lines 1275-1276. 'Sub-acute studies (e.g., 14-day) may be conducted providing the basis for the selection of appropriate doses to be used in the sub-chronic setting.': Do the sub-acute studies need to be notified, as they are not used to determine a safe dose, but rather to give an indication for further studies?	Please refer to the response to comment 627. The Panel noted that notification of studies is out of the scope of this Guidance, and will be addressed in the relevant administrative Guidance for novel food applications.
682	Atova Regulatory Consulting SL	(Line 1278-1326, page 40-41) We recommend referring to the 2017 EFSA guidance on the assessment of substances present in food intended for infants below 16 weeks of age. We also recommend EFSA making it clear when modified protocols can be applied to combine certain endpoints.	Please refer to the response to comment 31 and 713. It should be noted that the optional endpoints suggested by OECD TG 408 should be considered, or at least samples should be kept for possible follow-up testing.

Table 56: 8.4.2 Tier II repeated-dose toxicological studies

Comment number	Commentor	Comment	EFSA NDA Panel responses
45	Intertek	Lines 1334 to 1335 - there is a long list of OECD Test Guidelines for studies that are very different, with no explanation as to when each study type would be appropriate to be used. Recommend to include an explanation of when each of the OECD Test Guidelines would be appropriate to use.	The Panel considers that the findings and available data can vary significantly between cases, making it impractical to cover specific scenarios within this Guidance document. The selection of a specific Tier 2 reproductive or developmental toxicity study protocol depends on the data obtained from Tier 1, the concerns about particular endpoints, and the stage of the reproductive or developmental cycle that needs to be assessed.
134	Medfiles Ltd	8.4.2.1 Reproductive, endocrine and developmental toxicity P42 L1334: Please add the titles for the OECD studies (e.g. Feedap does this in their guidance) as it makes the text more informative. In addition, is OECD 415 still appropriate method to be used? Isn't OECD 415 rather considered to be obsolete nowadays?	The text has been revised to provide further clarity. Next to each OECD TG, the respective reference has been linked, for direct access to the full title of each OECD TG.
174	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 1328-1343 The following references could also be a consideration to add here, in order to provide further reassurance at Tier 1 for absence of reproductive/developmental concern/provide information for dosing of tier II studies. OECD 422 OECD (2016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test - https://doi.org/10.1787/9789264264403-en). Where OECD 408 (i.e. 90-day exposure) can actually be combined with a reproductive toxicity screen OECD 421(1995 - Reproduction/Developmental Toxicity Screening Test - https://doi.org/10.1787/9789264070967-en.)	Please refer to the response to comment 713.
280	Ministry of Regional Affairs and Agriculture	Line 1335-1336 Would it be possible to point out examples based on current practice?	Please refer to the response to comment 45. The Panel notes the recommendation but considers that expanding the section goes beyond the scope of this Guidance.

Comment number	Commentor	Comment	EFSA NDA Panel responses
498	Undisclosed (Personal Capacity)	Why is a subchronic toxicity still part of Tier 1, are there no animal-live savings alternatives available as part of Tier 1.	Despite being present in Tier 1, animal studies may not be necessary, depending on the available body of evidence. Please refer to section 8.2 of the Guidance. The Panel considers that no change to the Guidance is needed.
524	PETA Science Consortium International e.V.	1. Line 1332 Please consider adding the suggested sentences in [brackets] to highlight the dynamic nature of research in reproductive and developmental toxicity and its implications for testing strategies. These additions underscore the promising but evolving status of in vitro assays in this domain, advocating for a nuanced approach that integrates these assays into a broader, adaptive testing framework. This addition would enrich the guidance, aligning it with the latest scientific developments and promoting a forward-looking stance on reproductive and developmental toxicity testing. We recommend adding the following in [brackets]: 'Any indications of effects on reproductive organs or parameters, as observed in vitro and/or in vivo, may trigger the need for testing for reproductive and developmental toxicity. Potential additional tests include, but are not limited to, studies covered by OECD TG 414, 415, 416, 421, 422, 426, 440, 441, 455, 456 and 493. Reproductive and developmental toxicity testing may not be required if scientifically justified on a case-by-case basis. [In vitro assays for reproductive and developmental toxicity are currently under development. When qualified in vitro assays assessing reproductive development toxicity are established, a testing strategy based on a combination of assays and their assignment to an adverse outcome pathway (AOP) in a tiered and/or battery approach may be used. (ref.18)]' 2. Line 1345 We suggest highlighting the importance of resorting to animal testing only as a last resort, by adding, for example, the following text in [brackets]: 'The need for other studies, e.g., studies on neurotoxicity, cardiovascular effects, immunotoxicity, hypersensitivity and food intolerance, mechanism (mode of action), may be triggered by findings	1. Please refer to the response to comments 117 and 39. 2. Please refer to the response to comments 518 and 519, as well as to the General Principle 11 of the Guidance.

Comment number	Commentor	Comment	EFSA NDA Panel responses
		reported in the literature or in Tier I or II. [It should be noted that applicants shall ensure that testing on vertebrate animals is carried out only when non-animal methods are unavailable.]` References 18. Beekhuijzen M. The era of 3Rs implementation in developmental and reproductive toxicity (DART) testing: Current overview and future perspectives. Reprod Toxicol. 2017;72:86-96. doi:https://doi.org/10.1016/j.reprotox.2017.05.006	
629	Cellular Agriculture Europe	Lines 1328 - 1344: OECD 422 OECD (2016), Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, https://doi.org/10.1787/9789264264403-en. Where OECD 408 (i.e. 90 day exposure) can actually be combined with a reproductive toxicity screen (OECD 421 OECD (1995), Test No. 421: Reproduction/Developmental Toxicity Screening Test, OECD Publishing, Paris, https://doi.org/10.1787/9789264070967-en.) This could be a consideration to add here, in order to provide further reassurance at Tier 1 for absence of reproductive/developmental concern/provide information for dosing of tier II studies etc.	Please refer to the response to comment 713.

Table 57: 8.4.3 Tier III repeated-dose toxicological studies

Comment number	Commentor	Comments	EFSA NDA Panel responses
32	Undisclosed (Personal Capacity)	Lines 1359-1362 Generally speaking here the mention of kidney for example highlights the fact that effects may be adaptive (i.e. reversible) or not. It is recommended to discuss this here and possibly under sub-chronic tier 1 as this allows for modification of OECD 408 protocol design to allow for reversibility and treatment free periods etc.	Reversibility can be evaluated using a recovery group in a subchronic toxicity study conducted according to OECD 408 guidelines. Whether an observed effect is adaptive, reversible, or adverse should be assessed on a case-by-case basis.
46	Intertek	Lines 1361 to 1362 - does this mean that kidney effects in a subchronic toxicity study always trigger the need for a long-term toxicity study?	No, findings on kidney-related endpoints in a subchronic toxicity study (Tier 1) do not automatically trigger the need for a long-term

Comment number	Commentor	Comments	EFSA NDA Panel responses
			toxicity study (Tier 3). The text has been revised to provide further clarity.
525	PETA Science Consortium International e.V.	1. Line 1349 To future-proof the guidance, please consider adding the following in [brackets]: 'Tier III studies comprise toxicological studies of high complexity regarding the duration and the required number of animals. [Due to this and considering their limitations,3 animal tests should be pursued only when robustly scientifically justified and when no non-animal methods are available to clarify the concern with equal or better predictivity.]' 2. Line 1359 As explained above, rat and mouse lifetime bioassays lack modern validation and scientific rigor. We urge EFSA to rephrase as follows by removing the text in quotes and replacing with the text in [brackets]: Remove '8.4.3.2. Chronic toxicity and carcinogenicity' and replace with [8.4.3.2. Additional Tier III testing] Remove 'Carcinogenicity studies may be requested following indication of hyperplasia in toxicity studies or following positive in vitro or in vivo genotoxicity tests, but only if the mechanism of genotoxicity is clearly identified and if it is not directly DNA reactive. Further guidance on the triggers for these studies and their implementation are outlined in the respective OECD Test Guidelines (OECD TG 451, 1366 452 or 453).' Replace with [There may also be situations where the available data from Tier I or Tier II concern potential chronic toxicity or carcinogenicity. Such cases may require follow-up investigations, and decisions about potential follow-up studies should be made on a case-by-case basis and with robust scientific justification.]	1. The Panel considers that no change to the Guidance is needed. 2. The Panel does not agree with the proposal. However, it should be noted that the text in section 8.4.3.2 has been revised to provide further clarity.
630	Cellular Agriculture Europe	Lines 1359 - 1362: Generally speaking here the mention of kidney for example highlights the fact that effects may be adaptive (i.e. reversible) or not. It is suggested discussing this here and possibly under sub-chronic tier 1 as this allows for modification of OECD 408 protocol design to allow for reversibility and treatment free periods etc.	Please refer to the response to comment 32.
658	Pen & Tec Consulting	Lines 1356-1358. 'Indications of such toxic effects (from the literature, in vitro, in vivo, and/or human studies) may trigger	The text has been revised in line with the comment.

Comment number	Commentor	Comments	EFSA NDA Panel responses
	S.L.U. (trading as Argenta®)	the request from an EOGRTS without the need for Tier II studies.': Suggested edit for clarity - 'for' instead of 'from'.	

Table 58: 8.5 Human data

Comment number	Commentor	Comments	EFSA NDA Panel responses
175	Synpa, French association of specialty food ingredients manufacturers and distributors	What are the guidelines considered relevant by EFSA to conduct clinical trial including safety endpoints? Clinical trial phase I or phase II preferred? For NF intended to be used in food supplements only, could one or two DB-RCT clinical trial conducting with the NF for duration of 3 months and including safety endpoints (physical and clinical examination, haematology, biochemistry, urinalysis and other function tests + adverse events) be sufficient to avoid animal testing?	The Panel notes the recommendations but considers that the provision of detailed protocols for human safety trials goes beyond the scope of this Guidance. However, a reference to another guidance document (EFSA NDA Panel, 2024) has been introduced into this chapter. That document contains detailed information (Appendix B) with respect to the structure and content of full study reports of human studies. Concerning the question related to the use of the novel food as a food supplement only, it is clarified that the safety of a novel food needs to be unambiguously demonstrated, irrespective of the proposed use (i.e., as food ingredient or as a food supplement).
275	Dwayne Holmes (Personal Capacity)	Page 43, Line 1378-79 - It is recommended to clarify that for complex or whole foods (such as cultured meat and seafood) that a strong hypothesis for an effect on psychological or mental health must exist (e.g. from identified media components) before human studies on this aspect of food safety would be required. In addition, case examples of NFs that may require or require such analysis could be given.	The Panel notes the recommendations but considers that this issue is already implicitly covered by the text. As indicated in this section, only in particular cases human studies might indeed be needed. This requirement is triggered

Comment number	Commentor	Comments	EFSA NDA Panel responses
			by adverse effects that were observed in toxicological studies (or other types of data) or reported in the literature. It is not based on any hypothesis but on observations and/or literature data.

Table 59: 9 Nutritional information

Comment number	Commentor	Comments	EFSA NDA Panel responses
10	Undisclosed (Personal Capacity)	Lines 1389-1406 The new Figure is well received. This paradigm should also have direct relevance for toxicological requirements, since it measures ULs as well as DRVs.	The Panel appreciates the feedback on EFSA's work. A cross-reference to this section has been included in the section 'Toxicological information'.
146	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 1391-1392 The new Figure is well received. This paradigm should also have direct relevance for toxicological requirements, since it measures upper intake levels (ULs) as well as dietary reference values (DRVs).	Please refer to the responses to comments 10 and 34.
197	EU Specialty Food Ingredients	Lines 1392-1395: 1. We would like to take the opportunity to point out that only an excess intake of nutrients is considered, while a minimum intake is not. In some cases, e.g. nutrients in infant formula, it might be relevant to also set a minimum intake level to ensure that vulnerable consumer groups are sufficiently supplied with the relevant nutrients in form of novel foods. 2. The guidance should clearly state this is in terms of a standard consumer diet or should be revised to express different diet choices of consumers. An excess intake of nutrients is dependent on what that nutrient actually is, i.e., excess sugar would be problematic, excess protein especially in keto diets would not be an issue.	This guidance addresses not only the potential adverse effects of excessive nutrient intake from novel foods but also the risks associated with inadequate intake, as these can impact the consumer's nutritional status. For novel foods intended as new sources of micronutrients, including those proposed for use in fortified foods, food supplements, and foods for specific groups (FSG)—such as infant and follow-on formulas—applicants should refer to the

Comment number	Commentor	Comments	EFSA NDA Panel responses
			guidance on new micronutrient sources, where all these factors are thoroughly evaluated (EFSA NDA Panel, 2024). It should also be clarified that compositional requirements, including the minimum and maximum levels of nutrients and other substances for certain FSG, are regulated under Regulation (EU) No 609/2013. Additionally, in accordance with Regulation 2015/2283, the target population for assessments includes the general population, encompassing vulnerable groups. There is no provision that allows or justifies a case-by-case approach based on specific dietary patterns. The Panel considers that no change to the Guidance is needed.
344	Jeremy Coller Foundation	Line 1435-1436, page 45 - To clarify, this does not mean nutritional equivalence? E.g. if a new product has lower saturated fat content as lower fat option, but slightly lower protein content, would this be ok as not disadvantageous?	Nutritional equivalence must be demonstrated under the proposed conditions of use, and novel foods intended to replace conventional foods should not pose any nutritional disadvantages for consumers under these conditions. This requirement applies to both macronutrients and micronutrients. The Panel considers that no change to the Guidance is needed.
549	Novonesis (merger of former Novozymes and Chr. Hansen)	page 43, lines 1392-1395: We would like to take the opportunity to point out that only an excess intake of nutrients is considered, while a minimum intake is not. In some cases, e.g. nutrients in infant formula, it might be relevant to also set a minimum intake level to ensure that vulnerable consumer groups are sufficiently supplied with the relevant nutrients in form of novel foods.	Both the excess intake of nutrients (section 9.1) and the inadequacy of nutrient intake (section 9.2) should be considered. The text has been revised.

Comment number	Commentor	Comments	EFSA NDA Panel responses
573	Aletheia: il segreto del buon vivere	Cell-based meat should be designed to be biologically equivalent to traditional meat. This means it should have a similar protein content to conventional meat. However, the exact protein content can vary depending on the specific methods used in the production process. It's important to note that while the goal is for cell-based meat to match the nutritional profile of conventional meat, including protein content, there may be differences. These could be due to factors such as the type of cells used, the growth medium, and the maturation process. In the same way, the lipid content can vary depending on the specific methods used in the production process. In one study, a scaffold was synthesised using gelatine and soymilk to create a friendly environment for myogenesis and adipogenesis in C2C12 and 3T3-L1 cells, respectively. The fat-containing cell-based meat was fabricated with an aligned muscle-like layer and adipose-like layer by stacking these layers alternately. Regarding micronutrient intake, Traditional meat is a rich source of highly available iron and zinc, potassium, phosphorus, magnesium, calcium, vitamin B12, and all other B vitamins except folic acid. At the same time, almost nothing is noted about cell-based meat micronutrients. Currently, cultured meat is still in development and not widely available, so more research is needed to determine its exact nutritional composition in terms of macro and micronutrients. Given the complexity and novelty of the production process, the risks that can occur can't be entirely predicted. The dysregulation of cell lines associated with the great number of cell divisions is one of the most discussed issues. Moreover, to date, the specific impact of cell-based meat on the human gut microbiota may vary and there is completely missing data on the impact of cultured meat on the human gut microbiota thus, there is a strong need of study on humans.	To date, EFSA's risk assessment of NFs addresses the safety and nutritional requirements through a thorough compositional analysis of the NF, comparison with the composition of the food it seeks to replace in the EU market, and an evaluation of whether any observed differences could result in adverse health outcomes for consumers under conservative consumption scenarios. Particular attention is given to macro- and micronutrients, especially those for which the conventional comparator food is a significant dietary source for the European population. While cell culture-derived 'meat' is often designed to mimic the biological properties of traditional meat, it was discussed at the 'EFSA Scientific Colloquium 27: Cell Culture-Derived Foods and Food Ingredients' (EFSA, 2024) that these products cannot, in fact, be considered as meat according to the definition set out in Regulation (EC) No 853/2004. Despite their similarities, they remain distinct commodities. Nonetheless, the nutrient profile of these products will be assessed based on their proposed uses and levels of consumption. While the comment raised goes into a level of detail which is too specific for inclusion in a general guidance document for the submission of NF applications, such detailed information will be considered by EFSA when

Comment number	Commentor	Comments	EFSA NDA Panel responses
			assessing the specific products when submitted for risk assessment. Regarding the impact of NFs on gut microbiota, The Panel notes the recommendation but concludes that no changes to the current chapter are required. If evidence indicates that the NF or its derived components are not absorbed in the small intestine, studies simulating the human gut and its microbiota dynamics should be conducted. For more information on the impact of gut microbiota and their associated enzymes on the biotransformation, activation and detoxification of chemicals in NFs, please refer to section 7.2.1.
598	Cellular Agriculture Europe	Lines 1389 - 1406: The new Figure is well received. This paradigm should also have direct relevance for toxicological requirements, since it measures ULs as well as DRVs.	Please refer to the response to comment 10.
663	Atova Regulatory Consulting SL	(Line 1389-1406, page 43-44) We welcome the addition of Figure 3.	Please refer to the response to comment 10.
691	FoodDrinkEurope	(Line, 1389) The new Figure is welcomed. This paradigm should also have direct relevance for toxicological requirements since it measures upper intake levels (ULs) as well as dietary reference values (DRVs).	Please refer to the response to comment 10.

Table 60: 9.1 Excess intake of nutrients

Comment number	Commentor	Comments	EFSA NDA Panel responses
34	Undisclosed (on Personal Capacity)	Lines 1407-1419 This section should also be cross-referenced to toxicological information general principles	The text has been revised in line with the comment.

Comment number	Commentor	Comments	EFSA NDA Panel responses
103	Undisclosed (Personal Capacity)	Comprehensive Nutrient Analysis Missing (Page 45, Lines, 1410–1415) Comment: The document lacks a comprehensive analysis of all nutrients that could potentially exceed the Tolerable Upper Intake Levels (ULs) when no UL is established. It should include a risk assessment model that considers both macro and micronutrients without established ULs, utilising risk assessment methodologies such as Benchmark Dose (BMD) approaches for a more comprehensive safety margin analysis. Insufficient Consideration of Combined Intake Sources (Page 45, Lines, 1415–1419) Comment: The section does not adequately address the cumulative exposure to nutrients from other dietary sources alongside the novel food. Detailed guidance on assessing combined intakes and potential nutrient interactions within the diet should be included to prevent nutrient imbalances and potential toxicities.	The Panel emphasises that for nutrients without an established Upper Level (UL), applicants should determine whether other Health-Based Guidance Values (HBGVs), such as the Acceptable Daily Intake (ADI) for copper (EFSA Scientific Committee, 2023), are applicable. These should be considered during the safety assessment. The Panel finds the commenter's reference to the Benchmark Dose (BMD) approach unclear. This approach is used to identify a reference point (RP) for the substance tested in the experiment used for modelling (EFSA Scientific Committee, 2022b). If the test substance is a novel food, this approach could be used to establish an RP for the entire novel food, rather than for its individual components, such as macro- or micronutrients. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.
176	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 1407-1419 This section should also be cross-referenced to toxicological information general principles	Please refer to the response to comment 34.
631	Cellular Agriculture Europe	Lines 1407 - 1419: We suggest that this section is also cross-referenced to toxicological information general principles.	Please refer to the response to comment 34.

Comment number	Commentor	Comments	EFSA NDA Panel responses
659	Pen & Tec Consulting S.L.U. (trading as Argenta®)	Line 1410. 'Tolerable Upper Intake Levels (ULs)49.': A reference to EFSA DRV Finder is provided. However, it has been noticed that not all information in this tool is updated in a timely manner. Therefore, relying on the information in the tool may mislead the applicant in certain instances.	The Panel acknowledges the comment. The link to the DRV Finder has been replaced with a link to the UL summary report, titled 'Overview on Tolerable Upper Intake Levels as derived by the Scientific Committee on Food (SCF) and the EFSA NDA Panel on Dietary Reference Values.' This report is updated whenever a new opinion is published and can be accessed at the following link: https://www.efsa.europa.eu/sites/default/files/2024-05/ul-summary-report.pdf. EFSA is working towards developing a more agile system that will enable the continuous updating of the DRV Finder content in the future.

Table 61: 9.2 Inadequate intakes of essential nutrients

Comment number	Commentor	Comments	EFSA NDA Panel responses
104	Undisclosed (Personal Capacity)	General Overview and Criteria for Nutrient Adequacy (Page 45, Lines, 1420–1425) Comment: The section introduces the concept of inadequate intakes of essential nutrients but lacks specific criteria or quantitative thresholds that define what constitutes inadequacy. The document should include explicit values or ranges, possibly referencing Dietary Reference Values (DRVs) established by health authorities, to guide the evaluation of nutrient levels in novel foods. Assessment of Antinutrient Effects (Page 45, Lines, 1421–1427) Comment: While the section mentions antinutrients like phytates and oxalates that can interfere with nutrient absorption, there is no guidance on how to quantitatively assess these effects in the context of the total diet. Incorporating standard methods for measuring the impact of	The Panel clarifies that, theoretically, the risk of inadequate nutrient intake in populations can be assessed by comparing estimated micronutrient intake with Dietary Reference Values (DRVs) for dietary requirements (i.e., Average Requirements (ARs) and Adequate Intakes (AIs)) (EFSA NDA Panel, 2010). However, this approach requires estimating the total nutrient intake from the entire diet and is challenging to implement for predicting the impact of specific foods.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		antinutrients on the bioavailability of essential minerals and vitamins would strengthen the assessment process.	The assessment of the novel food's potential to lead to inadequate intakes of essential nutrients should be guided by compositional analyses and comparisons with similar foods, as outlined in the guidance (sections 9.2.1 and 9.2.2). The Panel notes the recommendation but considers that a detailed expansion of this section goes beyond the scope of this Guidance.
177	Synpa, French association of specialty food ingredients manufacturers and distributors	Lines 1407-1419 This section should also be cross-referenced to toxicological information general principles.	Please refer to the response to comment 34.
714	FoodDrinkEurope	1. (Line, 1422) This is the first definition of 'Antinutrient', we would suggest providing the definition earlier in the text line 762) 2. (Line, 1422) Further clarity is welcomed on which ones, the list must be prioritised. This is still a difficult field analytically speaking. Depending on the method used it will be difficult to compare with the literature. Sometimes methods are not available, or there too many available methods which provide too different data. 3. (Lines, 1422–1431) Can EFSA explain how the antinutritional activity is measured (according to definition, this is limited to an interference with the absorption while the impact is related to an affected bioavailability of essential nutrients): is it based on absorption and how is it measured or on bioavailability? Absorption and bioavailability are two different things. Among the listed antinutrients, some (like trypsin inhibitors) are affecting rats but no other mammalian species (pigs, dogs, primates): should those be considered anyway? Amylase inhibitors are reducing the degradation of starch to glucose and is rather considered beneficial for dental health. Would glucose be considered as an essential nutrient?	1. Please refer to the response to comment 23. 2. The selection of what to analyse is up to the applicant and must be evidence-based, guided by literature search results and aspects of the production process. The chosen methods should be scientifically justified and appropriate for assessing the novel food. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance. 3. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance. 4. The Panel considers that no change to the Guidance is needed.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		4. (Lines, 1432–1445) This section should refer to Sections 5.1, 5.2 and 6.4 where intakes of and combined/replacement of existing foods and sources in the diet is discussed.	

Table 62: 9.2.1 Antinutrient content

Comment number	Commentor	Comments	EFSA NDA Panel responses
35	Undisclosed (Personal Capacity)	Lines 1422-1427 This is the first actual specification of what 'antinutrients' actually are, despite them being referred to earlier in the document	Please refer to the response to comment 23.
632	Cellular Agriculture Europe	1. Lines 1422 - 1427: This is the first actual specification of what 'antinutrients' actually are, despite them being referred to earlier in the document 2. Line 1422: Further clarity is welcome (i.e. which ones, priority list). This is still a difficult field analytically speaking. Depending on the method used it will be difficult to compare with literature. Sometimes methods are not available, or there are too many available methods which provide too different data. 3. Lines 1422 - 1431: Can EFSA explain how the antinutritional activity is measured (according to definition, this is limited to an interference with the absorption while the impact is related to an affected bioavailability of essential nutrients): is it based on absorption and how is it measured or on bioavailability? Absorption and bioavailability are two different things. Among the listed antinutrients, some (like trypsin inhibitors) are affecting rats but no other mammalian species (pigs, dogs, primates): should they be considered anyway? Amylase inhibitors are reducing the degradation of starch to glucose and are rather considered beneficial for dental health. Would glucose be considered as an essential nutrient?	1. Please refer to the response to comment 23. 2. Please refer to the response to comment 714. 3. Please refer to the response to comment 714.

Table 63: 9.2.2 Replacement of food(s) in the diet

Comment number	Commentor	Comments	EFSA NDA Panel responses
36	Undisclosed (Personal Capacity)	Lines 1432-1445 This section should also consider and refer to Sections 5.1, 5.2 and 6.4 where intakes of and combined/replacement of existing foods and sources in the diet is discussed	The Panel does not agree with the proposal. The section addresses the issue of inadequate intakes of essential nutrients. A novel food is deemed nutritionally disadvantageous if its consumption, under the proposed conditions of use, could negatively impact consumers' nutritional status by increasing the risk of insufficient nutrient intake. Special attention should be given to essential nutrients that are already consumed below recommended levels in European populations (EFSA NDA Panel, 2022d). Comparing with maximum intakes from background diets could overestimate nutrient intake, which is addressed in the scenarios for excess intake of nutrients, as outlined in Section 9.1.
633	Cellular Agriculture Europe	Lines 1432 - 1445: This section should also consider and refer to Sections 5.1, 5.2 and 6.4 where intakes of and combined/replacement of existing foods and sources in the diet is discussed.	Please refer to the response to comment 36.

Table 64: 9.3 Specific considerations for novel foods proposed as new sources of micronutrients

Comment number	Commentor	Comments	EFSA NDA Panel responses
683	Atova Regulatory Consulting SL	(Line 1452-1452, page 46) No full reference under References for (EFSA NDA Panel, 2024) guidance on new sources of micronutrients.	The text has been revised in line with the comment.

Table 65: 9.4 Specific considerations regarding novel protein sources

Comment number	Commentor	Comments	EFSA NDA Panel responses
37	Undisclosed (Personal Capacity)	Lines 1464-1469 Regarding Protein digestibility, here you have specific methods, whereas in Sections 7.1 (lines 1093-1095), 10.4.1 (Lines, 1578–1579) and 10.4.2 (lines 1593-1596 you refer to 'EFSA GMO Panel (2017, 2021, 2022))' it would be best if all these discussions are coordinated and leave the applicant with clear understanding of the method(s) EFSA expects	The Panel notes the recommendation but considers that a detailed expansion of this section goes beyond the scope of this Guidance. The Panel acknowledges that the referenced EFSA GMO Panel documents do not include relevant recommendations for digestibility testing to characterise the nutritional value of protein and have therefore been removed from the indicated section of the text.
47	Intertek	Line 1456 and footnote 57 - this indicates that when 12% of the energy of the novel food is provided by protein, the novel food is a source of protein. However, Regulation (EC) No 1924/2006 states that this 12% value applies to final food products (not the ingredients within them) and novel foods will typically be used as ingredients in foods. Therefore, it is recommended to clarify whether this 12% value applies to the novel food itself, or the final products it will be used in.	The text has been revised. The previous indication of 12% of the energy from the novel food is no longer applicable.
105	Undisclosed (Personal Capacity)	Lack of Specific Guidelines for Allergenic Potential (Page 46, Lines, 1460–1464) Comment: There is a general mention of protein quality assessment in terms of digestibility and amino acid composition. However, there's a lack of specific guidelines for evaluating the allergenic potential of novel protein sources. The document should include protocols for immunogenicity testing, particularly for proteins derived from non-traditional sources. Vague Methodology for Protein Quality Assessment (Page 46, Lines, 1464–1469) Comment: The guidelines for assessing protein quality through digestibility and indispensable amino acid scores are mentioned but not detailed. Clear, step-by-step analytical methods and criteria for the selection of control proteins in comparative studies should be explicitly stated to ensure consistency and reliability of the data.	The Panel notes the recommendation but considers that a detailed expansion of this section goes beyond the scope of this Guidance. Regarding allergenicity testing, please refer to the updated tiered approach presented in section 'Allergenicity'. The Panel considers that no change to the Guidance is needed.

Comment number	Commentor	Comments	EFSA NDA Panel responses
135	Medfiles Ltd	Comment P46 L1455-1460: The last line on L1460 does not read well with the text prior to it. Wouldn't it be better to delete line 1455 and move line 1560 to replace it and say something like 'Data on the protein quality of the novel food must be provided, when:'. Thank you for considering this. Comment: P46 L1464: EFSA states: Protein digestibility of the novel food is to be investigated in terms of the true ileal digestibility of each indispensable amino acid (EFSA NDA Panel, 2012), using validated methods, on preferably three independently produced batches of the novel food, alongside proper control samples (e.g., casein, egg white). The respective validation method data must be provided. Would you have any examples of validated methods to provide here? Medfiles notes that GMO provides some guidance on these methods and proposes to add the respective GMO statement and opinion as guidance (GMO 2021 statement, GMO 2022 opinion; already listed in the reference list.) These GMO outputs are far more informative than EFSA NDA Panel 2012 reference. Thank you.	The text has been revised in line with the comment. Please also refer to the response to comment 37.
178	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Line 1461 Even though 'could be followed' is part of the guidance, clearly this will become a necessary requirement for some if not all reviewers. This would lead to different requirements for different dossiers causing confusion to the dossier submitters. We suggest deleting this paragraph and indicating that the science behind allergenicity of complex mixtures and whole foods must be further established, including protocols and best practices needed for risk assessment. 2. Line 1461 For true ileal digestibility assessment, what validated methods are recommended? For true ileal digestibility assessment, what is the model recommended to preformed the studies? In vitro (TNO Gastro-Intestinal Model), vivo (pig or other model) or human? For true ileal digestibility assessment, should studies be performed according to GLP?' 3. Lines 1462-1463 The methods used to assess protein digestibility and the method used for the indispensable amino acid scoring need to be duly justified.' Given that guidance is provided on lines 1464-1469 how these analyses should be	1. The text has been revised. 2. Please refer to the response to comments 37, 105 and 135. 3. The text has been revised. 4. Alternative ways of assessing protein digestibility could be proposed by applicants when minimum requirement criteria are fulfilled and methods are accepted by the Panel during risk assessment. 5. Please refer to the response to comment 37.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		performed, I feel this sentence can (and should) be deleted – the need to 'duly justify' is too vague … 4. Lines 1461-1469 Considering many of the new protein sources are to be dedicated to the production of plant-based/vegetarian/vegan food products, EFSA should propose an alternative way of assessing the digestibility without animal trial, given the EFSA support of risk assessment, approaches which minimise and refine the use of experimental animals. The complexity, cost and invasiveness of the DIAAS method do not allow it to be used in routine, nor on humans or animals. It is urgent to develop and harmonise / standardise methodologies in vitro before implementing this rule of calculation of % digestibility, for general population and adapted to the specific populations as well. Animal studies are prohibited now, especially if we need 3 different batches: this is irrealistic and un-ethical. Additional questions: how the quality of the studies will be ensured? With reference controls or via accredited labs ? 5. Line 1464-1469 Considering proteins, EFSA should propose an alternative way of assessing the digestibility without the support of animal studies. Regarding Protein digestibility, here there are specific methods listed, whereas in Sections 7.1 (lines 1093-1095), 10.4.1 (Lines, 1578–1579) and 10.4.2 (lines 1593-1596) refer to 'EFSA GMO Panel (2017, 2021, 2022) it would be best if all these discussions are coordinated and leave the applicant with clear understanding of the method(s) EFSA expects.	
220	EU Specialty Food Ingredients	Lines 1461-1469: 1. Considering many of the new protein sources are to be dedicated to the production of plant-based/vegetarian/vegan food products, EFSA should propose an alternative way of assessing the digestibility without animal trials, given the EFSA support of risk assessment approaches which minimise and refine the use of experimental animals. 2. Concerning the phrase 'The methods used to assess protein digestibility and the method used for the indispensable amino acid scoring need to be duly justified', given that guidance is provided on lines 1464-1469 how these analyses should be performed, this sentence should be deleted – the need to 'duly	1. Please refer to the response to comment 178. 2. Please refer to the response to comment 178. 3. The Panel considers that no change to the Guidance is needed.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		justify' is too vague. 3. Suggest adding '(essential)' after the word 'indispensable'.	
316	Food Safety & Nutrition Consultancy	Only accepting DIAAS is too limited. EFSA should also make reference to other (acceptable) methods: such as PDCAAS and in vitro DIAAS.	Please refer to the response to comment 220.
634	Cellular Agriculture Europe	Lines 1464 - 1469: Regarding protein digestibility, specific methods are mentioned there, whereas in Sections 7.1 (lines 1093-1095), 10.4.1 (Lines, 1578–1579) and 10.4.2 (lines 1593-1596 the Guidance refers to 'EFSA GMO Panel (2017, 2021, 2022))'. For consistency and clarity's sake, we would welcome a coordinated approach on the method(s) EFSA expects.	Please refer to the response to comment 37.
684	Atova Regulatory Consulting SL	(Line, 1456, page 46) Could you specify the preferred method to calculate energy % from protein? (Line, 1464–1466, page 46) 'Protein digestibility of the novel food is to be investigated in terms of the true ileal digestibility of each indispensable amino acid (EFSA NDA Panel, 2012), using validated methods, on preferably three independently produced batches of the novel food, alongside proper control samples'. Could you please propose an example of a suitable in vitro method for the determination of digestibility? Could you please clarify in which cases the analysis of less than three independently produced batches would be acceptable? (Line, 1468–1469, page 46) (FAO, 2013) recommendation is calculating DIAAS based on in vivo data (digestibility in pigs, if possible). Can EFSA propose a suitable in vitro method to assess digestibility and protein quality?	In relation to the energy %, please refer to the response to comment 47. The text has been revised. Methods to measure the true ileal digestibility of amino acids in vivo have been established in animals and humans (FAO and IAEA, 2024). In vitro models have also been developed but yet not validated (FAO and IAEA, 2024). If an in vitro method is employed, the suitability of the method in consideration will be examined during the risk assessment. The assessment will also consider the minimum requirements outlined in section 9.4.
715	FoodDrinkEurope	1. (Line, 1462) Further clarity would be welcome on the protein digestibility methods to be used. We understand in the text that EFSA is recommending rather DIAAS with methodology reported under FAO (2013) 2. (Lines, 1464–1469) Regarding protein digestibility, here are specific methods listed, whereas in Sections 7.1 (lines 1093-1095), 10.4.1 (lines 1578-1579) and 10.4.2 (lines 1593 - 1596) we refer to 'EFSA GMO Panel (2017, 2021, 2022)' it would be best if all these discussions are coordinated and leave the applicant with clear understanding of the method(s) EFSA	1. Please refer to the responses to comments 37, 220, 684. 2. Please refer to the response to comment 37.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		expects. Considering many of the new protein sources are to be dedicated to the production of plant-based / vegetarian / vegan food products, EFSA should propose an alternative way of assessing the digestibility without the support of animal studies. The draft guidance indicates that the digestible indispensable amino acid score (DIAAS) should be calculated as a measure of protein quality.	

Table 66: 10 Allergenicity

Comment number	Commentor	Comments	EFSA NDA Panel responses
38	Undisclosed (Personal Capacity)	Line 1596 Please refer to comment for Section 9.4, where the actual protein digestibility methods are specified. There needs to be clarity and coordination of all statements in this guidance related to protein digestibility studies	The text has been revised for clarity (please refer to the current Guidance's section 10.4).
78	Swedish Food Agency	The Swedish Food Agency has reviewed the EFSA Draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 from the perspective of the risk analysis principle. Our response highlights the importance of the risk assessment as a base for proportional risk management measures. Both risk assessors and risk managers withing the Swedish Food Agency have contributed to the below response. The Swedish Astma and Allergy Association has recieved a draft of our reply and agree that the most important aspects are highlighted in our response. Weighing data in the risk assessment performed by Efsa The data needs to be weighed according to what kind of evidence of allergenicity such studies can provide. If the novel food is closely related to a known allergen then it is valuable to test for cross-reactivity. It is also valuable to describe whether there is published data on clinical allergy e.g. case reports. But the data needs to be weighed and put in the context of how many reactions that might occur, and the severity of these,in comparison to the millions of allergic reactions which occur to	The Panel agrees that the weighing of the data and the uncertainties should be part of the safety assessment and addressed in the opinion. Both 'severity' and 'prevalence' are required as per the Guidance. The Panel also supports reducing the data requirements for investigating potential cross-allergenicity, limiting it to Novel Foods for which there is available (read-across) information on potential allergens. The text has been revised accordingly.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		foods listed in Annex II of regulation (EU) no 1169/2011. The uncertainties regarding allergenicity risk assessment need to be described in the risk assessment. Within the medical field patients should not be tested for IgE antibodies against food they have not reacted to. IgE antibodies can be found without clinical allergy . Such principle should apply also to novel food. Our concern is that too strong measures will be suggested by risk managers if all the data suggested in the draft guidance is asked for and presented in the Efsa opinion without describing the uncertainties and what conclusions could be made from a clinical perspective and thus the risk for clinical reactions. The measures may then not be proportionate to the risk. Page 47, line 1489, 1490 It is not within the mandate of Efsa to propose possible measures. Risk management measures could include information via other channels. We suggest to amend to: Such evidence could support regulatory risk management measures. decision-making by risk managers, including possible labelling requirements.	
79	Swedish Food Agency	In regards to which foods are known to trigger allergic reactions in susceptible individuals, for the Swedish Food Agency it is important to follow the procedure for risk assessment as described in the FAO/WHO report 'Risk assessment of Food Allergens part 1 review and validation of Codex alimentarius priority allergen list through risk assessment: meeting report'. In this report only a few further food allergens than those listed in regulation (EU) no 1169/2011 are decribed e.g. buckwheat, kiwi, pulses and insects. It is important to base the risk assessment on prevalence, potency and severity. Including more than this would lead to a hazard principle instead of risk assessment. In the report it is also written that about 170 different foods have been shown to trigger allergic reactions. However, only single case reports exist for certain food. Thus the evidence for their allergenicity is low. In our opinion it is important that 10.3 only covers the few foods which are listed in the WHO/FAO report mentioned above or based on the same principle i.e. prevalence, potency and severity. In line 1512, 1513 in regards to which foods (or products thereof) that are	The concepts of 'prevalence,' 'potency,' and 'severity' are covered in the guidance (section 10.3 - points 1, 2 and 3). The rest of the points address information on allergenic proteins, their presence, and quantity. The Panel acknowledges the concerns expressed. The text has been revised.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		known to trigger allergic reactions in susceptible individuals, but which are not listed in Annex II of Regulation (EU) No 1169/2011, it needs to be further described what is meant by 'foods that are known to trigger allergic reactions in susceptible individuals'. A suggestion is to add the reference to the WHO/FAO report 'Risk assessment of Food Allergens part 1 review and validation of Codex alimentarius priority allergen list through risk assessment: meeting report'.	
80	Swedish Food Agency	Under Section 10.4 a and b), what is the purpose of asking for all the data? We would like to suggest a stepwise process; Step 1: • Are there any published case reports? Step 2: • Investigate whether the novel food is closely related to a known food allergen (e. g. the same family as any of the allergens listed in regulation (EU) no 1169/2011). Step3: If the answer is yes --> a follow-up analysis should be performed, such as human serum specific IgE-binding assay, as described in 10.4.1; 'Sera should come from patients with a clearly demonstrated food allergy (relevant history, symptoms and time of onset consistent with an IgE-mediated food allergy to a relevant food and evidence of sensitisation to that food). Immunoassay methods such as ELISA or electrophoresis combined with immunoblotting with serum IgE sera (if available), are considered adequate to assess cross-reactivity with known allergens.' o If no --> and only in case of several case reports the above follow-up analysis could be performed/ asked for.	The Panel acknowledges the concerns expressed. Greater emphasis has been placed on clearly expressing a tiered approach for investigating cross-reactivity and cross-allergenicity. The text has been revised.
88	BaseClear	In line 1544, the mention of 'allergenicity assessment' raises the question of whether specific recommendations exist for evaluating allergenic potential. Is it necessary to conduct all types of studies, including in silico, in vitro, in vivo, and human studies, to comprehensively assess allergenicity?	The Panel acknowledges the concerns expressed. Greater emphasis has been placed on clearly expressing a tiered approach for investigating cross-reactivity and cross-allergenicity. The text has been revised.
106	Undisclosed (Personal Capacity)	Evaluation of Non-Traditional Allergens (Page 47, Line, 1498–1501): Comment: The guidance mentions the absence of protein-derived allergens in certain novel foods but does not consider the potential allergenicity of novel biochemicals or	The Panel acknowledges the comment. It is important to note that current in silico methods for

Comment number	Commentor	Comments	EFSA NDA Panel responses
		metabolites unique to the production process. The document should include protocols for identifying and assessing the allergenic potential of such non-traditional allergens, especially when novel microbial or cell culture-based methods are used in the production. This could involve in silico allergenicity prediction followed by targeted immunological testing to ensure comprehensive safety assessments.	allergenicity prediction lack sufficient validation and/or predictivity.
115	Food Fermentation Europe	Lines 1586 to 1597 introduce a holistic approach that could be followed to characterise the allergenic potential of complex protein mixtures. The steps of the approach are listed in points a) to e). It is unclear whether EFSA recommends to follow all these steps consecutively for all types of protein mixtures/whole foods, or whether the steps are to be decided on a case-by-case basis, depending on the characteristics of novel food. Could the guidance also advise on the approach for specific groups of complex protein mixtures, for example produced from microorganisms? In case of novel foods produced from microorganisms where the proteins can be predicted, the bioinformatics study could be used as the starting point for the analysis. Food Fermentation Europe therefore respectfully requests that the draft guidance be revised to clarify the minimum requirements for allergenicity testing of complex protein mixtures and whole foods, if possible, providing a clarification for specific types of complex protein mixtures, such as foods produced from microorganisms.	The Panel acknowledges the concerns expressed. Greater emphasis has been placed on clearly expressing a tiered approach for investigating cross-reactivity and cross-allergenicity. The text has been revised.

Table 67: 10.1 Novel foods with no protein derived from the production process

Comment number	Commentor	Comments	EFSA NDA Panel responses
136	Medfiles Ltd	P48 L1504: Medfiles would appreciate that if solid evidence if provided this default assumption could in certain specific cases waived. E.g. based on the manufacturing process containing e.g. chromatographic purification step or crystallisation step to purify the novel food, analysis of the allergen and finally	Evaluating whether the provided data meet the necessary requirements for an exemption from mandatory labelling is beyond the scope of the novel food assessment. Applicants

Comment number	Commentor	Comments	EFSA NDA Panel responses
		carrying out a risk assessment (based on e.g. FAO/WHO RfDs)? Thank you for considering amending this section with the possibility of waiting the need for labelling (noting that risk managers will decide this).	seeking exemption from mandatory labelling for novel foods potentially containing allergens listed in Annex II of Regulation (EU) No 1169/2011 should file an application pursuant to Article 21, paragraph 2 of Regulation 1169/2011, following the respective EFSA 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.
137	Medfiles Ltd	1. P48 L1516-1529: Medfiles assumes that the data for a) - d) should be retrieved from the literature, while the data for e) - f) should be retrieved from analytical analysis. Is this assumption correct? If so, please correct the text to reflect this better. Thank you. 2. P48 L1518: with 'allergenic food' do you mean i.e. source? (similarly as above in c)). If so, please revise for consistency. 3. P49 L1579: Does EFSA mean that 'additional protein characterisation' should be based on analytical data conducted by the Applicant? If so, please clarify. 4. P49 L1573: What is meant by 'processing-induced modifications'? Does EFSA refer to manufacturing process of protein and modification therein? Medfiles would appreciate for the clarification. 5. P50 L1597: Medfiles would appreciate if some examples of in vitro/in vivo analysis could be provided by EFSA. Would EFSA agree to analyse immunogenicity as recommended by EMA or FDA? As regards sensitising capacity, could ECHA/Feedap skin sensitisation (e.g. in chemico method) approaches be applied here to get some indication?	1. The first 4 points in section 10.3 are indeed to be retrieved from the literature, whereas the last point concerns evidence to be generated by the applicant. The previous 'point f' has been removed from the list. 2. The text has been revised in line with the comment. 3. The text has been revised, and the requirements have been modified. 4. The text has been revised, and the requirements have been modified. 5. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.
147	Synpa, French association of specialty food ingredients	Protein< 2.5 Kda are considered too small to elicit Type I allergic reaction. Therefore, are any analysis required for protein mixtures with protein size less than 2.5 kDa?	If the applicant believes that analysis of protein mixtures with sizes less than 2.5 kDa is not necessary, they may provide a rationale for why such

Comment number	Commentor	Comments	EFSA NDA Panel responses
	manufacturers and distributors		analysis is not needed. The safety assessment will take into account the applicant's arguments and the overall composition of the protein mixture.

Table 68: 10.2 Novel foods derived from allergenic foods subject to mandatory allergen labelling

Comment number	Commentor	Comments	EFSA NDA Panel responses
179	Synpa, French association of specialty food ingredients manufacturers and distributors	Line 1499 How many batches of the NF are expected to be analysed for the quantification of the known allergen? If the analysis indicates no detection of the allergen, is mandatory labelling still required? If yes, why should the allergen be quantified.	The updated Guidance specifies the number of batches that need to be analysed for a known allergen in cases where such analyses are needed. It should be noted that labelling requirements fall outside the scope of EFSA's remit.
180	Synpa, French association of specialty food ingredients manufacturers and distributors	Line 1510 How many batches of the NF are expected to be analysed for the quantification of the known clinically relevant allergen?	Please refer to the response to comment 179.
181	Synpa, French association of specialty food ingredients manufacturers and distributors	Line 1535 If the literature review does not reveal any allergenicity potential (either negative responses in studies or absence of data), are any details required apart from amino acid sequence homology comparison? What is the recommended allergenicity assessment of complex mixture of whole foods containing a low proportion of protein? e.g. extracts when protein separation is expected but not full (e.g. with proportion of protein <10%)	The text has been revised for clarity.
182	Synpa, French association of specialty food ingredients	Lines 1578-1579 Please refer to comment for Section 9.4, where the actual protein digestibility methods are specified. There needs to be clarity and coordination of all statements in this guidance related to protein digestibility studies.	Please refer to the response to comment 38.

Comment number	Commentor	Comments	EFSA NDA Panel responses
	manufacturers and distributors		

Table 69: 10.3 Novel foods derived from allergenic foods not subject to mandatory allergen labelling

Comment number	Commentor	Comments	EFSA NDA Panel responses
183	Synpa, French association of specialty food ingredients manufacturers and distributors	1. Lines 1581 - 1597 a), b), c) should be sufficient to evaluate the allergenicity potential. Why adding d) and e) ? Lines 1586-1597 Such a 'holistic approach' seems to be an exaggerated requirement. Even if the first sentence mentions 'could be followed' which may mean that this is not required in all cases, we know EFSA well enough that this may pretty quickly turn into a generic requirement. And this is both not justified nor reasonably feasible for complex protein mixtures and whole foods. Suggestion to delete, stating as a reason that first the science needs to be established, before this should be mentioned in a guidance document, meaning that: - Identifying whether and to which extent this may be a meaningful risk for complex mixtures and whole foods in the first place (which may provide an indication how much effort applicants could and should spend on this issue) - Development of protocols and best practices how these approaches can be used in a meaningful and straightforward manner for risk assessment 2. Line 1596 Please refer to comment for Section 9.4, where the actual protein digestibility methods are specified. There needs to be clarity and coordination of all statements in this guidance related to protein digestibility studies.	1. The text has been revised, and the testing requirements have been simplified. 2. Please refer to the response to comment 38.
221	EU Specialty Food Ingredients	Lines 1586-1597: Such a 'holistic approach' seems to be an exaggerated requirement. Even if the first sentence mentions 'could be followed' which may mean that this is not required in all cases, we are afraid that this may pretty quickly turn into a generic requirement. And this is both not justified nor reasonably feasible for complex protein mixtures and whole	Please refer to the response to comment 183.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		foods. Our suggestion is to delete this paragraph, stating as a reason that first the science needs to be established, before this is be mentioned in a guidance document, which includes: o Identifying whether and to which extent this may be a meaningful risk for complex mixtures and whole foods in the first place (which may provide an indication how much effort applicants could and should spend on this issue); o Development of protocols and best practices how these approaches can be used in a meaningful and straightforward manner for risk assessment.	
223	Food Safety Authority of Ireland	Line 1516: It is difficult for regulators to obtain prevalence data for known priority allergens not to mind non-priority allergens, and so this requirement may be ambitious if not unfair to applicants. Prevalence should be based on medical diagnosis using the gold standard double blind placebo controlled analysis but not a small number of poor quality 'peer-reviewed' or even anecdotal reports about uncharacteristic reactions to a food.	The Panel acknowledges the concerns expressed. The text has been revised, stating that 'The information should be provided if available in the literature'.
224	Food Safety Authority of Ireland	Line 1537: Any conclusions drawn from literature searches must be cognisant of the limitations of tests like ELISA, Skin Prick Tests in detecting genuine allergenicity in humans.	The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance. However, such aspects are to be considered during the risk assessment.
256	The Good Food Institute Europe	Line 1512-1514: This section concerns novel foods derived from foods (or products thereof) that are known to trigger allergic reactions in susceptible individuals, but which are not listed in Annex II of Regulation (EU) No 1514 1169/2011. Comment: EFSA should consider replacing this sentence with: 'This section concerns novel foods derived from foods (or products thereof), or allergenic foods derived from a novel source, that are known to trigger allergic reactions in susceptible individuals,...' This would help to ensure that dairy or other potentially allergenic proteins produced through precision fermentation are in scope.	The Panel does not agree with the proposal.
319	EuropaBio	The whole section, even though a very useful opening to the challenging topic, should be thoroughly discussed before including it to the guidance. As in toxicological studies, a tiered approach could be considered. More detailed proposal is	Please refer to the response to comment 78.

Comment number	Commentor	Comments	EFSA NDA Panel responses
		urgently needed concerning the analysis of whole-genome sequence for the assessment of potential allergens (as in case of viable or non-viable non-GMMs as novel foods).	
330	National Food Institute, Technical University of Denmark	Section 10 on allergenicity is a real improvement from the old version. It is comprehensive and clearly written. We have the following comments	The Panel appreciates the recognition of EFSA's ongoing efforts.

Table 70: 10.4 Novel foods for which the allergenic potential is unknown

Comment number	Commentor	Comments	EFSA NDA Panel response
331	National Food Institute, Technical University of Denmark	Line 1506: proteins are NOT subject to mandatory labelling, foods are.	The text has been revised in line with the comment.
332	National Food Institute, Technical University of Denmark	Line 1518 c): Case reports can be used to identify culprit foods, not to determine minimal eliciting dose. This needs challenge data, where the dose is known. It may be near to impossible to predict the dose based on clinical history. Line 1510 section 10.3. Suggestion to add another subsection: Novel foods derived from allergenic sources that is not food e.g. grass (pollen).	The Panel considers that no change to the Guidance is needed.
333	National Food Institute, Technical University of Denmark	Line 1553 Cross-reactivity could also be used to estimate the risk of de novo sensitisation e.g. for strong allergens with very high similarity e.g. rape seed 2 S albumin and mustard 2S albumin.	The text has been revised.
334	National Food Institute, Technical	Add e.g. f) in vitro/in vivo analyses to identify cross-reactivity to related species e.g. insects and crustaceans	The text has been revised. The applicant may utilise methods of their choice to further investigate the

Comment number	Commentor	Comments	EFSA NDA Panel response
	University of Denmark		allergenicity profile of their novel food.
335	University Medical Center Utrecht	Is there a minimum protein level accepted? Detection limit of analysis? Maybe based on threshold levels?	No specific threshold can be provided in the Guidance concerning the minimum acceptable protein level or the detection limit of analysis.

Table 71: 10.4.1 Single protein and simple protein mixtures

Comment number	Commentor	Comments	EFSA NDA Panel response
336	University Medical Center Utrecht	Allergenic potency For allergenic food on the labelling list this information is available. Allergenic food with no/scarce evidence were not listed for labelling, because of the low amount of evidence. Do we expect that this information can be provided by the applicants? Clinical relevance of individual allergenic proteins is difficult. We never performed clinical studies with individual proteins, only with whole foods. This information is for most proteins not available.	The Panel acknowledges the concern that clinical relevance data for individual allergenic proteins are often unavailable. Parts of section 10.4.1 have been revised to provide further clarity, with greater emphasis on a comprehensively expressed tiered approach to investigate the allergenicity of single proteins and simple protein mixtures.
337	University Medical Center Utrecht	Use sera: Must sera contain IgE against homolog protein or come from patient allergic to the whole source of protein e.g. soy ? Sera with specific IgE to minor allergens is very difficult to find and not routinely determined. They will be very hard to find. Suggest to state that serum against whole product is required and not to individual protein. Also state how many serum is advised a) There is no evidence that certain PTM are related to allergenicity. When requiring this information than clear guidance is needed how to interpret the data b) There is no evidence that protein stability is relevant for allergenicity. Guidance on how to interpret data is needed c) There is no	Sera should be sourced from patients with a clearly demonstrated food allergy. The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel response
		evidence that digestibility is related to allergenicity. I know that digestion is needed for other part of the dossier but for allergenicity guidance on how to interpret data is needed	
338	University Medical Center Utrecht	a) identify proteins using proteomics. So no genomic sequencing? b) do not understand what is asked here. Why not phylogenetic relationship? c) bioinformatics: based om proteomics data. If a novel food is from a species than identification is already based on homology with other species, so you will not have the correct amino acid sequence. Besides you will find many false negative results. Also the databases are full of allergens with very low evidence (based on five positive sera, no clinical relevance) fragments, inhalant allergens etc. This always ends in IgE-binding studies with very rare allergenic proteins. Clear guidance also here needed. What is a relevant hit. And databases need to be updated. d) digestibility see remark 10.4.1 e) there are no methods to determine sensitising capacity that are validated and predictive yet. The only way is to investigate workers from facilities that produce the food	The Panel acknowledges the concerns expressed. Parts of section 10.4.1 have been revised to provide further clarity, with greater emphasis on a comprehensively expressed tiered approach to investigate cross-reactivity and cross-allergenicity, including phylogenetic relationships.
345	Ronald van Ree (Personal Capacity)	I have uploaded a file, but cannot see whether this was successful or not.	No file linked to this comment could be retrieved.
351	GAIKER	Interested in knowing if Allergenicity could be tested in vitro by β-hexosaminidase activity. Asses β-hexosaminidase secretion by RBL-2H3 cell line when incubated with ingredient/novel protein extract for 24h. Then collect the supernatant exposed medium and incubate with 4 methylumbelliferyl N-acetyl- β-D-glucosamide (1.2 mM in 40 mM sodium citrate buffer pH 4.5) for 1 h at 37ºC. Finally, determine β-hexosaminidase activity by fluorescence quantification at λex 380nm / λem 440nm.	The Panel acknowledges the comment. However, the Panel would like to highlight that this is not a validated assay for allergenicity testing.
352	Dwayne Holmes (Personal Capacity)	Page 48, Line 1532 - To avoid assumptions that could lead to settlement of binding standards, the reference to proteomic should be integrated by a broader 'proteomic (or other -omic techniques).'	Please note that the respective sentence has been removed from the Guidance. The text has been revised.
430	Solar Foods	Complex protein mixtures and novel whole foods can contain thousands of new protein sequences. Deriving meaningful results from such a vast number of proteins with the suggested	The Panel acknowledges the concerns expressed. Parts of section 10.4.1 have been revised to provide further

Comment number	Commentor	Comments	EFSA NDA Panel response
		approach will be difficult for the following reasons: 1) Suggested methods to detect proteins in the sample (SDS-PAGE, proteomics, shot-gun proteomics) are not comparable in analysis depth, sensitivity and accuracy. Variation in the methodology compromises reproducibility and the outcomes will not be comparable between products. 2) Unless a cut-off value is used to select proteins that are present in the sample in relevant amounts, proteomics using sensitive MS/MS excludes only a marginal proportion of the hypothetical translated proteome. Without a cut-off, there will be hundreds or thousands of protein in trace amounts going forward into the bioinformatics analysis. 3) Grouping of sequences is a very useful step in categorising the results and providing information, but does not promote narrowing down relevant sequences from non-relevant unless by grouping it is allowed to focus only on major allergens instead of minor allergens. 4) The 35% identity threshold over at least 80 amino acids has been criticised for allowing too many false positives. This has been a clear drawback already in single protein analyses. When applying this threshold to hundreds of protein sequences, it is not anymore possible to separate relevant hits from false positives. 5) In vitro/in vivo analysis steps are not feasible if steps a-c fail to cut down the list of protein candidates. In summary, more detailed instructions are required to conduct a meaningful, justifiable and equal analysis of various products. For instance, by setting a cut-off value to exclude non-relevant proteins from MS/MS proteomics data and by increasing the identity value in bioinformatics assay (and/or focusing on full fasta search instead of 80mer search), it could be possible to reach sufficient conclusions.	clarity and more simplified scientific requirements.

Table 72: 10.4.2 Complex protein mixtures and whole foods

Comment number	Commentor	Comments	EFSA NDA Panel response
512	Undisclosed (Personal Capacity)	When bioinformatic analyses indicate potential cross-allergenicity to a known allergen, a follow-up analysis should be performed such as human serum specific IgE-binding assay, depending on the availability of human sera and the clinical relevance of the allergenic protein. The guidance could benefit from a clearer guidance on this as many hits will be found in bioinformatic analysis, human specific IgE-binding assays only seem relevant when hits against major allergens are found and not minor allergens which are most often conserved in nature and to which no IgE specific serum samples exists.	The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance. Please note that in the Guidance there is a structured (four types of novel foods), tiered approach for investigating potential cross-allergenicity.
513	Undisclosed (Personal Capacity)	In vitro/in vivo analysis to identify immunogenicity and sensitising capacity. The guidance could benefit from more detailed information on what methods should be used, as it is not clear now from the guidance. Furthermore, it is difficult to assess de novo sensitisation, so it is not clear why analyses are needed to measure this. Do all these proposed studies in this section need to be performed or could EFSA maybe come up with a tiered approach as is done to generate tox data? In this case the remark on major and minor allergens is also valid, a distinctive approach should be followed.	The Panel notes the recommendation but considers that it goes beyond the scope of this Guidance. Please note that in the Guidance there is a structured (four types of novel foods), tiered approach for investigating potential cross-allergenicity. Parts of section 10.4.2 have been revised to provide further clarity and more simplified scientific requirements.
574	Aletheia: il segreto del buon vivere	Food processing can have many beneficial effects. However, processing may also alter the allergenic properties of food proteins. A wide variety of processing methods is available, and their use depends largely on the food to be processed. Food processing can potentially affect two aspects of the allergenic properties of proteins, as follows: a. In most investigations it is the impact of processing on the integrity of epitopes recognised by IgG antibodies or IgE antibodies that has been reported. Such changes are of potential importance because they will influence the ability of antibodies to bind to the modified protein, and in the case of IgE antibody binding this may result in an altered capacity to elicit an allergic reaction. b. Much less commonly the impact of processing on the ability of food proteins to induce allergic sensitisation has been investigated. Here, in the case of IgE-mediated food allergy, the question addressed is whether	The Panel acknowledges the concerns expressed and the issues raised, i.e., the alteration of allergenic properties of proteins and the impact of processing on the ability to induce de novo sensitisation. Food processing can potentially impact on the allergenic potential of a complex food (decreased, unchanged, or even increased). However, there is currently no overarching, validated method available to specifically investigate the impact of processing on the ability of food proteins to induce allergic reactions. The aspect

Comment number	Commentor	Comments	EFSA NDA Panel response
		processing has impacted on the capacity of a protein to stimulate the production of IgE antibody.	of altered allergenicity due to the production process is addressed within the guidance requirements set for novel foods derived from allergenic sources that are not subject to mandatory labelling. The default assumption adopted by EFSA is that processing does not eliminate any existing allergenic potential of a novel food.
581	AseBio - Spanish Bioindustry Association,	The whole section, even though a very useful opening to the challenging topic, should be thoroughly discussed before including it to the guidance. As in toxicological studies, a tiered approach could be considered. More detailed proposal is urgently needed concerning the analysis of whole-genome sequence for the assessment of potential allergens (as in case of viable or non-viable non-GMMs as novel foods).	Please note that in the Guidance there is a structured (four types of novel foods), tiered approach for investigating potential cross-allergenicity. Parts of section 10.4.2 have been revised to provide further clarity and more simplified scientific requirements. Please also refer to the response to comment 78.
636	Cellular Agriculture Europe	Line 1596: We would like to refer to the comment for Section 9.4, where the actual protein digestibility methods are specified. There needs to be clarity and coordination of all statements in this guidance related to protein digestibility studies.	Please refer to the response to comment 38.
685	Atova Regulatory Consulting SL	1. (Line, 1560–1561, page 49) 'This approach in isolation is highly conservative and has been criticised to trigger a high number of false positives'. We agree with this statement. According to Aalberse (2000) and Harper et al., (2012), While cross-reactivity can occur for allergens with a ~50% shared identity, it typically occurs at a level of shared identity of 70% or greater. Would EFSA consider increasing the threshold value of 35% identity to e.g., 50% identity? B. Harper, S. McClain, E.W. Ganko. Interpreting the biological relevance of bioinformatic analyses with T-DNA sequence for protein allergenicity, Regulatory Toxicology and Pharmacology, Volume 63, Issue 3, 2012, Pages 426-432, ISSN 0273-2300,	1. The Panel notes the recommendation but considers that establishing new threshold values(s) goes beyond the scope of this Guidance. 2. Please refer to the response to comment 38. The Panel cannot establish a specific peptide size that is universally recognised as having no allergenic potential.

Comment number	Commentor	Comments	EFSA NDA Panel response
		https://doi.org/10.1016/j.yrtph.2012.05.014. Rob C. Aalberse. Structural biology of allergens, Journal of Allergy and Clinical Immunology, Volume 106, Issue 2, 2000, Pages 228-238, ISSN 0091-6749, https://doi.org/10.1067/mai.2000.108434. (Line, 1572–1574, page 49) Could EFSA indicate how post-translational modifications should be assessed by applicants? 2. (Line, 1578, page 50) Could you indicate how EFSA interprets the digestibility of protein in the allergenicity assessment? Is there a peptide size that EFSA recognises as not having allergenic potential?	
692	FoodDrinkEurope	1. [Lines 1579 - 1579] Please refer to comment for Section 9.4, where protein digestibility methods are specified. There is a need for clarity and coordination of all statements in this guidance related to protein digestibility studies. 2. (Lines, 1840–1841) Typo error: Toxigenicity and pathogenicity strains	1. Please refer to the response to comment 38. 2. The text has been revised in line with the comment.

Table 73: Abbreviations

Comment number	Commentor	Comments	EFSA NDA Panel response
694	FoodDrinkEurope	(Line, 1845) QSAR is not correctly abbreviated/translated – should be quantitative structure activity relationship and not threshold of toxicological concern	The text has been amended.

Table 74: Abstract

Comment number	Commentor	Comments	EFSA NDA Panel response
76	European Industrial Hemp	As the European Industrial Hemp Association (EIHA), we'd like to highlight our main concerns regarding the EFSA's performance, particularly focusing on the Novel Food (NF)	Regarding the Novel Food application process in the EU, please note that the timelines for processing

Comment number	Commentor	Comments	EFSA NDA Panel response
	Association - EIHA	application process. The lengthy process imposes significant financial and operational challenges on our members, especially SMEs. Inconsistencies in application timelines and excessive demands complicate planning and innovation. Technical issues with the submission platform and the limited utility of the pre-submission phase further hinder efficient application submissions. We urge for a streamlined process and more practical considerations to facilitate innovation while ensuring food safety. We aim to support a regulatory environment that is both thorough and accommodating for all stakeholders.	applications are legally defined. Any additional time required when the clock is stopped is influenced by the quality of the submitted dossier and the responsiveness of the applicant in providing timely and high-quality comprehensive replies. It should be highlighted that the submission platform is not managed by EFSA, so concerns related to technical issues with the platform fall outside the scope of this Guidance. Consumers' safety is indeed the primary goal, ensuring that innovation in food products progresses alongside rigorous safety assessments.
81	BaseClear	In line 15, it is stated that missing information must be justified. It would be beneficial to clarify whether this justification applies to any missing information or only to specific types of data. Providing clarity on this aspect would help applicants ensure compliance with the guidance.	It should be noted that General Principles 5 and 9 offer further insights into this issue.
258	Mario Stahl (Personal capacity)	Feedback 'Draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283' When authorising products with so-called 'new processes', stakeholders often have questions about their use on an industrial scale and the need for an assessment or approval as a 'novel food'. The UV treatment of food is a 'new' process, although it was already in use before 1997 and is therefore not really new. There is still no general regulation at EU level regarding the use of UV treatment for must and wine. In Germany, however, there are regulations for the UV treatment of the surfaces of fruit and vegetable products, hard cheese during storage, drinking water, invert sugar and egg shells. Other EU countries have their own regulations. The International Organisation of Vine and Wine (OIV) is unsure how UV-treated must or wine should be assessed when used to stabilise the shelf life, reduce sulphur or influence the sensory	The determination of a product's 'novel status' due to a new process falls under the jurisdiction of risk managers, not EFSA. The definition of 'significant change' is also within the purview of risk managers, who may consult EFSA if needed. For specific guidance, please contact the competent authority in your member state. This comment falls outside the scope of this guidance document. Moreover, please refer to the response to comment 139.

Comment number	Commentor	Comments	EFSA NDA Panel response
		properties. Must is a foodstuff, wine is considered a luxury food. The OIV would like to avoid risks when drinking both and would therefore like an assessment from the EFSA, which is generally responsible for foodstuffs. Scientific studies carried out by the Max Rubner Institute (Federal Research Institute) in recent years on the use of UV radiation to reduce microorganisms have shown that UV-treated musts or wines can be classified as harmless in the relevant dose range (at a wavelength of 254 nm). Corresponding scientific documents are available, but no authorisation has yet been granted by the OIV. The term 'significant change in the composition or structure of the food' is not precisely defined in Regulation (EU) 2015/2283 and therefore repeatedly raises questions. Depending on the interest group, it is interpreted differently and the authorisation and application of this treatment in the international area is made more difficult. I therefore recommend that this term be precisely defined in Article 3 of Regulation 2015/2283, in the definitions §2a) vii, and that it be explained what is meant by 'significant changes in the composition or structure of the food' so that this must/wine stabilisation process can be used and the benefits for the industry and the consumer can be exploited (energy saving, conservation of resources, sustainability, sulphur reduction). Text passages of the reference: 254 vii. food resulting from a production process not used for food production within the Union 255 before 15 May 1997, which gives rise to significant changes in the composition or structure of a food, 256 affecting its nutritional value, metabolism or level of undesirable substances;	
261	Vaclav Bazata (Personal capacity)	NFR guidance - public consultation (PC-0824) on Draft guidance on the scientific requirements for an application for authorisation of a novel food until 14 April 2024.	No further feedback can be provided because the comment is unclear.
339	Jeremy Coller Foundation	Page 1, line 7 – We welcome the updated guidance on novel foods regulation by EFSA as a useful clarification on additional data requirements upon submitting a dossier. The EFSA approval process remains fit for purpose and this additional guidance will assist companies in collecting the necessary data in advance of submission, making the process smoother for	The Panel appreciates the acknowledgement of EFSA's continuous efforts to provide up-to-date guidance on scientific requirements.

Comment number	Commentor	Comments	EFSA NDA Panel response
		both the applicant and the regulator, whilst crucially maintaining food safety. The remainder of our comments in response to this consultation cover points where further clarity would be helpful in the final guidance to improve the quality of dossier submissions.	
567	Aletheia: il segreto del buon vivere	EU has never delivered any authorisation on animal products based on cell cultivation techniques so far. Hence, a transparent, science-based and comprehensive approach is necessary to assess the development of artificial cell-based meat production, which does not constitute a sustainable alternative to primary farm-based production. EFSA guidelines should cover certain aspects of evaluation currently provided for new pharmaceutical products, including pre-clinical and clinical studies that will be used as safety criteria for an opinion of EFSA. A comprehensive impact assessment of the Commission taking all the issues at stake into account, including EU consumers and citizens' views, should also be conducted.	Cell culture-derived foods are addressed in both the previous and current EFSA Novel Food Guidance documents. The EFSA NDA Panel has already assessed cell culture-derived foods of plant origin under the EU novel food regulatory framework.

Table 75: Keywords

Comment number	Commentor	Comments	EFSA NDA Panel response
77	Mario Stahl (Personal capacity)	novel food; food irradiation; UV treatment; ultraviolet	The Panel considers that the last three keywords provided are too specific for this Guidance. No changes are introduced.
305	Food Safety & Nutrition Consultancy	'authorisation' is not for EFSA to do - can be deleted 'food innovation' can be deleted too. that is not relevant for novel foods	The Panel considers that all these keywords are relevant to this Guidance.
353	Vaclav Bazata (Personal capacity)	fingerprint	The Panel considers that this keyword is too specific for this Guidance. No changes are introduced.

Comment number	Commentor	Comments	EFSA NDA Panel response
539	European Industrial Hemp Association - EIHA	Lengthy process, excessive demands, technical issues with the platform, useless pre-submission phase, stringent study notification policy.	The Panel considers that all these keywords are not relevant to this Guidance. No changes are introduced.
568	Aletheia: il segreto del buon vivere	EFSA guidance, novel foods, authorisation, food safety, food innovation, risk assessment, hazard identification, hazard characterisation, pre-clinical and clinical studies.	The Panel considers that the 'pre-clinical and clinical studies' are too specific for this Guidance. The rest of the proposed keywords were already included in the list.

Table 76: Annexes

Comment number	Commentor	Comments	EFSA NDA Panel response
66	Nutraveris - A FoodchainID company	- Are appendix A – Completeness checklist and appendix B summary tables for scientific data still mandatory?	The Panel noted that this aspect is outside the scope of this Guidance, and will be addressed in the relevant administrative guidance for novel food applications.

Please note that in final version of the Guidance, the section title has been changed to 'Appendices'.

Table 77: Annex A

Comment number	Commentor	Comments	EFSA NDA Panel response
198	EU Specialty Food Ingredients	'Toxigenicity and pathogenicity trains (EFSA FEEDAP Panel, 2018; EFSA, 2021e)'. Comment: Suspected typographical error - suggest this should be 'traits'. ROW: Presence of DNA in the novel food to be tested (EFSA FEEDAP Panel, 2018). Comments: 1. This cell of the second column is blank – suggest this should be 'N/A'. 2. The submission of these data should not be systematically requested for production strains used in contained	The text has been amended accordingly (regarding 'traits' and 'n/a'). Wherever such requirements are mandatory, this has been highlighted in the Guidance.

Comment number	Commentor	Comments	EFSA NDA Panel response
		use fermentation processes and for microorganisms used as Novel Food, as each application should be considered on a case-by-case basis, where a safety concern is demonstrated by EFSA (see also above comments in lines 451 - 452).	
320	EuropaBio	1840: The submission of these data should not be systematically requested for production strains used in contained use fermentation processes and for microorganisms used as Novel Food, as each application should be considered on a case-by-case basis, where a safety concern is demonstrated by EFSA (see also above comments in lines 451 - 452).	Please refer to response to comment 198.
582	AseBio - Spanish Bioindustry Association	Line: 1840 The submission of these data should not be systematically requested for production strains used in contained use fermentation processes and for microorganisms used as Novel Food, as each application should be considered on a case-by-case basis, where a safety concern is demonstrated by EFSA (see also above comments in lines 451 - 452).	Please refer to the response to comment 198.
599	Cellular Agriculture Europe	Line (1845): Abbreviation is not correct: QSAR. QSAR is not correctly abbreviated/translated – should be quantitative structure activity relationship and not threshold of toxicological concern.	Please refer to the response to comment 694.
664	Atova Regulatory Consulting SL	(Line, 1840, page 56) We understand that EFSA's requires to investigate the potential presence of acquired antimicrobial resistance genes using bioinformatic tools, and there is no need for in vitro phenotypic testing. (Line, 1840, page 56) Typo: Toxigenicity and pathogenicity 'traits'	Please refer to the response to comment 198.
693	FoodDrinkEurope	(Lines, 1840–1841) Typo error: Toxigenicity and pathogenicity strains.	The text has been amended accordingly.

Please note that in final version of the Guidance, the section title has been changed to 'Appendix A'.

Table 78: Annex B

Comment number	Commentor	Comments	EFSA NDA Panel response
11	Undisclosed (Personal capacity)	Lines 1182-1184 'COA' should be replaced with 'Specification' or 'COA or Specification'. This avoids all sorts of confidentiality issues and applicants may source from more than one supplier to the same specification. Hence specifications are more meaningful to have here, as had routinely been accepted by EFSA in the past.	The text has been amended accordingly
600	Cellular Agriculture Europe	'COA' should be replaced with 'Specification' or 'COA or Specification'. This avoids all sorts of confidentiality issues and applicants may source from more than one supplier to the same specification. Hence specifications are more meaningful to have here, as had routinely been accepted by EFSA in the past.	The text has been amended accordingly
665	Atova Regulatory Consulting SL	(Line, 1843–1844, page 57) Please replace by 'CoA or specifications'	The text has been amended accordingly

Please note that in final version of the Guidance, the section title has been changed to 'Appendix B'.

Abbreviations

Abbreviation	Explanation
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
AMR	antimicrobial resistance
AR	average requirement
BIOHAZ	Panel on Biological Hazards
BMD	benchmark dose
CEP	Panel on Food Contact Materials, Enzymes and Processing Aids
DIAAS	digestible indispensable amino acid score
DietEx	Dietary Exposure tool
DRV	dietary reference value
EC	European Commission
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EOGTRS	extended one-generation reproductive toxicity study
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAIM	Food Additives Intake Model
FAO	Food and Agriculture Organization of the United Nations
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
FoodEx	EFSA Food Classification System
FSG	goods for specific groups
FSMP	foods for special medical purposes
GMM	genetically modified microorganism
GMO	genetically modified organism
HACCP	hazard analysis critical control point
HBGV	health-based guidance values
IAA	indispensable amino acid
IAEA	International Atomic Energy Agency
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgE	immunoglobulin E
ISO	International Organization for Standardization
LOD	limit of detection
LOQ	limit of quantification
NAM	new approach methodology
NDA	EFSA Panel on nutrition, novel foods and food allergens
OECD	Organisation for Economic Co-operation and Development
PBTK	Physiologically based toxicokinetic
PPR	Panel on Plant Protection Products and their Residues
QPS	qualified presumption of safety
SCF	Scientific Committee on Food
TDI	tolerable daily intake
TG	Test Guideline
TTC	threshold of toxicological concern
TU	taxonomic unit
UL	tolerable upper intake level
WGS	whole genome sequence
WHO	World Health Organization

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Appendix A Attachment to Public Consultation comment number 76

This appendix contains the attachment for Public Consultation comment number 76, submitted by European Industrial Hemp Association - EIHA. The original format of this attachment was a PDF document.

EIHA
European Industrial Hemp Association

Evaluation of the EFSA Performance 2017-2024

As a representative of the European Industrial Hemp Association (EIHA), we wish to offer our feedback on the performance evaluation of the European Food Safety Authority (EFSA). Our feedback centres on the challenges observed within the Novel Food (NF) application process, which we consider crucial for both the EFSA and the European Commission to address.

We acknowledge and endorse EFSA's dedication to enhancing transparency in the approval and authorization processes, as outlined in Articles 32c and 32d of the new Transparency Regulation and we hope that our comments will be considered in the purpose of a constructive dialogue. This endeavour toward greater transparency is vital for upholding the integrity and dependability of food safety in the EU.

The following feedback is intended to constructively contribute to the ongoing evaluation of the EFSA's performance and the operationalization of the Transparency Regulation, aiming for a regulatory environment that balances the need for thorough and transparent assessment with practical and fair considerations for stakeholders.

1. The **duration** of the NF application process imposes a significant burden on companies, particularly affecting SMEs. The extended timelines, sometimes stretching up to nine years, not only postpone market entry but also place substantial financial and operational pressures. Furthermore, when a product takes nearly one decade to reach the market, its innovative edge and relevance can be significantly compromised, affecting competitive advantage and return on investment. This is even more striking compared to swifter procedures in non-EU countries. It is essential to streamline this process while upholding stringent safety standards.

2. **Inconsistent adherence to deadlines** from the EFSA side exacerbates uncertainties and impedes effective planning for applicants. A more predictable and strictly followed timeline would greatly benefit applicants, enabling improved resource management and project scheduling.

3. Concerns have also emerged regarding the **demands** placed on applicants, often perceived potentially **exceeding what is necessary** for ensuring food safety. Such perceptions can deter innovation, especially for smaller entities considering the development of new products. A balanced approach that prioritizes food safety while fostering innovation is essential.

4. Another major concern relates to the **operational functionality of the EFSA's submission platform**. Our members have faced various technical issues, including system bugs and difficulties uploading files of significant size. These technical limitations not only impede the efficient submission of detailed and comprehensive application dossiers but also worsen the already lengthy and complex application process. It is crucial to address these technical shortcomings to facilitate a smoother and more accessible application procedure for all stakeholders, especially those from

SMEs who may struggle to navigate these additional hurdles effectively due to limited resources.

5. The **pre-submission phase**, meant to assist applicants, has been found to offer **limited utility**. The EFSA staff's inability to provide comments on the specifics of the contents or studies during this phase undermines its intended purpose, resulting in frustrations among applicants. This phase does not significantly contribute to preparing for a successful application, raising doubts about its effectiveness and efficiency. The introduction of the Transparency Regulation, aimed at improving the transparency and sustainability of EU risk assessments, has inadvertently added further complexity to the submission process, without clearly simplifying or reducing the administrative burden for businesses.

6. Another particular point of concern is the necessity for stakeholders to notify EFSA in advance of **planned studies for applications**. While this requirement aims to guarantee transparency and thoroughness in the evaluation process, it has posed practical difficulties. There have been cases where, due to various reasons, studies intended for inclusion in an application dossier were not communicated to EFSA in advance. Within the current framework, such oversights can jeopardize the validity of an entire dossier, even though the studies might provide additional useful information and represented significant investments. This scenario could potentially discourage the submission of valuable data crucial for scientific assessment and ensuring public safety. Therefore, we suggest that this issue could be alleviated by implementing more flexible provisions for accepting studies notified with a delay, as long as these studies meet EFSA's rigorous criteria for quality and relevance. Such flexibility would not compromise the validity of the dossier or trigger the subsequent 6-month penalty, thus avoiding unjust penalization of stakeholders.

About EIHA

The European Industrial Hemp Association (EIHA) represents the common interests of hemp farmers, producers and traders working with hemp fibres, shives, seeds, leaves and cannabinoids. Our main task is to serve, protect and represent the hemp sector in the EU and international policy-making.

For more info please visit www.eiha.org and contact us at info@eiha.org

Appendix B Attachment to Public Consultation comment number 96

This appendix contains the attachment for Public Consultation comment number 96, submitted by The Good Food Institute Europe. The original format of the attachment was a PDF document.

gfi / Good Food Institute Europe

Contribution to EFSA public consultation on the revised draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283

Submitted 12th April 2024

GFI Europe welcomes the opportunity to respond to EFSA's consultation on its revised draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283.

We strongly support the ambition of both EFSA and the European Commission to ensure that recent EU regulatory updates in the novel food area are properly reflected in the scientific guidance, and to proactively consider advances in food research and innovation that have taken place in recent years. We also welcome the overall commitment to ensuring that the guidance remains a practical and updated tool for applicants and a reference document for risk assessors, particularly in light of ongoing technological and scientific innovation across the novel food space.

In responding to this consultation, GFI Europe's feedback is grouped into two sections. At the conclusion to this response, GFI Europe has set out feedback on aspects of the revised guidance in a line-by-line format with specific reference to the line and page numbers to which the comments relate. However, we have also provided some more holistic reflections on the revised guidance, and the role that EFSA and the European Commission can play in enabling innovation in the EU that contributes to policy objectives around sustainability and food security.

The role of alternative proteins in a future-proofed EU food system

Establishing the European Union at the forefront of the protein transition will help to make our food system more resilient, healthy and sustainable. It also aligns with EU policy priorities including consolidating EU food security and food sovereignty, reaching net zero carbon emissions by 2050 and addressing antimicrobial resistance. Making meat from plants and cultivating it from cells can provide the European public with the foods they love at a fraction of the cost to the environment. Plant-based meat production emits up to 90% fewer greenhouse gas emissions and uses up to 99% less land than conventional meat. When produced with renewable energy, cultivated meat could cut the climate impact of meat by 92% and use 95% less land.

At the same time, increasing production and consumption of these alternative proteins can fortify Europe's food security. Europe currently feeds 45% of all the crops we produce to animals and uses half of its farmland for animal agriculture. In an increasingly uncertain world, we need a more sustainable system that supports Europe's food sovereignty. Plant-based and cultivated meat could deliver the meat people want with up to 90% less land, and fermentation can make nutritious food from crops that would otherwise go to waste, creating more space for sustainable farming and freeing up land for increased domestic food production – supporting home-grown food production and reducing overseas competition for our farmers.

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How the regulatory framework impacts on the innovation potential of alternative proteins

For alternative proteins to fulfil their environmental and food security potential, consumers must be confident in the food they eat. In the EU most products require authorisation under the Novel Food Regulation, a framework amongst the most robust in the world which balances support for innovation with a rigorous focus on consumer safety.

However, while the regulatory framework itself remains fit for purpose and robust, there is a growing concern amongst producers in the alternative protein space that a lack of substantive, differentiated and up to date guidance - which takes into account rapidly emerging production techniques and evolving scientific evidence - is hampering the ability of innovative products to reach the EU market. As such, EFSA's revision of the scientific guidance is a welcome step - and GFI Europe has provided detailed comments on how this revision could be further enhanced to maximise utility for producers. However, at the same time there are more general reflections on the wider guidance process which EFSA could take into account to ensure the authorisation process remains relevant and accessible, enabling innovation whilst maintaining the high standards of food safety and consumer protection that citizens in the EU demand.

Regular updates

To enable innovation in the EU that supports food security and a more sustainable food system, it is essential to ensure that EFSA's scientific - and administrative - guidance for novel food producers is kept regularly updated and iterated in line with developing scientific evidence and new production systems. Prior to the current revision, EFSA's scientific guidance was last revised in 2021, solely in light of the incoming Transparency Regulation. This therefore represents an extended period where the guidance has not been amended in light of developing scientific evidence, or amended to include references to emerging food production techniques.

In order to ensure EU producers are supported in bringing innovative products to market, EFSA should commit to reviewing the scientific and administrative guidance for the novel food authorisation process on a more regular and systematic basis - for example using checkpoint reviews every 2 years as baseline timeline and amending this as necessary in light of emerging evidence. This approach would mirror the process undertaken by some of the most progressive food safety regulators globally such as the Singapore Food Agency, whose Requirements for the Safety Assessment of Novel Foods and Novel Food Ingredients is reviewed and amended multiple times annually to account for the latest scientific and risk assessment evidence to ensure it is fit for purpose and relevant to novel food producers.

Further differentiation of guidance

The revised novel food guidance demonstrates a welcome commitment from EFSA to the utilisation of cutting edge scientific evidence and data sets to inform risk assessment approaches. However, the guidance could go further in providing an effective resource for

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applicants through a greater degree of differentiation between different production platforms and the associated guidance and safety recommendations that accompany these.

This differentiation should include the detailing of requirements and safety thresholds which are specific to the novel food categories - for example, including guidance on good cell practice, scaffold design and analysis in sections on "food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, microorganisms, fungi or algae". Equally, for certain fermentation derived products, thresholds or specific criteria for producers to demonstrate that genome instability and genetic drift would not result in the production of undesirable substances in the end-product would be welcomed, providing necessary clarity to inform dossier submission and safety testing.

Structuring and accessibility of guidance

Many of the stakeholders engaging with the guidance for novel food authorisations are likely to be small or medium size enterprises (SMEs) who have a high degree of scientific and technological expertise but - potentially - less experience in regulatory and legislative considerations within the EU context. In light of this, efforts should be made to ensure that EFSA's guidance is as user-friendly and accessible as possible for a wide range of audiences, ensuring that technical regulatory knowledge and an understanding of pre-existing EU risk assessment precedents is not a barrier to engagement for producers. The current guidance, whilst holistic and thorough, could benefit from being accompanied by an easy-to-use explainer document, or could be reviewed to ensure that all regulatory and legal jargon is limited to situations where it is strictly necessary for accuracy. Similarly, EFSA could consider the inclusion of graphic and pictorial explainers to support clarification of the guidance, including using decision trees, checklists and diagrams as appropriate to ensure the guidance remains as accessible as possible to the full range of relevant stakeholders.

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Line by line feedback on revised draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283

Section	Lines	Original text	Comments and revisions
General principles	301-303	*Applications which concern an already authorised novel food may relate to changes of the production process, specifications, or the conditions of use, e.g. adding a target population, adding uses (add new food categories to which a novel food is intended to be added) or use levels.*	EFSA should clarify what specific elements of "changes of the production process" would make re-authorisation necessary. For example, whether a material input change would always reflect a production process change. EFSA should also urgently consider the imposition of "amendment notification processes", such as those used by the US Food and Drug Administration, which provide clarity on the path to notification for pre-authorised products with amendments to production processes or input materials.
Characterisation of the novel food, technical and scientific data	347	*The full characterisation of the novel food under assessment is a key element of the risk assessment.*	EFSA should consider adding further specificity on the characterization metrics necessary as part of the risk assessment process, including whether it should include chemical, nutritional and/or physical characterisation. EFSA could even provide examples on acceptable degrees or thresholds for the characterisation for novel foods.
1. Identity of the novel food	367-370	*"...and must bear no nutrition or health claims according to Regulation (EU) 2015/2283"*	EFSA should reconsider whether such a blanket approach to nutritional or health claims is appropriate within the confines of the novel food authorisation process. It could be considered that these aspects are regulatory issues which can be deliberated on a case by case basis as part of dossier evaluation. On some occasions, the scientifically accurate name of a novel food could include nutrition or health claims, and these should be permitted if fully compliant with applicable regulations and not misleading to consumers.
1.2 Foods consisting of, isolated from or produced from	412-418	*Foods consisting of, isolated from or produced from microorganisms*	We would like to put on record our firm support for the inclusion and expansion of section 1.2 on Foods consisting of, isolated from or produced from microorganisms.

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microorganisms			
1.2 Foods consisting of, isolated from or produced from microorganisms	456-458	*The presence of DNA from the production strain in the novel food has to be tested for i) GM production strains, and ii) non-GM production strains harbouring acquired AMR genes (additional requirements in section 2.1.3 of EFSA FEEDAP Panel, 2018).*	It should be noted that FEEDAP gives two protocols that need to be satisfied, phenotype testing and whole-genome sequencing. Equally EFSA could consider replacing the term "tested" with "analysed" to enable a greater scope of methodological approaches.
1.3 Food consisting of, isolated from or produced from plants, macroscopic fungi and algae, or their parts.	459	*Food consisting of, isolated from or produced from plants, macroscopic fungi and algae, or their parts*	EFSA should provide greater clarity on the meaning of the term "...or their parts", including potentially including examples for specific reference points.
1.5.1 Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals	512-513	*Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals*	We would like to put on record our firm support for the inclusion and expansion of section 1.5.1 Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals. EFSA could consider including a further bullet point requirement in this section, stating that "A veterinary certificate and identification number is required for the source animal which must meet or exceed the same standard required for food producing animals in the EU."
1.5.1 Foods consisting of, isolated from or produced from cell culture or tissue culture	517-518	*Information on whether the cells or tissues sourced from a non-GM animal have been genetically modified.*	EFSA should further clarify the definition of "genetically modified" in this section, with references or examples which could cross reference the techniques listed in Part 1 of Annex 1A of Dir. 2001/18/EC).

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derived from animals			
1.6 Foods containing or consisting of engineered nanomaterials	527	*Foods containing or consisting of engineered nanomaterials*	EFSA should clarify whether protein molecules from precision fermentation could be included in the definition of 'engineered nanomaterials' if they are less than 100nm, or whether they would fall into conventional materials risk assessment as long as they lose nanospecific properties as per Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health. This is particularly pertinent for proteins with localisation or trafficking tags that are not a 1:1 copy of a food protein.
2.1 General provisions	541-544	*"Moreover, every material in contact with food during the production process (e.g., plastic containers) should comply with Regulation (EC) No 1935/2004…*	EFSA should clarify whether "every material" in this section refers to packaging materials, or has a broader scope to include materials used during production processes.
2.1 General provisions	551-552	*"The applicant has to inform whether a production process is novel, i.e., not used for food production within the EU before 15 May 1997, and characterise the novel aspects of the process."*	EFSA should clarify the definition of "novel aspects of the process." Many of the steps involved in the production of novel foods are already found in other food industry settings - it is the combination of these steps into one process that defines them as 'novel'. EFSA should provide greater clarification on the specific aspects of processes that are necessary to characterise, or consider deleting this sentence.
2.3 Considerations for specific novel food categories	619 - 620	*For foods consisting of, isolated from, or produced from cell culture or tissue culture, information is to be provided on the type of cells used as source (e.g., primary cells or established cell lines).*	EFSA should note that the term "cell culture" or "tissue culture" has been applied to any plant, animal, fungal, algael, microbe cultivation earlier in this guidance document (e.g. line 252). As such, this section could be perceived as applying to microbial, fungal, and plant cell cultures as well as cells derived from animals. EFSA should consider adding clarifying statements.
2.3 Considerations for specific novel food categories	630 - 632	*The genetic stability of the cells throughout the production (e.g., karyotypes, whole genome sequencing) is to be demonstrated, by comparison of the starting material and the cells at the end of the production process.*	As per above, if EFSA means to include for example microbes under the definition of "cell culture", this section may be problematic as genetic compositions of microbes could be changed due to random mutations that naturally occur. In this situation EFSA should clarify the extent of genetic change that would represent an issue for risk assessment purposes.

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2.3 Considerations for specific novel food categories	632 - 634	*Also changes of the morphology, markers of differentiation and other phenotypic features of the cells at the start and at the end of the production process should be investigated and described.*	EFSA should clarify what the acceptable levels of changes to morphology are during cultivation, and define what actionable steps are included in the definition of "investigated".
2.3 Considerations for specific novel food categories	634-637	*Information on the compliance with Good Cell Culture Practices should be provided, as well as on the compliance with applicable relevant standards, such as those outlined in the EMA Guidance document on the derivation and characterisation of cell substrates used for production of biotechnological/biological products.*	While references to compliance with Good Cell Culture Practice and EMA guidance documents are welcome cross-references, it is important that EFSA qualifies these by noting that this may not be necessary in all cases. Many of the requirements outlined in the EMA guidance are not applicable to cells used for the production of food, and it is therefore the case that full adherence or compliance with these guidance provisions would neither be possible nor appropriate.
3.1.2 Addressing compositional variability	677-678	*"The analytical information should be provided on at least five representative batches of the novel food that have been independently produced"*	In line with international regulators (including the FDA), EFSA could consider replacing the need for "five representative batches" with "at least three representative batches" or enabling the testing of a lower number of batches if this is supported by scientific arguments. Equally, EFSA should define "independent batches", as some production processes - particularly for cultivated meat products - may draw on continuous culture that limit the ability to define "independent" batches for analysis.
3.1.4 Compositional analytes	703 - 705	*"For…substances produced by microbial fermentation, the presence of undesirable metabolites should be investigated;"*	EFSA should clarify the definition of "undesirable metabolites" and specify whether this refers exclusively to mycotoxins and microcystins, or is broader in scope.
3.1.4 Compositional analytes	732 - 733	*"Considering their nature and in order to avoid unnecessary testing, some categories of novel foods do not require a priori a nano-specific risk assessment, e.g., (i) microorganisms."*	Based on the language used in this section, any microorganism that is processed (spray drying, filtrations) will need to go through the nanomaterial risk assessment. EFSA should clarify whether there is any exemption to the nanomaterial risk assessment if these substances show dissolution or solubility as per the guidance document on nanomaterials.
3.4 Stability	799-829	*The monitoring period of the stability test has to cover at least the end of the proposed shelf-life.*	EFSA should clarify here whether safety dossiers can be submitted with ongoing shelf-life stability studies, providing the applicant provides sufficient data as part of this process.

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7.1 General considerations	1093-1096	*Where there is a potential concern about the protein in the novel food, appropriate protein digestibility studies should be performed as part of the weight of evidence approach for the assessment of the nutritional, toxicological and allergenic properties (e.g., EFSA GMO Panel, 2017, 1096 2021, 2022)*	EFSA should provide greater clarity - potentially through explicit examples - of the digestibility studies and methods required to meet the definition of "appropriate". This could also include reference to specific sections of the EFSA GMFF guidance.
7.1.1. Tier I ADME testing	1124-1127	*Existing models include cell-based systems of various levels of complexity (e.g., MDCK, Caco1125 2, human small intestinal and liver organotypic 3D culture models). Such in vitro models could complement in vivo models to assess absorption and metabolism, noting the interrelationship between the Tiers.*	EFSA should consider removing the term "could complement" and replacing this with "could eliminate the need for in vivo models" in line with the reduce, replacement and refinement of animal studies (3R) which is an important risk assessment principle that is supported by EFSA among other international regulatory agencies.
8.3 Genotoxicity	1240-1241	*Specific approaches should be followed based on the characteristics and compositions of the novel food.*	EFSA could consider providing specific examples of the format, structure and methodology of the various genotoxicity testing to be completed for various novel production techniques including precision fermentation and cultivated meat.
10.3 Novel foods derived from allergenic foods not subject to mandatory allergen labelling	1512 - 1514	*This section concerns novel foods derived from foods (or products thereof) that are known to trigger allergic reactions in susceptible individuals, but which are not listed in Annex II of Regulation (EU) No 1514 1169/2011.*	EFSA should consider replacing this sentence with: "This section concerns novel foods derived from foods (or products thereof), or allergenic foods derived from a novel source, that are known to trigger allergic reactions in susceptible individuals,..." This would help to ensure that dairy or other potentially allergenic proteins produced through precision fermentation are in scope.

Appendix C Attachment to Public Consultation comment number 237

This appendix contains the attachment for Public Consultation comment number 237, submitted by VTT, Technical Research Centre of Finland. The original format of the attachment was a Word document. The content of the attachment:

To whom it may concern,

We are writing to provide comments on the draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283.

We appreciate the efforts of the European Food Safety Authority (EFSA) to update and clarify the scientific criteria and data requirements for novel food applications.

However, we have some suggestions and concerns that we would like to share with you, in order to improve the quality and applicability of the guidance. These are:

1 Identity of the novel food

Page 12, Lines 367-370 nomenclature of novel foods

"*The name of the novel food in the application submitted has to reflect its characteristic elements, e.g., its source, the main part(s) of organisms used, specific elements of the production process*". "*scientific names according to the most recent taxonomy or scientific nomenclature are to be included*."

Comment: Naming of microbial products and biomasses is suggested partially to be in accordance with the descriptive or customary name as described in the food information regulation (1169/2011) for traditional animal and plant-based foods. We consider that microbial naming system is not informative to consumers and may cause confusion. Taxonomical naming system is evolving, and nomenclature is changed frequently by time. Hence, we propose that food business operators have the liberty to devise more descriptive names of products consisting of, or isolated from or produced from microorganisms, cell culture, macroscopic fungi, or algae for consumers.

1.2 Foods consisting of, isolated from or produced from microorganisms

Page 14, Lines 424-426:

"*only GMM categories 1 ('chemically defined purified compounds and their mixtures in which both GMMs and newly introduced genes have been removed'*) *and 2 ('complex products in which both GMMs and newly introduced genes are no longer present'),* "

Comment: Newly introduced genes "*no longer present*" is without the GMM residue limit and refers to zero tolerance. We consider that this could be more specific and presented in a quantifiable limit and the requirement should be the at the same level as given to traditional foods and food ingredients. Among traditional foods the presence of GMOs is below 0.9% of the food/feed, or if the ingredient is adventitious or technically unavoidable, labeling of GMO is not required. We propose that the same threshold of GMM content is used for novel foods as for conventional foods.

Page 15, Lines 439-442

"*Unambiguous taxonomic identification at species level and certificate of deposition (including accession number) in an internationally recognised culture collection having acquired the status of International Depositary Authority under the Budapest Treaty (EFSA FEEDAP Panel, 442 2018; EFSA, 2021e)*;"

The text in the current version is suggested to be reconsidered. There are two issues that should be addressed:

1. The necessity of proper taxonomic identification and request to deposit in collection with International Depositary Authority (IDA) status should not be combined, but rather stated separately.
2. The issue of mandatory deposit to the collection with IDA status. As formulated now in the draft document it can be a public deposit, safe deposit or patent deposit. The Budapest Treaty governs the procedure for the deposit of biological material solely for patent purposes and IDA status is given to the collection that performs deposits of the microorganisms under the the Budapest Treaty rules.
    1. If patenting is obligatory for Novel Food applications, this should be stated in the document. If filing a patent is not obligatory for an application for authorisation, but EFSA prefers the deposit to be done in IDA, we advise clarifying this in the guidance. We proposed to mention, for instance, that "Safe Deposit" or "Confidential Deposit" should be done in IDA.

2.2 Considerations for specific production process steps

Page 19, Lines 593-595:

"*In case the food enzymes have not been assessed or the risk assessment is still in progress, additional data on the microorganisms used to produce the food enzymes could be requested to establish the safety of the novel food, in line with the scientific criteria outlined in relevant EFSA guidance documents"*

Comment: We consider it challenging to request an applicant to provide safety data on food enzymes which are in the prolonged risk assessment process in the EU. These food enzymes are available for food grade use as processing aids for traditional food ingredients. Moreover, the applicant of novel food is demanding to response on safety on behalf of another party i.e. enzyme manufacturer.

2.3 Considerations for specific novel food categories

Page 20, Lines 616- 618:

"*The applicant should investigate, and report whether the specific production conditions of the novel food (e.g., due to processing aids or component of the media) may trigger the formation of toxic compounds by microorganisms"*

Content: This sentence is suggested to be more specific on how to investigate the formation of toxic compounds. Should the applicant analyze toxicity of end-product in the range of processing conditions? We suggest that this advising text should be more specific.

Appendix D Attachment to Public Consultation comment number 258

This appendix contains the attachment for Public Consultation comment number 258, submitted by Mario Stahl. The original format of the attachment was a Word document. The content of the attachment:

Feedback "Draft guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283"

Author: Dr.-Ing. Mario R. Stahl

When authorising products with so-called "new processes", stakeholders often have questions about their use on an industrial scale and the need for an assessment or approval as a "novel food".

The UV treatment of food is a "new" process, although it was already in use before 1997 and is therefore not really new. There is still no general regulation at EU level regarding the use of UV treatment for must and wine. In Germany, however, there are regulations for the UV treatment of the surfaces of fruit and vegetable products, hard cheese during storage, drinking water, invert sugar and egg shells. Other EU countries have their own regulations.

The International Organisation of Vine and Wine (OIV) is unsure how UV-treated must or wine should be assessed when used to stabilise the shelf life, reduce sulphur or influence the sensory properties. Must is a foodstuff, wine is considered a luxury food. The OIV would like to avoid risks when drinking both and would therefore like an assessment from the EFSA, which is generally responsible for foodstuffs.

Scientific studies carried out by the Max Rubner Institute (Federal Research Institute) in recent years on the use of UV radiation to reduce microorganisms have shown that UV-treated musts or wines can be classified as harmless in the relevant dose range (at a wavelength of 254 nm). Corresponding scientific documents are available, but no authorisation has yet been granted by the OIV.

The term "significant change in the composition or structure of the food" is not precisely defined in Regulation (EU) 2015/2283 and therefore repeatedly raises questions. Depending on the interest group, it is interpreted differently and the authorisation and application of this treatment in the international area is made more difficult.

I therefore recommend that this term be precisely defined in Article 3 of Regulation 2015/2283, in the definitions §2a) vii, and that it be explained what is meant by "significant changes in the composition or structure of the food" so that this must/wine stabilisation process can be used and the benefits for the industry and the consumer can be exploited (energy saving, conservation of resources, sustainability, sulphur reduction).

Text passages of the reference:

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

Appendix E Attachment to Public Consultation comment number 261

This appendix contains the attachment for Public Consultation comment number 261, submitted by Vaclav Bazata. The original format of the attachment was a Word document. The content of the attachment:

- In existing „Administrative guidance on the submission of applications for authorisation of a novel food pursuant to Article 10 of Regulation (EU) 2015/2283" (doi:10.2903/sp.efsa.2018.EN-1381) it is „chemical fingerprinting" of the botanical material (recommended) **only for „Complex mixtures and whole foods derived from plants"**

It is not clear or technically substantiated why in Part 1.3 of the DRAFT is in sentence starting with **line 470** NEW requirement f.i. **chemical fingerprint** *practically for each single plant* (The following information must be provided in the case of novel foods consisting of, isolated from or produced from plants20*) :

- „For plants, experimental verification of the identity of the plant (e.g., authentic plant specimen deposit in a recognised herbarium, macroscopic/microscopic verification with comparison to an authentic standard**, chemical fingerprint** compared to standard, DNA-based authentication);
- The DRAFT is appropriate in chapter „3.3 Complex mixtures and whole foods" where the chemical fingerprinting is in **line 778**

- Generally the chromatographic fingerprinting to support the composition stability is a valuable tool , when markers are established , but not mentioned in DRAFT´s guidance in chapter 3.4 Stability

*) cit. 20/page 15 : „EFSA Scientific Committee guidance on the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA Scientific Committee, 2009)" is not yielding any substantiation.

Chemical fingerprinting is obligatory in EP (Ph.Eur./ European Pharmacopoeia) monographs of plant drugs especially by TLC (also GLC and HPLC) and until standard method of TLC of herbal API is experimentally established and peer verified there is no possibility of comparison in case of new FI in Novel Food applications.

Appendix F Attachment to Public Consultation comment number 262

This appendix contains the attachment for Public Consultation comment number 262, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

Definitions

Page 8

Line 232 - The meaning of "significant degree" is not clear and further definition with references or examples could be used.

.....

The above comments were prepared and approved by the following:

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Appendix G Attachment to Public Consultation comment number 263

This appendix contains the attachment for Public Consultation comment number 263, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

General Principles

Page 11

Line 315 – Clearly define cases or criteria when systematic review following EFSA, 2010 guidance would be applicable.

.....

The above comments were prepared and approved by the following:

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Appendix H Attachment to Public Consultation comment number 264

This appendix contains the attachment for Public Consultation comment number 264, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

Characterisation of the novel food, technical and scientific data

Page 12

Line 347 – For complex mixtures or whole foods (e.g. cultured meat and seafood) qualify what is meant by "full characterization". It would also be helpful to provide some examples based on previously assessed novel foods and outline the implications of when a novel food cannot be 100% fully characterized.

.....

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Appendix I Attachment to Public Consultation comment number 265

This appendix contains the attachment for Public Consultation comment number 265, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

1.4 Food consisting of, isolated from, or produced from animals or their parts

Page 16

Line 495-496 – The original sources of cells for cultured meat and seafood products may not be traditional livestock or obtained from vendors. Guidance would be useful to include cells sourced from animals, or animal materials, obtained in the wild (e.g. wild animals sampled, fish caught, eggs found, etc.) or from non-vendor entities (e.g. noncommercial laboratorial stocks, donations, etc.).

.....

The above comments were prepared and approved by the following:

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Appendix J Attachment to Public Consultation comment number 266

This appendix contains the attachment for Public Consultation comment number 266, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

1.5.1 Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals

Page 17

Line 508 – Cells used for cultured meat or seafood may come from exotic species, or technologies used to produce cells from novel species that are not well characterized. It may be useful for guidance to consider when sources are not common species.

Line 513 – In case there is an EU/EC regulation related to inspection requirements, the number could be mentioned.

Line 515 – Regarding testing for prions, it is suggested to rephrase as "testing for prions in the case of limited health information on the source animal where relevant and where recognized methods exist".

.....

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Appendix K Attachment to Public Consultation comment number 267

This appendix contains the attachment for Public Consultation comment number 267, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

2.1 General provisions

Page 18

Line 556 – The most updated regulation on hygiene of foodstuffs is EC 2021/382 which amended the EC 852/2004. If the reference in this section is to language from the original document, it may still be useful to add a notation "as amended by EC 2021/382."

.....

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Appendix L Attachment to Public Consultation comment number 268

This appendix contains the attachment for Public Consultation comment number 268, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

2.2 Considerations for specific production process steps

Page 19

Line 593-596 – What about recombinant proteins used as processing aids that are not enzymes (e.g. recombinant growth factors for use in cultured meat and seafood production). Should applicants follow the same approach outlined for enzymes? Further, as such culture components are identified and safety documented, it could be useful to produce and maintain a qualified presumption of safety (QPS) list similar to that used for microorganisms.

.....

The above comments were prepared and approved by the following:

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Appendix M Attachment to Public Consultation comment number 269

This appendix contains the attachment for Public Consultation comment number 269, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

2.3 Considerations for specific novel food categories

Page 20

Line 622 – While "absence of pathogens" would be important to document, "overall sterility" may not be appropriate for cultured meat and seafood production processes. In addition to the potential for using co-cultures (including beneficial microorganisms), having sterile products may be problematic from a safety standpoint. It is possible that inoculation with benign microorganisms could be part of a production step to introduce competitors to prevent pathogenic microorganisms.

Line 625 - 626 - Use of the term "modifications" in this section may cause confusion as that is usually associated with genetic modification, which is generally not performed/does not happen during cell isolation or differentiation but may occur during immortalization or reprogramming, however all were mentioned together in the same list. Perhaps it would be better to use phrasing such as "physical changes to cells (e.g. chemical, genetic, etc.)" or "alterations" in place of "changes."

Page 21

Line 634 - 637 – Since the book referenced for Good Cell Practices (30) is a non-open access source, it might be useful to indicate other valid guidance (e.g. ISO, etc.).

Furthermore, as many of requirements outlined in the EMA guidance are not applicable to cells used to produce food it makes full adherence or compliance inappropriate. Reference to compliance with EMA guidance documents (and similarly Good Cell Practices) should be qualified by a statement saying, "only where relevant."

Finally, as cell lines and methods of cell culture for food production are identified and best practices emerge, it might be useful to produce and manage a list of approved lines or procedures similar to the qualified presumption of safety (QPS) list used for microorganisms.

.....

The above comments were prepared and approved by the following:

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Appendix N Attachment to Public Consultation comment number 270

This appendix contains the attachment for Public Consultation comment number 270, submitted by Dwayne Holmes. The original format of the attachment was a Word document.

The content of the attachment:

Response to EFSA Draft NF Guidance Document

3.1.4 Compositional analytes

Pages 23-24

Line 697 - Section "3.1.4 Compositional analytes" - To use structural alerts for substances obtained by chemical synthesis. This reference could be mentioned here: EFSA Scientific Committee 2019.

Line 733-38 Clarity on exemption from analysis for small particles for cultured meat and seafood (a "whole food") which may have limited potential due to small scale/early step filtration.

Line 735-736 - These production processes are used extensively in the food industry for non-novel foods. To make this clearer, we suggest including examples from recent novel food submissions to help applicants when the small particle guidelines apply.

.....

The above comments were prepared and approved by the following:

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Appendix O Attachment to Public Consultation comment number 271

This appendix contains the attachment for Public Consultation comment number 271, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

3.3 Complex mixtures and whole foods

Page 25

Line 775-776 – "Particular attention should be given to the possible presence of genotoxic and/or carcinogenic substances." - This reference could be mentioned here: EFSA Scientific Committee 2019.

.....

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Appendix P Attachment to Public Consultation comment number 272

This appendix contains the attachment for Public Consultation comment number 272, submitted by Dwayne Holmes. The original format of the attachment was a Word document.

The content of the attachment:

Response to EFSA Draft NF Guidance Document

7.2 Tiered approach to conduct ADME studies

Pages 34-35

Line 1113 - Section 8.2.1 is indicated in the text, however it is not in the index nor found in the guidance.

Line 1114-1115 - (Including text within Figure 1) It would be useful for EFSA to provide greater clarity in this section, particularly related to absorption of cultured meat and seafood "or its constituents"(e.g. digested and bioavailable amino acids, fats, etc.). We understand that this would not apply to constituents of cultured meat and seafood where no substances of concern were verified and that after digestion they would be absorbed. However, as it is stated it may lead to misunderstanding, and it can be concluded that moving to Tier2 is mandatory for instance for the example provided.

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Appendix Q Attachment to Public Consultation comment number 273

This appendix contains the attachment for Public Consultation comment number 273, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

7.1.1. Tier l ADME testing

Page 35

Line 1125-1126 – In the sentence, "Such in vitro models could complement in vivo models..." the word complement suggests that in vivo models must still be used. If they can be used in place of in vivo models, it might be better written "Such in vitro models could be used as an alternative to in vivo models..."

.....

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Appendix R Attachment to Public Consultation comment number 274

This appendix contains the attachment for Public Consultation comment number 274, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

8.1 General considerations

Pages 36-38

Line 1160-1207 – In this section it should be clearly defined when toxicological studies are not required as per Section 4.1 of the Food Enzyme Guidance. Also including a section on the test item and dose-level as this is often an issue for applicants.

.....

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Appendix S Attachment to Public Consultation comment number 275

This appendix contains the attachment for Public Consultation comment number 275, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

8.5 Human Data

Page 43

Line 1378-79 - It is recommended to clarify that for complex or whole foods (such as cultured meat and seafood) that a strong hypothesis for an effect on psychological or mental health must exist (e.g. from identified media components) before human studies on this aspect of food safety would be required. In addition, case examples of NFs that may require or require such analysis could be given.

.....

The above comments were prepared and approved by the following:

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Appendix T Attachment to Public Consultation comment number 352

This appendix contains the attachment for Public Consultation comment number 352, submitted by Dwayne Holmes. The original format of the attachment was a Word document. The content of the attachment:

Response to EFSA Draft NF Guidance Document

10.3 Novel foods derived from allergenic foods not subject to mandatory allergen testing

Page 48

Line 1532 - To avoid assumptions that could lead to settlement of binding standards, the reference to proteomic should be integrated by a broader "proteomic (or other -omic techniques)."

.....

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Appendix U Attachment to Public Consultation comment number 538

This appendix contains the attachment for Public Consultation comment number 538, submitted by Undisclosed. The original format of the attachment was a PDF document. The content of the attachment is provided below.

"Scale-up economics for cultured meat": https://doi.org/10.1002/bit.27848