FEASTS
Fostering European Cellular Agriculture for Sustainable Transition Solutions

Guidelines for CM/CSF Regulatory Framework: Policy and Practice in the EU

Deliverable 5.1

Author (s)

Name	Organization
L. **Escajedo San-Epifanio** (Principal Researcher), M. E. **Ibáñez Pérez-Zamacona**, E. **Suñén Pardo**, A. **Jelenkovic Moreno**, E. **Rebato Ochoa**, A. **Poveda Zabala**, R. X. **Anthony**, I. **Filibi,** J. **Uncetabarrenechea,** A. **Lasa.López**, I. **Alonso Sanz,** P. B. **. Thompson** Reviewers:, Maria Victoria Jiménez Martinez, Seth Roberts; Anna Hadrych; Dwayne Holmes.	EU-Frames Research Group, **EHU** (University of the Basque Country, Spain)
https://euframes.com/	eu-frames.info (at) ehu.eus

Funded by the European Union

Project acronym: FEASTS

Project title: Fostering European Cellular Agriculture for Sustainable Transition solutions

Call: HORIZON-CL6-2023-FARM2FORK-01

Start date of project: 01.12.2023

Duration: 36 months

Deliverable title: Guidelines for CM/CSF regulatory framework – layout

Date of deliverable: 30.04.2025

Deliverable Lead Partner: EHU (University of the Basque Country, Spain)

Dissemination level: Public

Funded by the European Union's research and innovation program under Grant Agreement no. 101136749.

Executive Summary

1. The FEASTS project is a collaborative and multidisciplinary research initiative aimed at generating a comprehensive and objective knowledge base on cultured foods—both meat and aquatic (CM/CSF)—and their integration into contemporary food systems. Within this Framework, Work Package 5 (WP5 – Food safety, nutrition and regulatory assessment) focuses on the analysis of nutritional, food safety, and regulatory aspects of these products. This report constitutes the project's first regulatory deliverable and is dedicated to mapping and structuring the relevant regulatory framework at the European Union (EU) level concerning premarket approval, scientific evaluation processes, and decision-making mechanisms for Cultivated Foods (CM/CSF) in the Context of the FEASTS Project.

2. At present, the products referred to as CM/CSF within the FEASTS project do not constitute an autonomous legal category under European Union food law. In general terms, these products fall under the category of “cell-based products” regulated as novel foods, in accordance with Regulation (EU) 2015/2283. However, any novel food product -including CM/CSF products- that consist of genetically modified organisms (GMOs), or which contain such ingredients—including those obtained through new genomic techniques—are subject to the specific legal framework governing genetically modified food and feed, as established by Regulations (EC) No. 1829/2003 and 1830/2003.

3. The identification and analysis of the regulatory framework applicable to the food products identified as CM/CSF by the FEASTS project require an integrated reading of the various legal instruments that make up European Union food law, which is structured around Regulation (EC) No. 178/2002, commonly referred to as the General Food Law. In this context, the report reviews the development of novel food legislation in the EU, tracing its origins in the 1990s through to the consolidation of Regulation (EU) 2015/2283. It also provides a detailed account of the authorization procedure applicable to non-GMO novel foods.

4. The report specifically highlights the role of the *European Food Safety Authority* (EFSA) in the scientific assessment of the safety and quality of CM/CSF. It further outlines the key elements for the implementation of the EFSA guidelines issued in autumn 2024 in this regard. The technical analysis focuses on the specific requirements that cell-based products must meet in order to obtain market authorization. These include the identification of the food through its entire lifecycle, a detailed description of the production process, composition, stability, technical

specifications, toxicological and nutritional profile, estimated intake, potential allergenicity risks, and ADME parameters (absorption, distribution, metabolism, and excretion).

5. The document also explores the distribution of competences among the institutional actors involved—namely the European Commission, EFSA, and the Member States—and examines the role of the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF), which is responsible for final decision-making. In addition, it addresses issues related to procedural transparency, the possibility of national restrictions, and the debate surrounding the naming and labelling of such products.

6. For novel foods that are or contain GMOs, the text outlines the specific procedures in place, with particular attention to risk assessments for human and animal health and the environment, as well as the applicable requirements regarding labelling and post-market monitoring. Lastly, the analysis considers the ongoing legislative review on new genomic techniques (NGTs) and reflects on its potential implications for the regulatory regime applicable to CM/CSF. The document concludes with final remarks and includes a set of annexes providing further information on the structure and functioning of EFSA, its scientific panels, and guidance tools used in evaluation processes.

Abbreviations and Definitions

AAS – Amino Acid Sequence

ADI – Acceptable Daily Intake. An estimate of the amount of a substance in food or drinking water that can be consumed daily over a lifetime without presenting an appreciable risk to health1.

ADME – Absorption, Distribution, Metabolism, Excretion

Adverse effect – Change in the morphology, physiology, growth, development, reproduction or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity to compensate for additional stress or an increase in susceptibility to other influences (FAO/WHO, 2009; EFSA Scientific Committee, 2017c).

AMR – Antimicrobial Resistance

Antimicrobial – An active substance of synthetic or natural origin which destroys microorganisms, suppressing their growth or their ability to reproduce in animals or humans, excluding antivirals and antiparasitic agents.

Antinutrients – Antinutrients are naturally occurring or synthetic compounds that can interfere with the absorption of essential nutrients.

ARfD – Acute Reference Dose

Average requirement (AR) – The level of intake of a defined group of individuals estimated to satisfy the physiological requirement or metabolic demand, as defined by the specified criterion for adequacy for that nutrient, in half of the healthy individuals in a life stage or sex group, on the assumption that the supply of other nutrients and energy is adequate (EFSA NDA Panel, 2022e).

Benchmark dose (BMD) – A dose level, estimated from the fitted dose–response curve, associated with a specified change in response relative to the control group (background response), the benchmark response (BMR) (EFSA Scientific Committee, 2022b).

Bioavailability – Nutrient fraction which is absorbed and becomes available to normal metabolic and physiological processes (EFSA NDA Panel, 2022e).

BIOHAZ – Panel on Biological Hazards

CDEP – Communication, Dissemination and Exploitation Plan

CEP – Panel on Food Contact Materials, Enzymes and Processing Aids

ChEBI – Chemical Entities of Biological Interest database

CM/CSF – Cultured Meat and Cultured Seafood

COL – Catalogue Of Life

DIAAS – Digestible Indispensable Amino Acid Score

1

Dietary Reference Values (DRV) – A set of nutrient reference values that includes the average requirement, the population reference intake, the adequate intake and the reference intake range for macronutrients (EFSA NDA Panel, 2017).

DietEx – Dietary Exposure tool

DOMP – Digital Outputs Management Plan

DRV – Dietary Reference Value

ECHA – European Chemicals Agency

EFSA – European Food Safety Authority

EFSA NDA panel – Panel on nutrition novel foods and food allergens

EMA – European Medicines Agency

EOGTRS – Extended One-Generation Reproductive Toxicity Study

EOL – Encyclopaedia of Life

EU – European Union

EUCAST – European Committee on Antimicrobial Susceptibility Testing

FAIM – Food Additives Intake Model

FAO – Food and Agriculture Organisation of the United Nations

FASTA – sequence similarity search with a protein query

FBO – Food Business Operator

FEEDAP – Panel on Additives and Products or Substances used in Animal Feed

FISH – Fluorescence In Situ Hybridisation

FooDB database of the macro and micronutrients of a wide range of non-processed foods

FSG – Foods for Specific Groups

FSMP – Foods for Special Medical Purposes

FT-IR – Fourier Transform Infrared Spectroscopy

GBIF – Global Biodiversity Information Facility

GCP – Good Clinical Practice

GFL – EU General Food Law (Regulation (EC) No. 178/2002)

GI – Gastrointestinal

GLP – Good Laboratory Practice

GM – Genetically Modified

GMM – Genetically Modified Microorganism

GMO – Genetically Modified Organism

GMP – Good Manufacturing Practice

GRIN – Germplasm Resources Information Network

HACCP – Hazard Analysis Critical Control Point

HBGV – Health-Based Guidance Values

Health-base guidance value (HBGV) – - Umbrella term for values that are established as the result of the risk assessment of chemical substances and provides guidance on the safe consumption of substances, taking into account current safety data, uncertainties in these data, and the likely duration of consumption2.

IAA – Indispensable Amino Acid

IAEA – International Atomic Energy Agency

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

InChI – International Chemical Identifier

IPNI – International Plant Names Index

ISO – International Organization for Standardization

ITIS – Integrated Taxonomic Information System

LOD – Limit Of Detection

LOQ – Limit Of Quantification

Margin of exposure (MoE): The MOE is the ratio of the no-observed-adverse-effect level (NOAEL) or benchmark dose lower confidence limit (BMDL) for the critical effect to the theoretical, predicted, or estimated exposure dose or concentration to a substance for a given population.

MDCK – Madin-Darby Canine Kidney

NF – Novel Food

NGT – New Genomic Techniques

NMR – Nuclear Magnetic Resonance

NOAEL No-observed-adverse-effect-level - Highest dose of a substance, found by experiment or observation, that does not cause a statistically significant or biologically relevant adverse effect.

OECD – Organisation for Economic Co-operation and Development

QPS – Qualified Presumption of Safety

RA – Risk Assessment (evaluation of risk, carried out by EFSA or other independent scientific bodies)

RASFF – Rapid Alert System for Food and Feed

RC – Risk Communication (one of the pillars of risk analysis —alongside RA and RM—, see Articles 8–10 GFL)

[2] Depending on their nature and applications, an HBGV for oral exposure may be termed tolerable upper intake level (UL) (nutrients), acceptable daily intake (ADI) (food additives, pesticides), tolerable daily intake (TDI) (contaminants) or acute reference dose (ARfD) (EFSA Scientific Committee, 2021c).

REACH – Registration, Evaluation, Authorisation and Restriction of Chemicals

Read-across – Approach used in chemical risk assessment that allows for the screening, classification, prioritisation and hazard assessment of chemicals based on the toxicological data for similar chemicals, and is the most common alternative to animal testing. In read-across, known information from one or more source (data-rich) substances is used to predict the same property for a (data-poor) target substance.

RM – Risk Management (carried out by the Commission, the Member States, or both)

RP – Reference Point

SCFCAH (ScoPAFF, PAFF) – Standing Committee on the Food Chain and Animal Health (now Standing Committee on Plants, Animals, Food and Feed) (art. 58 GFL).

SHIME – Simulator of the Human Intestinal Microbial Ecosystem

SMILES – Simplified Molecular Input Line Entry System

Taxonomic Units (TUs) – The lowest taxonomic level for which the QPS status is granted - the species level for bacteria, yeasts and protists/algae, and the family level for viruses.

TDI – Tolerable Daily Intake

TG – Test Guideline

Threshold of Toxicological Concern (TTC) – The TTC approach is a screening and prioritisation tool for the risk assessment of chemicals when hazard data are incomplete and human exposure can be estimated (EFSA Scientific Committee, 2019a, 2019b).

Tolerable upper intake levels (UL) – The maximum level of total chronic daily intake of a nutrient (from all sources) which is not expected to pose a risk of adverse health effects to humans. (EFSA NDA Panel, 2022e).

TR – Transparency Regulation

TTC – Threshold of Toxicological Concern

UL – Tolerable Upper Intake Level

UF – Uncertainty factor. Uncertainty: General term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question.

Weight of evidence – A process in which evidence is integrated to determine the relative support for possible answers to a question

WGS – Whole Genome Sequence

WHO – World Health Organization

XRD – X-ray Diffraction

Table of Contents

1. Introduction

1. Context of this deliverable: The regulatory issues addressed by WP5 (objectives and methodology)

1. Work Package 5 (WP5) of the FEASTS project, titled *Food Safety, Nutrition and Regulatory Assessment,* aims to critically analyse the requirements and procedures governing the production and marketing of cell-based meat and seafood (CM/CSF, hereafter) in the European Union, and to compare them with regulatory frameworks currently being developed in other regions such as the United States, Australia, New Zealand, and Singapore.

2. A key objective of WP5 is to identify early indicators of potential future developments and emerging risks associated with CM/CSF, particularly in relation to safety and nutritional profiling, as well as strategies for conveying this information to consumers through appropriate labelling practices and public safety/health awareness campaigns.

3. Task 5.1, from which this deliverable originates, focuses specifically on the analysis of regulatory frameworks. It addresses the current lack of clarity surrounding the EU premarket approval process for CM/CSF and highlights the need to determine the existing regulatory status and relevant guidelines, both within the European Union and in third countries engaged in research, development, or commercialization of these products.

4. The authors of this report are the researchers from the *EU-Frames Research Group* at the University of the Basque Country (led by principal researchers Leire Escajedo San-Epifanio and Igor Filibi), along with experts in Food Quality and Safety, and Nutrition Anthropology from the UPV/EHU. The team also includes researchers from the University of Granada, as well as experts such as Raymond X. Anthony (University of Alaska Anchorage) and Paul B. Thompson (Professor Emeritus and the inaugural W.K. Kellog Chair in Agricultural, Food and Community Ethics, and co-editor of the Encyclopaedia of Food and Agriculture Ethics, Springer and past co-editor The International Library of Environmental, Agricultural and Food Ethics, Springer). EU-Frames is a research group at the University of the Basque Country that adopts a dynamic, transdisciplinary approach to the development of innovative regulatory frameworks within the EU.[3] The group focuses particularly on disruptive scientific and technological advancements and complex issues within the European integration process. Throughout these processes, the group is especially

[3] https://euframes.com/

concerned with human rights, democratic values, sustainability, inclusion, fair labour practices and social justice.

5. The main objectives of Task 5.1 are: (1) to examine the status of CM/CSF within the applicable requirements and procedures established under the EU General Food Law Regulation; (2) to identify regulatory gaps; and (3) to propose improved regulatory guidelines that take into account the specific characteristics of CM/CSF.

6. Although the action plan for this task was initially scheduled for months 1–36 of the project, progress has been accelerated: the complex EU regulatory framework has already been examined in detail during the first 16 months, as presented in this deliverable, while the comparative analysis of other jurisdictions has been scheduled for the second phase of the project (months 19–36). As part of this action plan, the University of the Basque Country (EHU) is responsible for collecting and analysing both social science and humanities (SSH) literature and institutional documents, including relevant legislation potentially applicable to the production, marketing, and consumption of CM/CSF. Requirements for the EU premarket approval process and decision-making mechanisms, along with relevant guidelines, are being reviewed and subsequently compared with those adopted or under discussion in countries such as the United States, Australia, New Zealand, and Singapore.

7. The methodology combines desk-based legal and policy research, analysis of peer-reviewed literature, internal workshops and targeted interviews with researchers and companies involved in CM/CSF development, to map the landscape of existing products and assess their legal status under EU and third-country legislation.

2. Summary

1. This report provides a systematic overview of the European Union (EU) regulatory framework for novel foods, with a particular focus on cell-based foods, namely, cell-based meat/cultured seafood CM/CSF), and whether they contain genetically modified organisms (GMOs) or not. The threefold aim of this review is to: i) provide detailed guidance on the applicable regulatory requirements, ii) describe (and examine?) the institutional actors involved, and iii) the evaluation and authorization process within the European context.

2. This report begins by reviewing the historical evolution of the novel food regulation in the EU from its integration in the 1990s to the entry into force of Regulation (EU) 2015/2283, which replaced the previous regime. Next, the premarket approval procedure for non-GM novel foods is described in detail, highlighting the importance of the scientific and technical evaluation primarily carried out by the European Food Safety Authority (EFSA), and distinguishing between GM and non-GM products.

3. The report's third section focuses on the specific requirements that cell-based foods must meet to be authorized as novel foods. Key aspects such as product identification, production process description, composition, stability, technical specifications, toxicological and nutritional profile, and intake estimation are addressed. Information on allergenicity and the behaviour of the food in the body (ADME) is also required.

4. The fourth section analyses the role of the European institutions involved (European Commission, EFSA, Member States) in the regulatory process, as well as the functioning of the Standing Committee on the Food Chain and Animal Health (SCoPAFF), which is responsible for final decisions regarding novel foods/food safety issues such as shared competences, transparency, temporary national restrictions, and product naming are discussed.

5. The fifth section addresses the specific procedures applicable when the novel food is a GM product or contains GM ingredients, with particular emphasis on risk assessment for human, animal, and environmental health, as well as labelling requirements and post-market monitoring.

6. Finally, the report examines the ongoing legislative review of new genomic techniques (NGT) and examines? their potential impact on novel food regulation. The report concludes with final observations and a series of informational annexes about EFSA's structure, its scientific panels, and information related to the evaluation processes.

2. The Evolution of the Regulatory Framework for Novel Foods in the Economic and Political Integration Process of the EU

2.1 The Historical Evolution of EU Agri-food Market Integration: Key Aspects Regarding Novel Foods

1. The European Union (EU) is a unique supranational organization comprising 27 member states committed to political, economic, and legal integration.[4] Its institutional structure allows for the

[4] Uncetabarrenechea, J., Filibi, I. (2023). "Democracy Beyond the Nation-State: From National Sovereignty to Pluralist European Sovereignty". In: Zabalo, J., Filibi, I., Escajedo San-Epifanio, L. (eds) *Made-to-Measure Future(s) for Democracy?. Contributions to Political Science*. Springer, Cham. https://doi.org/10.1007/978-3-031-08608-3_8

delegation of sovereign powers in key areas such as trade, competition, agriculture, the environment, and, to some extent, foreign and security policy. This integration model goes beyond the traditional framework of International Law, since it establishes an autonomous legal order with directly applicable and binding rules for both states and citizens. Through institutions such as the European Commission, the European Parliament, the Council of the EU, and the Court of Justice of the European Union, a multilevel governance system is articulated, ensuring joint decision-making and the primacy of EU law over national legal systems.[5] This regulatory and competence framework makes the EU an unparalleled entity in comparative law, offering a unique model of shared sovereignty and legal and institutional cooperation.

2. Although the EU is not solely a market, the single market constitutes one of the fundamental pillars of this unique supranational structure.[6] Based on the four freedoms — free movement of goods, people, services, and capital — the single market has allowed for the removal of internal barriers, the harmonization of legislation, and the creation of an integrated economic space that promotes competition, innovation, and the economic development of member states.[7] The right to the free movement of goods originating in Member States, and of goods from third countries which are in free circulation in the Member States, is one of the fundamental principles of the Treaty on the Functioning of the European Union (Article 28 of the TFEU, 2009).[8]

Customs and measures of equivalent effect to that of custom duties (charges, quantitative restrictions etc) are prohibited. Though, some restrictions on imports, exports or good in transit may be justified (art. 36 TFEU) on grounds of: public morality, public policy or public security; the protection of health and life of humans, animals or plants; the protection of national treasures possessing artistic, historic or archaeological value; or the protection of industrial and commercial property. Such prohibitions or restrictions shall not, however, constitute a means of arbitrary discrimination or a disguised restriction on trade between Member States.

3. Beyond its economic dimension, the single market has been a key driver for the deepening of European integration, facilitating regulatory convergence, administrative cooperation, and the creation of common policies in areas such as consumer protection, the environment, and labour

[5]Filibi, I. (2024). Autonomía estratégica y soberanía europea, Europa Bilduma – EHU Press, passim.

[6] Uncetabarrenechea, J., Filibi, I. (2023). "Democracy Beyond the Nation-State: From National Sovereignty to Pluralist European Sovereignty", cit.

[7] Zilgaviris, P. (2014) The Need for an Innovation Principle in Regulatory Impact Assessment: The Case of Finance and Innovation in Europe, in: Policy and Internet 6:4 (Wiley), 377 et seq.

[8] The Treaty on the Functioning of the European Union (TFEU) was established under the Treaty of Lisbon, which was signed on 13 December 2007 and entered into force on 1 December 2009. Consolidated version of the Treaty on the Functioning of the European Union, art. 102, 2012 O.J. (C 326) 47 [hereinafter TFEU], 2016.

rights. Thus, it functions not only as a tool for economic efficiency but also for social and territorial cohesion within the European project.

4. The establishing of the single market for food products has, therefore, required a delicate balance between the need to set common standards that enable the achievement of shared objectives and advance respect for national sensitivities. The Common Agricultural Policy (CAP) has been one of the key instruments in this process, not only to ensure the economic viability of the European agri-food sector but also to guarantee common standards in areas such as food safety, traceability, animal welfare, and environmental protection. Through this policy, the EU has sought to reconcile the objectives of the internal market with the particularities of rural areas and the strategic priorities of each member state.[9]

5. Furthermore, EU food law has evolved towards a comprehensive approach that incorporates principles such as precaution, transparency, and consumer information. The establishment of the EFSA and the increasing harmonization of regulations in areas such as additives, labelling, and genetically modified organisms reflect this effort to create a market that not only operates efficiently from an economic perspective but is also legitimate and socially accepted.

6. Another key element has been the consolidation of a community acquis in food law. Specifically, EU food law has evolved towards a more comprehensive approach that incorporates principles such as precaution, transparency, and consumer information.[10]

2.2 Foundations of the First Community Regulation on Novel Food, from the Late 1990s

1. At the time the first EC Regulation on Novel Food was adopted, the EU had 15 member states. These countries were: Germany, Austria, Belgium, Denmark, Spain, Finland, France, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Sweden, and the United Kingdom.

[9] European Commission (2021). The future of the Common Agricultural Policy. Luxembourg: Publications Office of the European Union. Available at: https://ec.europa.eu/info/food-farming-fisheries/key-policies/common-agricultural-policy/future-cap_en

[10] Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety

The 1990s marked a decisive push for the consolidation of the single market within the European Union.[11] The entry into force of the Single European Act in 1987,[12] followed by the Maastricht Treaty in 1993,[13] initiated a phase focused on the effective removal of physical, technical, and fiscal barriers between member states, with the aim of creating a borderless space for goods, people, services, and capital.[14]

During this decade, intensive legislative activity aimed at harmonizing national regulations and ensuring mutual recognition of products and services took place[15]. Strategic sectors such as transport, telecommunications, and food underwent profound transformations, and the foundations for the future economic and monetary union were established.[16] This period largely set the necessary conditions for the current functioning of the internal market.

2. In terms of food law, and specifically regarding novel foods, the 1990s witnessed the adoption of the first European regulation dedicated to novel foods and novel food ingredients. This regulation encompassed all categories of novel food, including those produced from genetically modified organisms (GMOs), the deliberate release of which for commercial purposes had already been addressed by Council Directives 90/219/EEC and 90/220/EEC,[17] Regulation (EC) No. 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients represented a regulatory milestone.[18] It established, for the first time,

[11]Dinan, D. (2007). Fifty years of European integration: a remarkable achievement. *Fordham Int'l LJ*, 31, 1118; Swinnen, J. F. (2002). Transition and Integration in Europe: Implications for agricultural and food markets, policy, and trade agreements. The World Economy, 25(4), 481-501; Sinopoli, D., & Purnhargen, K. (2016). Reversed harmonization or horizontalization of EU standards: Does WTO law facilitate or constrain the Brussels effect. Wis. Int'l LJ, 34, 92.

[12] Single European Act, Official Journal of the European Communities, L 169, 29 June 1987.

[13] Treaty on European Union, Official Journal C 191, 29/07/1992 P. 0001 – 0110.

[14] In 1985, a group of Member States reached an agreement to promote the free movement of persons (the Schengen Agreement), which entered into force in 1995.

[15] Vo Van Regnault, G., Costa, M. C., Adanić Pajić, A., Bico, A. P., Bischofova, S., Blaznik, U., ... & Margaritis, I. (2022). The need for European harmonization of nutrivigilance in a public health perspective: A comprehensive review. *Critical Reviews in Food Science and Nutrition*, 62(29), 8230-8246; Escajedo San-Epifanio, L. (2013). "Ensayos clínicos con alimentos funcionales en la Unión Europea", UE, Sociología y Derecho alimentarios: estudios jurídicos en honor de Luis González Vaqué / Leticia A. Bourges (aut.), 2013, ISBN 978-84-9014-439-8, 287-301.

[16] The entry into force of the euro on 1 January 1999 was another emblematic expression of the strong political will behind integration.

[17] Shohet, S. (1996). Biotechnology in Europe: Contentions in the risk-regulation debate. Science and Public Policy, 23(2), 117-122.

[18] The impact of the European Novel Food Regulation on trade and food innovation based on traditional plant foods from developing countries. Food policy, 34(6), 499-507.

a specific legal framework for the pre-market evaluation and authorisation of foods not significantly consumed within the European Union.[19] The Regulation introduced a centralised authorisation system based on safety criteria, transparency, and the protection of public health—reflecting the EU's increasing sensitivity to food-related risks and the need for harmonised regulation.

3. Regulation (EC) No. 258/97 established that, for a product to be considered a 'novel food', it must not have been consumed to a significant degree in the European Union before 15 May 1997. This meant that an assessment had to be carried out to determine whether the food had been substantially consumed Regulation (EC) No. 258/97 on novel foods generated tensions from the outset, as it included genetically modified in the EU prior to that date (see ANNEX 4). For this purpose, applicants were required to provide detailed information on the food's prior use, including the taxonomic name of the source organism (in the case of plants, animals, or microorganisms), the part of the organism used before that date, the form or concentration of the product, and, in the case of ingredients used in food supplements, the quantity employed. In addition, information on the chemical substance itself had to be provided, such as the product's IUPAC name, its purity, and a description of the production process.

Although in certain cases the *history of safe consumption*[20] of a food can be reasonably inferred from a substantial body of evidence —such as extensive sales data—, the reference date for establishing such a history within the European Union is prior to 15 May 1997, that is, before the entry into force of Regulation (EC) No. 258/97.[21] Article 7 of Regulation (EU) 2015/2283 upholds this same reference date. This means that the available evidence may be dated, which makes verification more difficult.[22] Therefore, it is essential to conduct a comprehensive assessment of

[19] Huggett, A. C., & Conzelmann, C. (1997). EU Regulation on Novel Foods: Consequences for the food industry. Trends in Food Science & Technology, 8(5), 133-139; Hermann, M. (2009).

[20] Pisanello, D., Caruso, G., Pisanello, D., & Caruso, G. (2018). Novel Foods: The 'History of Safe Use'Approach. Novel Foods in the European Union, 47-54.

[21] Constable, A., Jonas, D., Cockburn, A., Davi, A., Edwards, G., Hepburn, P., ... & Samuels, F. (2007). History of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms. Food and Chemical Toxicology, 45(12), 2513-2525.

[22] Engel, K. H., Vogel, R. F., Knorr, D., Habermeyer, M., Kochte-Clemens, B., & Eisenbrand, G. (2011). The role of the concept of "history of safe use" in the safety assessment of novel foods and novel food ingredients. Opinion of the Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG). Molecular nutrition & food research, 55(6), 957-963.

the food's consumption history and to consider alternative sources of information that may help determine whether it was consumed to a significant degree before the aforementioned date.[23]

5. The process of determining whether a food has been si*gnificantly consumed for human use in the European Union before the reference date* must rely on reliable and well-documented information from verifiable sources.[24] Such information must relate to products that were legally placed on the EU market. It is acknowledged that a single piece of evidence may not suffice to demonstrate that a product was available in significant quantities, as import or distribution records may not clearly indicate the intended use of the product (e.g. food, cosmetics, medicinal purposes, etc.). Therefore, all available data should be considered collectively, including invoices, recipes, cookbooks, catalogues, and other relevant materials. In addition, both national and EU legislation must be taken into account to determine whether a food falls within the scope of Regulation (EC) No. 258/97, since certain products —such as specific types of fruit— may be subject to sectoral regulations that exclude them from being classified as "novel foods".[25]

6. Regarding the extent of use of a novel food in relation to the established reference date, the assessment of "significant consumption" should not be based solely on the total quantity consumed. It is also necessary to consider the product's market availability and the type of commercial outlets in which it is sold. Commercially available and regularly consumed foods are more likely to be regarded as having been significantly used. Furthermore, the assessment should take into account whether the product was consumed only at a local or regional level, or whether its use was widespread throughout the European Union. In some cases, foods used exclusively as ingredients in food supplements may not be considered as having been significantly consumed. Additionally, the use of new technologies in food production may alter the nature of the product. If such changes result in characteristics that differ significantly from those of the original food, a safety assessment under Regulation (EC) No. 258/97 would be required.

7. To assist stakeholders in determining whether a product falls under the scope of the Novel Food Regulation and, if necessary, ensuring that all relevant information is provided to the

[23] Ververis, E., Ackerl, R., Azzollini, D., Colombo, P. A., de Sesmaisons, A., Dumas, C., ... & Gelbmann, W. (2020). Novel foods in the European Union: Scientific requirements and challenges of the risk assessment process by the European Food Safety Authority. Food Research International, 137, 109515.

[24] Engel, K. H., Vogel, R. F., Knorr, D., Habermeyer, M., Kochte-Clemens, B., & Eisenbrand, G. (2011). The role of the concept of "history of safe use" in the safety assessment of novel foods and novel food ingredients. Opinion of the Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG). Molecular nutrition & food research, 55(6), 957-963; Pisanello, D., Caruso, G., Pisanello, D., & Caruso, G. (2018). Novel Foods: The 'History of Safe Use'Approach. Novel Foods in the European Union, 47-54.

[25] Hermann, M. (2009). The impact of the European Novel Food Regulation on trade and food innovation based on traditional plant foods from developing countries. Food policy, 34(6), 499-507.

Competent Authorities, a proposed decision tree -combined with a questionnaire should be used-.[26] These tools also help stakeholders identify when the available evidence is insufficient to demonstrate that the product was significantly consumed before 15 May 1997. The decision tree has served, and continues to serve, as a key guide to determine whether a product is subject to Regulation (EC) No. 258/97, or to the Regulation that replaced it in 2015. However, it is important to note that since 2003, genetically modified foods have their own regulatory framework (see below, section 5) and fall outside the scope of the Novel Food Regulation. Given the diversity of novel foods, it is not always possible to reach a simple "yes" or "no" answer, which is why several sub-criteria must be considered. The questionnaire, which requires more detailed information, facilitates this assessment (see ANNEX 3).

8. Regulation (EC) No. 258/97 covered a broad range of products, from foods made with new sources to those obtained through innovative technological processes. It became a key tool for managing the introduction of potentially disruptive products into the single market. Its adoption anticipated debates that would remain relevant in the following decades, such as those concerning genetically modified organisms, food biotechnology, and the balance between innovation and precaution in the agri-food sector.

9. Regarding novel foods, the adoption of Regulation (EC) No. 258/97 represented a proactive approach by the European Union, as it avoided the traditional sequential model where member states first legislated at the national level, later requiring the harmonization of divergent regulations. Instead, a common framework was directly established from the outset, which helped prevent market fragmentation and ensured uniform access for economic operators. This prior harmonization also provided greater legal certainty, facilitating the development of innovative products under a clear system of evaluation and authorization. Furthermore, it strengthened consumer protection by applying uniform safety criteria across the entire Union and avoided potential regulatory conflicts between states, fostering a more predictable and coherent environment for the introduction of emerging foods.

[26] Van der Spiegel, M., Noordam, M. Y., & Van der Fels-Klerx, H. J. (2013). Safety of novel protein sources (insects, microalgae, seaweed, duckweed, and rapeseed) and legislative aspects for their application in food and feed production. Comprehensive reviews in food science and food safety, 12(6), 662-678; Sakihara, M. C. (2018). Integrated Decision-Tree for the Classification of Food Ingredients with Technological Properties: A Proposal for a EU Regulatory Guide for Their Development and Use in Food Products. Eur. Food & Feed L. Rev., 13, 494.

2.3. Initial Amendments to Regulation (EC) No. 258/97 Following the EU General Food Law and GM Food and Feed Regulations, and Its Replacement by Regulation (EU) 2015/2283 on Novel Food

2.3.1. Initial Amendments to Regulation (EC) No. 258/97 on Novel Foods, as a Result of the Implementation of the EU General Food Law

1. The adoption of Regulation (EC) No. 178/2002, known as the *EU General Food Law* (acronym GFL), marked a structural transformation in the governance of food safety across Europe.[27] This regulation laid down the general principles and requirements of food law throughout the EU, introducing a comprehensive "farm to fork" approach. It established key elements such as the precautionary principle,[28] mandatory traceability, and the responsibility of food business operators as fundamental pillars.[29]

This regulatory shift was driven by the White Paper on Food Safety,[30] published by the European Commission in 2000 in response to several major food crises during the 1990s (such as BSE or "mad cow disease") that had severely undermined public trust. The White Paper proposed over 80 measures, including the creation of an independent scientific authority and the adoption of a

[27] Van der Meulen, B. M., & van der Velde, M. (2004). Food Safety Law in the European Union. An introduction (No. 1). Wageningen Academic Publishers.

[28] European Commission. (2000). White paper on food safety (p. 52). Brussels, Belgium: Office for Official Publications of the European Communities. ; Szajkowska, A. (2010). The impact of the definition of the precautionary principle in EU food law. Common Market Law Review, 47(1); Dreyer, M., & Renn, O. (2009). Food safety governance (pp. 111-120). Berlin: Springer.

[29] van der Meulen, B., & Wernaart, B. (Eds.). (2020). EU Food Law Handbook (p. 20210282601); de Boer, A. (2019). Scientific assessments in European food law: Making it future-proof. *Regulatory Toxicology and Pharmacology*, *108*, 104437.

[30] Millstone, E., Lang, T., Naska, A., Eames, M., Barling, D., Van Zwanenberg, P., & Trichopoulou, A. (2000). 'European Policy on Food Safety': comments and suggestions on the white paper on food safety. *Trends in Food Science & Technology*, 11(12), 458-466.

coherent legislative framework, leading to the establishment of the EFSA[31] and the eventual adoption of the General Food Law.

2. The food regulations that were prior to the adoption of Regulation (EC) No. 178/2002, the General Food Law (GFL), like Regulation (EC) No. 258/97 on novel foods,[32] were not immediately repealed, although they did have to be adapted to align with the new principles and structures established by the General Food Law.

In the specific case of the novel food regulation, this adaptation was reflected in several key areas. On one hand, the general food safety principles, such as the precautionary principle and traceability, were integrated. On the other hand, the role of EFSA in the scientific risk assessment process was gradually incorporated, in line with the new European food governance system. Additionally, the requirement for decisions on authorizations to be based on solid scientific evidence and transparent risk assessments was reinforced.

3. Despite these adaptations, Regulation 258/97 was increasingly considered insufficient in the face of emerging technological and scientific challenges, which led to its eventual replacement by Regulation (EU) 2015/2283 (see below 2.3.3.). This new framework not only consolidated the previous reforms but also introduced a centralized and more efficient procedure for the authorization of novel foods, fully in line with the system established by the General Food Law.

2.3.2. Tensions surrounding Regulation (EC) Nº 258/97

1. Regulation (EC) No. 258/97 on novel foods generated tensions among the EU Member States from the outset,[33] as it included genetically modified (GM) foods as just one category among others, without clearly distinguishing their specific premarket approval requirements. Since its adoption in 1997, the regulation has undergone significant changes, largely driven by the development of new European legislation.[34]

---

[31] Kearney, J. M. (2024). What Is EFSA and Why Is it Important? *Nutrition Today*, 59(2), 73-78.

[32] Millstone, E., Lang, T., Naska, A., Eames, M., Barling, D., Van Zwanenberg, P., & Trichopoulou, A. (2000). 'European Policy on Food Safety': comments and suggestions on the white paper on food safety. Trends in Food Science & Technology, 11(12), 458-466.

[33] Scarpa, Bruno, and Stefania Dalfrà. "Regulating the novel foods sector: moving forward." European Food and Feed Law Review (2008): 292-299.

[34] See EFSA (2010). Guidance on the application of the Novel Food Regulation (EC) No. 258/97 to foods from genetically modified organisms. EFSA Journal, 8(4):1473. https://doi.org/10.2903/j.efsa.2010.1473. This document addresses the evaluation of novel foods derived from genetically modified organisms, emphasizing the importance of studying their stability over time.

2. Initially regulated under the novel food framework, GM food and feed became subject to a dedicated legal regime starting in 2003 with the adoption of Regulations (EC) No. 1829/2003 and No. 1830/2003,[35] which were based on Directive 2001/18/EC on the deliberate release of GMOs. These new regulations introduced an independent pre-market approval procedure, along with strict requirements for labelling and traceability, thus definitively separating the regulatory treatment of GM products from that of other novel foods within the European Union.

2.3.3. EU Novel Food Regulation (EU) 2015/2283

1. Over time, Regulation (EC) No. 258/97 came to be viewed as inadequate for addressing technological advances and the emergence of new categories of food, ultimately leading to its repeal and replacement by Regulation (EU) 2015/2283 on novel foods, which entered into force in January 2018. Regulation (EC) 258/97 had been widely criticised for its slow procedures, lack of procedural clarity, and limited effectiveness in fostering food innovation. In particular, the individual authorisation system for each applicant, combined with the absence of specific deadlines and the complexity of the evaluation process, created legal uncertainty and posed significant barriers for economic operators seeking to introduce new products into the EU market.[36]

2. These shortcomings led to the adoption of Regulation (EU) 2015/2283, which introduced several important changes. A centralised authorisation procedure was established, managed by the European Commission with scientific opinions from EFSA; clearer timeframes were defined; and a simplified notification system was introduced for traditional foods from third countries. Additionally, the definition of “novel food” was broadened, transparency was enhanced, and data protection rights were granted for the scientific evidence submitted by applicants—thus aiming to strike a balance between ensuring food safety and promoting innovation.

3. According to art. 7 of the Novel Foods Regulation (EU) 2015/ 2283, these are the main requirements for a novel food:

A novel food must:

[35] Escajedo San Epifanio, L. (2003), Revocación de autorizaciones relativas a OMG al amparo del principio de precaución (con especial atención a la doctrina del TJCE), Revista de derecho y genoma humano: genética, biotecnología y medicina avanzada, ISSN 1134-7198, Nº 18, 2003, págs. 139-161; Escajedo San-Epifanio, L. (2008), Biotechnologie, santé et environnement dans l'Union européenne: aspects politiques et juridiques. Revue de l'Union Européenne, ISSN 0035-2616, Nº 517, 2008, págs. 255-266.

[36] Haber, Bernd, and Andreas Meisterernst. "Proposals for a Revision of Regulation (EC) 1924/2006." Eur. Food & Feed L. Rev. 6 (2011): 27.

- Be safe.
- Not mislead the consumer, especially when the novel food is intended to replace another food.
- Not be nutritionally disadvantageous where it is intended to replace another food.

4. Regulation (EU) 2015/2283 expands and clarifies the definition of "novel food" compared with its predecessor. According to Article 3(2)(a), a novel food is defined as any food that was not consumed to a significant degree within the Union before 15 May 1997, and that falls into at least one of the ten categories listed in the same provision.

Category	Description	Examples
1. New or intentionally modified molecular structure	Foods with a new or intentionally modified molecular structure not used in the EU market before 15 May 1997.	Modified starches, altered proteins for better digestibility.
2. Microorganisms, fungi, or algae	Foods consisting of, or isolated or produced from, microorganisms, fungi, or algae.	Spirulina, yeast extracts, algae-based products like algae oil.
3. Material of mineral origin	Foods consisting of, or isolated or produced from, material of mineral origin.	Salt from new sources, mineral-based food additives.
4. Plants or parts of plants	Foods consisting of, or isolated or produced from, plants or parts of plants not used for food in the EU before 15 May 1997.	Novel plant species, new types of seeds, or fruit and vegetables not previously cultivated for food.
5. Animals or parts of animals	Foods consisting of, or isolated or produced from, animals or parts of animals not used for food in the EU before 15 May 1997.	Insects (e.g., crickets for protein), cultured animal cells.
6. Cell or tissue culture	Foods consisting of, or produced from, cell or tissue cultures derived from animals, plants, microorganisms, fungi, or algae.	Lab-grown meat, cultured seafood.
7. New production process	Foods resulting from a new production process not previously used for food production in the EU, significantly altering their composition or structure.	Plant-based protein made through fermentation, novel dairy processes.
8. Artificial nanomaterials	Foods consisting of artificial nanomaterials.	Foods containing nano-encapsulated nutrients, nanoparticle-based additives.
9. Vitamins, minerals, and other substances	Foods containing vitamins, minerals, or other substances that have undergone a new production process or contain nanomaterials.	Nano vitamins, novel minerals added to food, food supplements in new formats.
10. Exclusive use in food supplements	Foods that were exclusively used in food supplements before 15 May 1997 but are now intended for use in other food categories.	Omega-3 fatty acids, probiotics, or other food ingredients that were only available in supplement form.

Table of own creation based on Regulation 2015/2283

4. These categories include, among others: foods with a new or intentionally modified molecular structure; foods isolated from or produced using microorganisms, fungi, or algae; those derived from mineral sources; foods from cell cultures or tissue cultures of animals, plants,

microorganisms, fungi, or algae; foods resulting from new production processes; and traditional foods from third countries. This classification provides greater legal clarity and facilitates the assessment of products based on their origin or production process, contributing to a more systematic and transparent approach to risk management and food innovation. (See details in the Annex. 4).

5. The relevant category for CM/CSF is cell-based food products (vi) – food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae.

6. Classifying novel foods into categories facilitates the organisation and assessment of the safety and potential risks associated with foods of a novel nature or composition, since each category may involve different types of risks or require different authorisation procedures.

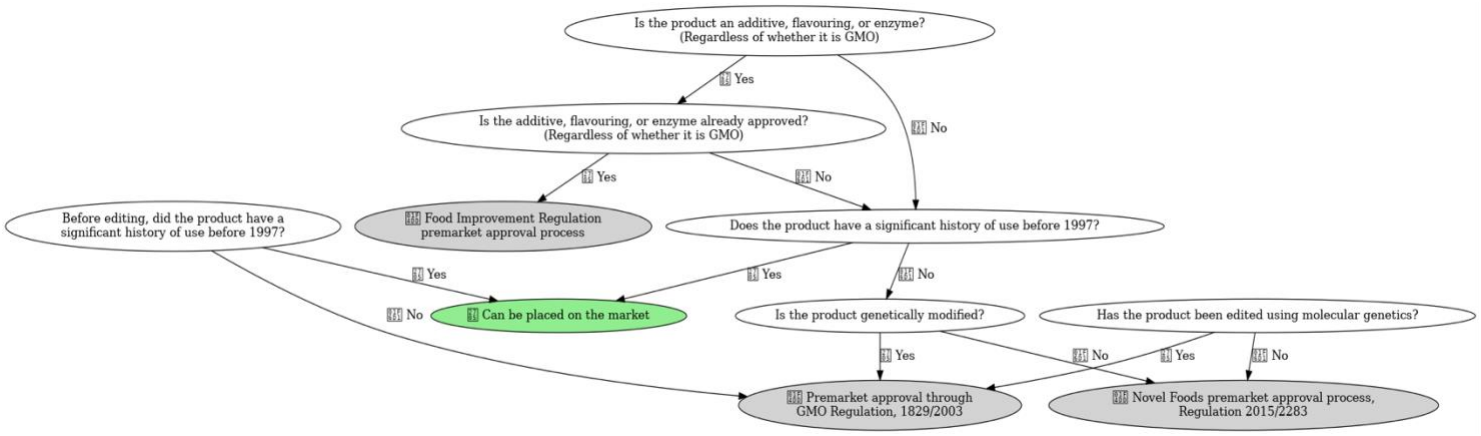
By distinguishing these categories, the regulation ensures that the rules are appropriate and tailored to the specific characteristics of each type of food. This allows the authorisation and safety assessment procedures to be adapted to the nature of each new food, thereby ensuring adequate consumer protection and effective management of food innovation.

2.3.4 Decision Tree on Whether a Product Falls Under the Premarket Approval Procedure of Regulation (EU) 2015/2283

1. The European Union has established distinct regulatory pathways to ensure the safety and oversight of innovative food products before they enter the market. The Food Improvement Agents Package provides the framework for authorising food additives, flavourings, and enzymes, whether or not they are derived from genetically modified organisms (GMOs). If such substances are already approved, they must still undergo a premarket approval process under this package before being marketed or used in food production (Regulations (EC) Nos 1331/2008, 1333/2008, 1334/2008, and 1332/2008).

2. For products that are genetically modified or have undergone molecular genetic editing, the relevant framework is the GMO Regulation (EC) No. 1829/2003, which governs the market placing of GM food and feed. This regulation requires a comprehensive safety assessment by EFSA and authorisation by the European Commission prior to commercialisation.

3. Separately, the Novel Foods Regulation (EU) 2015/2283 applies to products that do not have a significant history of consumption in the EU before 15 May 1997 and are not GMOs. These foods must also undergo a centralised premarket authorisation procedure, which includes a safety evaluation by EFSA and approval by the Commission. This tripartite regulatory architecture ensures that new food products—regardless of their origin or technology—are assessed for safety, properly labelled, and subject to appropriate risk management measures before reaching European consumers.



2.3.5. Keys of the novel foods' premarket approval process (art. 10)

The authorisation procedure for novel foods in the European Union is centralised and managed by the European Commission. According to art. 10 of the Regulation EU 2015/ 2283, the procedure involves the following key steps:

a) Application Submission -The process begins when an applicant submits a request for authorisation to the European Commission. This application must include detailed information about the novel food, including its composition, nutritional value, intended use, and safety data.

b) EFSA Safety Evaluation. The European Commission forwards the application to the EFSA, which carries out a scientific risk assessment to determine whether the novel food is safe for human consumption under the proposed conditions of use. EFSA must deliver its opinion within nine months of receiving a valid application.

c) Commission Decision. The Commission prepares a draft implementing act authorising or rejecting the novel food based on EFSA's scientific opinion and other legitimate factors (such as ethical, societal or environmental considerations). This draft is submitted to the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee) for a vote.

d) Inclusion in the Union List. If the novel food is authorised, it is added to the Union List of authorised novel foods, specifying the conditions of use, labelling requirements, and, if applicable, post-market monitoring obligations.

This report will analyse sections a and b in detail in the next block below (3 - Authorisation Requirements for Cell-Based Novel Foods in the EU), with particular attention to the Guidance published by EFSA in 2024, and it will focus on sections c) and d) in block (4- Some Clarifications on Decision-Making Bodies, Competencies, and Key Instruments in Relation to Novel Foods).

2.3.6. A structured and time-bound procedure involving multiple institutional actors

1. The authorisation process for novel foods (NF) and traditional foods (TF) in the European Union is governed by a rigorously structured, transparent and time-bound regulatory process involving multiple institutional actors. The process begins when an applicant submits a dossier that complies with the requirements outlined in the relevant EFSA Guidance for Novel Food or Traditional Food applications. This initial step is critical, as the completeness and scientific robustness of the dossier go someway to determining the feasibility and speed of the subsequent assessment stages.[37]

2. Once the dossier is submitted, the European Commission is responsible for validating it. In the case of novel foods, upon validation, the Commission mandates EFSA to perform a scientific risk assessment. This step is specific to novel foods and does not apply to traditional foods notified under Article 14 of Regulation (EU) 2015/2283. For traditional foods, the process may proceed without a full risk assessment if Member States or EFSA raise no safety objections.[38]

3. EFSA has a legal obligation to asses the dossier and adopt the respected scientific opinion on the novel food within nine months, but can take longer based on a variety of factors including the completeness of the dossier submitted and the analysis and testing deemed necessary by EFSA. During this period, EFSA may request additional information from the applicant if it considers that the submitted data are insufficient to complete the assessment. In the case of traditional foods from third countries, EFSA or Member States may raise duly reasoned safety objections within four months, which can lead to a more detailed assessment similar to the NF pathway (EFSA, 2024).

[37] European Food Safety Authority (EFSA). (2024). Guidance on the preparation and submission of applications for authorisation of novel foods.

[38] European Commission. (2023). Novel food: Procedures and responsibilities under Regulation (EU) 2015/2283.

4. The final step in the authorisation process is carried out by the Standing Committee on Plants, Animals, Food and Feed (ScoPAFF),[39] composed of representatives from all EU Member States and the European Commission, which chairs the committe. This committee evaluates the outcome of the scientific assessment and other relevant considerations, such as consumer protection and trade implications. If their authorisation opinion is favourable, the novel food is included in the Union list of authorized novel foods, allowing it to be marketed across the EU under the specified conditions.[40]

2.3.7 The relevant role of EFSA in the EU food safety landscape

The European Food Safety Authority (EFSA) plays a pivotal role in the food safety landscape within the European Union. However, it is essential to delineate what EFSA does and does not do in its capacity as an independent scientific body.

a) **What EFSA Does Not Do**. EFSA is not involved in the development of food safety policies or legislation. This task falls under the jurisdiction of EU lawmakers and policymakers, such as the European Commission and the European Parliament, who are responsible for creating and enacting regulations. Additionally, EFSA does not adopt regulations, authorize the marketing of new products, or define food labelling standards. These activities are handled by other institutions within the EU, such as the European Commission and national authorities. Moreover, EFSA does not enforce food safety legislation. Enforcement, including the monitoring of food safety compliance, is carried out by national authorities across EU Member States.[41]

b) **What EFSA Does**. EFSA's core function is to provide independent scientific advice and support to EU risk managers and policymakers, particularly on issues related to food safety. It assesses potential risks in the food chain and offers evidence-based recommendations that help inform decision-making processes at the EU level. EFSA's role is crucial in ensuring that public health and consumer protection remain central to EU food safety policy.[42]

[39] More details below, block 4.

[40] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods; European Food Safety Authority (EFSA). (2024). Guidance on the preparation and submission of applications for authorisation of novel foods.

[41] European Food Safety Authority. (2023). EFSA's Role and Responsibilities.

[42] European Food Safety Authority. (2024). EFSA Guidance on Food Safety.

Additionally, EFSA develops and provides up-to-date guidance on food safety, ensuring that stakeholders within the food industry, scientific community, and public health sectors have access to the most relevant and current scientific information. This guidance supports the consistent and coherent? application of food safety standards across the EU.

EFSA is also tasked with communicating independently and in a timely manner about potential risks in the European food chain. This communication is essential for transparency and for ensuring that the public, as well as which? E.g., food system or broader? stakeholders, are well-informed about food safety concerns. Lastly, EFSA promotes scientific cooperation among various stakeholders, fostering collaborative efforts between EU member states, international organizations, and research institutions to address emerging food safety challenges.[43]

3. Authorisation Requirements for Cell-Based Novel Foods in the EU

By acknowledging the needs and concerns of diverse audiences, FEASTS will plan and deliver tailored communications to the project stakeholders, fostering their engagement with the project where possible. The dissemination of relevant results across the target groups will ensure that project findings and reports reach the audiences that have the potential to magnify FEASTS' impact.

3.1 Premarket Approval Process: Scientific-Technical Evaluation and Decision-Making

3.1.1 GM or Non-GM? Implications for the Regulatory Status of Novel Foods in the EU

1. The premarket approval process for cell-based novel foods involving genetically modified organisms (GMOs) in their production falls at the intersection of two regulatory frameworks within the European Union.

On one hand, Regulation (EU) 2015/2283 on novel foods sets out the conditions under which innovative foods—defined as those not consumed by humans to a significant degree within the EU before 15 May 1997—may be authorised. This Regulation explicitly covers a broad range of

[43] European Food Safety Authority. (2024). EFSA Guidance on Food Safety.

food categories, including cell-based products (see Article 3(2)(a)(viii)), and requires a prior safety assessment by the EFSA before such products can be placed on the market (Article 10).

On the other hand, where genetically modified organisms are used at any stage of the production process, Regulation (EC) No. 1829/2003 on genetically modified food and feed and Regulation (EC) No. 1830/2003 on traceability and labelling of GMOs become applicable. These regulations impose additional requirements, regardless of the final detectability of the GMO in the end product. This includes a separate risk assessment (Article 5 of Regulation 1829/2003), mandatory GMO labelling (Article 12), and comprehensive traceability obligations (Article 4 of Regulation 1830/2003).

Consequently, cell-based foods produced with GMOs must also undergo the GM food authorisation process, in accordance with the applicable regulatory requirements.

2. The scientific panels of the EFSA – see Annex 2 – are the independent expert groups responsible for conducting scientific risk assessments across a wide range of areas related to food and feed safety and will also be involved in making GMO-related food safety assessments (something like this?). These panels address issues such as the risks associated with food and feed products, chemicals, additives, contaminants, and animal and plant health.

EFSA Scientific Panels List (2024–2029)

Scientific Committee (SC)	Provides overarching scientific opinions and guidance across EFSA's work.
Panel on Food Additives and Flavourings (FAF)	Evaluates the safety of chemical substances added to food and consumer exposure to them.
Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)	Assesses the safety of substances used in food contact materials, enzymes, flavourings, and processing aids.
Panel on Food Enzymes (FEZ)	Evaluates the safety of food enzymes.
Panel on Biological Hazards (BIOHAZ)	Provides scientific advice on biological hazards in relation to food safety and food-borne diseases.
Panel on Contaminants in the Food Chain (CONTAM)	Assesses the risks of contaminants in the food chain.
Panel on Dietetic Products, Nutrition and Allergies (NDA)	Deals with questions related to human nutrition, novel foods, nutrient sources, foods for special medical purposes, and food allergens.
Panel on Genetically Modified Organisms (GMO)	Provides independent scientific advice on food and feed safety, environmental risk assessment, and molecular characterisation of genetically modified organisms.
Panel on Plant Health (PLH)	Assesses plant health risks and provides scientific advice on plant protection.
Panel on Plant Protection Products and their Residues (PPR)	Provides scientific advice on the risk assessment of pesticides for operators, workers, consumers, and the environment.
Panel on Animal Health and Welfare (AHAW)	Assesses animal health and welfare risks and provides scientific advice on these matters.

Each panel comprises scientists with specialised expertise in disciplines including toxicology, nutrition, microbiology, and public health. Their composition and operation are governed by Regulation (EC) No. 178/2002, particularly Articles 22–23, which establish EFSA and define its role in providing independent scientific advice.

The work of these panels is essential for ensuring that the European Commission, the European Parliament, and EU Member States receive evidence-based and impartial scientific evaluations. These evaluations underpin decision-making processes concerning food safety and regulatory measures.

In addition, the panels provide guidance on the implications of emerging technologies and practices within the food chain, such as biotechnology and genetic modification. This scientific advice contributes to the assessment of novel foods, including those involving new genomic techniques (NGTs) or genetically modified organisms (GMOs), as outlined in relevant legislation such as Regulation (EU) 2015/2283 (novel foods) and Regulation (EC) No. 1829/2003 (genetically modified food and feed). See Annex 2 for the full list of EFSA scientific panels.

3. Within the category of novel foods, when a food product is or contains genetically modified organisms (GMOs), the application is assessed by a different scientific panel within EFSA—specifically, the GMO Panel (EFSA Panel on Genetically Modified Organisms). This panel has expertise tailored to the risk assessment of genetically modified food and feed, making it more specific in scope than the NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), which typically handles novel foods not involving genetic modification.

Although no explicit legal provision establishes a formal hierarchy or delimitation between panels, in practice, the GMO Panel takes precedence when GMO-related issues are involved. This is due to its specialised mandate, as set out in Regulation (EC) No. 1829/2003, which requires EFSA to conduct a scientific assessment of GM food and feed applications (see Article 6).

Ultimately, it is the European Commission, where appropriate assisted by the Standing Committee on the Food Chain and Animal Health (established under Regulation (EU) No. 182/2011, Article 5), that determines the appropriate regulatory route and assigns the relevant panel. This procedural discretion ensures consistency with the nature of the product and the applicable legal framework.

3.1.2. Scientific Risk Assessment in the Strict Sense and EFSA NDA Guidance 2024

1. In the context of EU food law, scientific risk assessment in the strictly refers to the independent, evidence-based evaluation of potential risks to human, animal, and environmental

health carried out by the EFSA. [44] This function is defined by Regulation (EC) No. 178/2002, notably in Article 22(6), which mandates EFSA to perform scientific assessments separately from risk management, the latter being the responsibility of the European Commission, Member States, and the European Parliament, as specified in Article 6(2) of the same Regulation.

To ensure transparency, consistency, and scientific rigour in its evaluations, EFSA issues guidance documents detailing how data should be collected, analysed, and presented to support food-related authorisations. While not legally binding, these documents are essential guardrails for compliance with the procedural and scientific standards expected in the EU's regulatory framework[45].

2. As part of this system, and under Regulation (EU) 2015/2283 on novel foods, EFSA first adopted a scientific and technical guidance for novel food applications in 2016. Following a request from the European Commission, EFSA updated this guidance to align it with the provisions of Regulation (EU) 2019/1381 on transparency and sustainability of the EU risk assessment process in the food chain, in force since 27 March 2021.

3. The revised guidance, formally adopted on 27 June 2024 and applicable to all novel food applications submitted from 1 February 2025 onwards, is titled: "Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283".[46]

4. This document provides applicants with a comprehensive framework for demonstrating the safety of novel foods. It outlines the required information concerning the identity and detailed description of the novel food, the production process, compositional data, specifications, intended uses and use levels, and estimated intake. It also requires evidence relating to the food's history of use and/or source, its absorption, distribution, metabolism and excretion (ADME), toxicological profile, nutritional impact, and potential allergenicity. Applicants must integrate and

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

[45] Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351, 30.12.2017, p. 64.

[46] Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 – adopted on 24 June 2024 and published in September 2024: EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, et al. Published in the EFSA Journal, full access available at: https://doi.org/10.2903/j.efsa.2024.8961

assess these data to support the overall safety of the novel food under the proposed conditions of use. If any risks are identified, they must be evaluated in relation to the expected intake and target populations.

5. Furthermore, EFSA has produced separate guidance for other regulatory pathways under Regulation (EU) 2015/2283, such as notifications of traditional foods from third countries (Article 14) or applications under Article 16. These documents assist applicants in preparing submissions, though they do not cover all administrative aspects of the process.

Together, these guidance documents play a critical role in upholding scientific integrity, legal predictability, and public confidence in the EU's food safety system.

3.1.3. Relevant information for Applicants

To obtain information on the application procedure for the authorisation of novel foods under the current regulations, applicants:

a) Must consult the EFSA's administrative guidelines related to Article 10 of Regulation (EU) 2015/2283, which include requirements for study notifications, pre-submission consultations, and aspects related to transparency and confidentiality.

b) Should also consider the EFSA's scientific documents, such as those concerning the safety and bioavailability of new sources of micronutrients, which may be relevant depending on the type of food.

c) Must, in each application provide data on the identity of the food, its production process, composition, proposed uses, and safety, including its history of use, metabolism, toxicology, and allergenicity, unless the omission of any of these data is justified.

d) Must detail, alongside their impact on the composition and safety, any changes in the production process, uses, or levels of already authorised foods. Applicants must also conduct a comprehensive literature search, ensure that trials are carried out in qualified facilities, and comply with the relevant regulations, minimizing the use of animals in studies in accordance with EU and EFSA guidelines.

3.2 Cell-Based Products as a NF Category and the Identity of Each Novel Food

1. The EFSA guidance on novel food assessment requests (updated 2024)[47] outlines specific guidelines regarding the identity of a new food. The applicant is required to provide detailed information about this identity, in accordance with the relevant subsections, which may be multiple in certain cases. These subsections differ from the categories described in Article 3 of Regulation (EU) 2015/2283, to which the applicant must assign their product when submitting the application.

The novel food under evaluation **must be the final product of the production process**, excluding non-novel ingredients or excipients, unless they are essential to maintaining the product's characteristics (such as stability or physical form). In such cases, compounds used to standardize composition should not be considered part of the novel food, neither in its identity nor in the composition analysis.

The **denomination of the novel food** in the application should reflect its characteristics, including its origin, parts of the organism used, product form (e.g., dry, frozen, powdered), and specific elements of the production process. Updated scientific names should be used, avoiding commercial names or registered trademarks.

2. Considerations for **Animal-Origin Products.** If the source of the novel food is animal-based, even if only for the extraction of cells, the following considerations must be taken into account:

When new foods originate from animals or their parts, detailed information should be provided, including:[48]

a) Scientific name (family, genus, species, subspecies, breed, if applicable).
b) Accepted synonyms and common names used to identify the product.
c) Verification of identity, such as certification or genetic authentication (DNA).
d) Suitability for human consumption according to EU regulations.

[47] Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 – adopted on 24 June 2024 and published in September 2024, EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, et al. Published in the EFSA Journal, full access available at: https://doi.org/10.2903/j.efsa.2024.8961

[48] See also Regulation (EU) 2017/625 on official controls and Regulation (EC) 853/2004 on hygiene of foodstuffs of animal origin.

e) Compliance with sanitary and regulatory requirements. It is necessary to demonstrate compliance with regulations such as Regulation (EU) 2017/625 on official controls and, where applicable, Regulation (EC) 853/2004 on the hygiene of foodstuffs of animal origin. Furthermore, the health status of the animal, its age, and the health certification of the herd or batch should be included.

f) Origin and conditions of the animals. The geographical origin of the animal (continent, country, region), farming and husbandry conditions, and the source of the livestock (e.g., national repository) should be specified. If the food comes from external suppliers, supporting documents must be presented.

g) Non-GMO declaration. A non-GMO declaration must be provided, along with information regarding the source material used in the food's production.

3. Cell-based products derived from Isolated cells[49]

3.1. Foods that consist of, are isolated from, or are produced from cell cultures or tissues derived from animals, plants, macrofungi, or macroalgae must meet specific requirements. For animal-derived cell or tissue cultures, detailed information must be provided about the identity of the organism, the nature of the cells (whether primary or from an established cell line), and safety tests such as the absence of infective risks from viruses or zoonotic agents. If the cells or tissues undergo genetic modification after the biopsy, this modification must also be documented.

> Example: If animal cells are modified genetically to improve growth rates or nutritional composition, this modification must be explicitly stated and accompanied by relevant safety data; e.g. bovine muscle cells are genetically edited post-biopsy to enhance protein synthesis, this genetic modification must be explicitly indicated in the dossier, along with supporting safety data.

3.2. For foods derived from plant, macrofungi, or macroalgae cell cultures or tissues, information must be provided about the identity of the source organism, the type of cells or cell lines used, and their genetic stability. Furthermore, if these cells or tissues, originally unmodified genetically, are altered after collection, such modifications must also be indicated.

> Clarification: If the plant or algae cells are altered post-harvest (e.g., through selective breeding or other processes), such changes must be specified in the food application. Similarly, if algal cells are collected in their wild-type form but subsequently engineered to enhance lipid content, this modification must be declared and justified.

[49] See EFSA Guidance on the risk assessment of nanomaterials in food, and Regulation (EU) 2015/2283 on novel foods.

3.3. For novel foods that contain artificial nanomaterials, detailed identification and characterization parameters must be submitted, as outlined in the guidance on the risk assessment of nanomaterials. In the case of foods containing small particles at the nanometric scale that are not considered artificial nanomaterials, other requirements are specified in the corresponding section of the guidance.

> Example: If a food product contains nanoparticles (e. g. minerals in powdered form) that are not engineered for a specific function (e.g., those naturally occurring or used without modification), the guidelines specify different assessment procedures. This kind of products would be subject to different safety and labelling criteria compared to foods containing purposefully engineered nanoscale additives.

3.3 Information to be provided on the process (or processes) used to produce a novel food.

1. In a novel food authorisation application,[50] the production process or processes employed (e.g. chemical synthesis, enzymatic catalysis, fermentation, or isolation from a natural source), as well as all input materials used during manufacturing, must be thoroughly described. This level of detail is essential to ensure that all critical parameters and steps involved in the process are clearly identified, allowing for a comprehensive assessment of potential food safety risks. The description must include specifications for raw materials, processing aids (e.g. fermentation auxiliaries)[51] and any substances that come into contact with the food during the manufacturing process.[52] This information forms the basis for evaluating the composition, specifications, bioavailability, nutritional value, and overall safety of the novel food.

2. Throughout the entire production process, the yield—i.e. the quantity of novel food obtained from the input materials—must be calculated, including the use of processing factors where

[50] Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 – adopted on 24 June 2024 and published in September 2024: EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, et al. Published in the EFSA Journal, full access available at: https://doi.org/10.2903/j.efsa.2024.8961

[51] 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 specifications.

[52] Regulation (EC) No. 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC, OJ L 338, 13.11.2004, p. 4.

relevant.[53] Regarding safety, the description must also include information on potential by-products, impurities, or contaminants. Additionally, the possibility of contaminant formation during processing should be assessed depending on the methods used. This includes providing details on the parameters that may contribute to generating such contaminants.

3. The production of a novel food must be supported by a food safety management system based on the principles of Hazard Analysis and Critical Control Points (HACCP), in accordance with Regulation (EC) No. 852/2004 on the hygiene of foodstuffs. Operational limits and key process parameters must be clearly defined. Furthermore, all measures implemented to monitor and ensure product quality and safety—such as HACCP, Good Manufacturing Practices (GMP), and relevant ISO standards—should be detailed. These procedures must include information on critical control points, operational prerequisite programmes, monitored parameters, corrective actions, verification procedures, analysis frequency, and the analytical methods used. A production flow diagram must also be provided, indicating quality and safety controls, as well as standardisation criteria, including specific markers relevant to the novel food.

4. According to the EFSA guidance on novel food assessment requests (updated 2024)[54] and without prejudice to other general requirements or those arising from specific subsections applicable to cell-based foods, the following additional requirements apply specifically to this novel food category.

4.1. For foods consisting of, isolated from, or produced from cell cultures or tissues derived from animals, plants, macroscopic fungi, or macroalgae, detailed information must be provided on the type of cells used (e.g., primary cells or established cell lines). If primary cells are employed, the application must include data on their source, purification and isolation procedures, cell selection, subculturing steps, and evidence of the absence of pathogens and contaminants. For established cell lines, information must be provided on their origin, preparation and storage methods, and the number of passages of the cells used in the production process.

4.2. Any modifications introduced to the cells—such as selection, differentiation, immortalisation, adaptation, or reprogramming—must be clearly described, particularly in relation to their role in producing substances of interest. All procedures related to the

[53] The ratio of the concentration of a chemical substance in a product to the concentration of the same substance in the starting material (the source).

[54] Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 – adopted on 24 June 2024 and published in September 2024, EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, et al. Published in the EFSA Journal, full access available at: https://doi.org/10.2903/j.efsa.2024.8961

treatment, extraction, screening, and selection of cells or tissues must be described in detail. This includes the chemicals and biological materials used, as well as any impurities or by-products that may result from these processes.

4.3. The genetic stability of the cells throughout the production process must be assessed by comparing the original material (e.g., cells derived from biopsy or cell lines) with samples collected at different stages of production (e.g., during propagation).

In addition, any changes in morphology, differentiation markers, and other phenotypic characteristics must be analysed and described both at the beginning and at the end of the production process.

4.4. Information must be provided on compliance with Good Cell Culture Practice (GCCP) and applicable regulatory frameworks, such as the EMA guideline on the derivation and characterisation of cell substrates used for the production of biotechnological/biological products.

The safety of microbial-derived growth factors used during the production process (e.g., recombinant proteins, vitamins, amino acids) must also be assessed, in line with EFSA's scientific requirements for the identification and evaluation of hazards related to microorganisms used in the food chain, as set out in the relevant guidance documents.

5. In addition to the previously mentioned requirements, it is crucial to note that when a consortium of producers or multiple producers is involved in producing a novel food, a **clear description of any variability or differences in production methods is required**. This approach ensures that the safety and quality of the final product remain consistent, even if there are variations in manufacturing processes or batches produced by different parties.

Key points include:

5.1. Variability in batches and processes:

When multiple producers or processes are involved (e.g., drying raw materials using different methods), it must be demonstrated that the products are equivalent in terms of composition, safety, and quality. This requires providing analytical data from several representative batches, showing that all products meet the same food safety standards.

5.2. Food safety management:

All producers must implement food safety management systems, such as a Hazard Analysis and Critical Control Points (HACCP) plan, covering the entire production process, from raw material sourcing to the final product. This is essential to minimize public health risks throughout all stages of production.

5.3. Variability of raw materials:

Assessing the variability of supplied raw materials is important, as factors such as ingredient quality can influence the final product. The analytical data that is provided must account for this variability to ensure that even if raw materials slightly vary, the final product remains safe and of high quality.

5.4. Changes during the risk assessment

If the production process changes during risk assessment, the applicant must notify the EFSA. This ensures that new methods or adjustments do not compromise food safety and maintains consistency in the risk assessment process.

In summary, this regulation aims to ensure that all novel foods on the market are safe for human consumption, regardless of differences in manufacturing processes or the producers involved. It also provides a framework for traceability and control during the evaluation process.

3.4. Information to be provided on the composition of a novel food

1. The 2024 EFSA guidance on novel food (in force since February 2025)[55] outlines how compositional data must be presented in applications. These qualitative and quantitative data are used to characterise the novel food and its components, taking into account their origin and production process. An analysis of batch-to-batch variability is required to assess the consistency and reproducibility of the product, which also contributes to hazard identification and the setting of specifications. The guidance distinguishes three sections: one with general requirements applicable to all novel foods, and two others with specific requirements depending on the type of product (single substance, simple or complex mixture, or whole food).

2. Regarding the general requirements, these can be summarised as follows:

[55] Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 – adopted on 24 June 2024 and published in September 2024: EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, et al. Published in the EFSA Journal, full access available at: https://doi.org/10.2903/j.efsa.2024.8961

2.1. Analyses must be carried out using validated methods, preferably those recognised at national or international levels (e.g., AOAC, European Pharmacopoeia, ISO). Each method must be described, including its limits of detection and quantification (LOD/LOQ), and supported with certificates of analysis and accreditation. If in-house or modified methods are used, they must be thoroughly justified and described, including details of their validation. A summary table listing the methods used and the analytes tested must be included in all cases (EFSA NDA Panel, 2024).

2.2. Analytical data must be based on at least five independent and representative batches of the novel food, ideally produced at industrial scale. This information should be used to establish the product specifications, considering variability due to raw materials, processing methods, or presentations (e.g., powdered, frozen). If different production processes are proposed, data must be provided for each. The justification for the representativeness of the batches and any deviations must be clearly explained. Published data may also be used if they meet the methodological requirements (EFSA NDA Panel, 2024).[56]

2.3. Representative sampling must be ensured, with justification of the sampling plan applied and reference to applicable legal or standard guidelines. Each certificate of analysis must include the batch name, production date, and analysis date.

2.4. Information must be provided on impurities, residues, and relevant chemical or microbiological contaminants based on the origin and production process of the novel food (e.g., residual solvents, by-products, mycotoxins, heavy metals). Protein content must be determined using a conversion factor of 6.25, and if protein levels are substantial, a full amino acid profile must also be included. Where the food contains specific proteins or is enriched with them, their detailed profile must be described, including sequence and degree of hydrolysis. Additional analyses may be required for allergenicity assessment (EFSA NDA Panel, 2024; EFSA Scientific Committee, 2010). [57]

2.5. If the novel food qualifies as an engineered nanomaterial under Regulation (EU) 2015/2283, it must be characterised in accordance with EFSA's guidance on the risk

[56] EFSA NDA Panel (2024). EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA); Turck, D., Bohn, T., Castenmiller, J., et al. Guidance on the scientific requirements for the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA Journal, 22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

[57] EFSA Scientific Committee (2010). Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal, 8(7):1625. https://doi.org/10.2903/j.efsa.2010.1625

assessment of nanomaterials (EFSA Scientific Committee, 2021). [58] If it is not considered a nanomaterial but may contain small or nano-sized particles due to the production process, the applicant must demonstrate their absence or justify that conventional assessments adequately cover these risks. Certain categories—such as microorganisms, unmodified proteins, or whole foods—may be exempt from such evaluation if no small particles are generated during processing.

3. In addition to the general requirements for compositional information, the EFSA guidance adds two specific sections.

3.1. The first concerns individual substances and simple mixtures, defined as those in which all components can be fully chemically characterised. In these cases, the identity and relative proportions of all components must be provided—allowing for a complete mass balance—along with the relevant analytical data. If the substance or mixture is produced using genetically modified organisms (GMOs), the requirements for Category 1 GMOs apply, as described in EFSA's 2011 guidance on genetically modified food and feed applications.[59]

3.2. The second section addresses complex mixtures and whole foods, where it is not feasible to identify all components. A qualitative and quantitative characterisation of the main constituents is required (using sum parameters and proximate analysis), and the unidentified fraction must be quantified and kept to a minimum.

3.2.1. Relevant natural or chemical components (e.g., nutrients, anti-nutrients, dietary fibre), potentially hazardous substances (e.g., toxins, allergens, contaminants), and any processing effects must be described. If novel proteins are present, proteomic characterisation is mandatory.

3.2.2. In addition to batch analysis, a comprehensive literature review must be carried out, following the EFSA guidelines on literature search strategies.[60] The presence of

[58] EFSA Scientific Committee (2021). Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health. EFSA Journal, 19(8):6768. https://doi.org/10.2903/j.efsa.2021.6768

[59] EFSA (2011). EFSA Panel on Genetically Modified Organisms (GMO). Guidance for risk assessment of food and feed from genetically modified plants. EFSA Journal, 9(5):2150. https://doi.org/10.2903/j.efsa.2011.2150

[60] EFSA (2010) EFSA Scientific Committee. Guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health. EFSA Journal, 8(2):1489. https://doi.org/10.2903/j.efsa.2010.1489

substances of concern—such as genotoxic compounds or heavy metals—must be evaluated, particularly in the case of botanical materials. For these, chemical fingerprinting and the use of tools like the Compendium of Botanicals and OpenFoodTox are recommended.

3.2.3. For complex mixtures produced with GMOs, the requirements for Category 2 GMOs apply (i.e., no viable GMOs or inserted genes present). In the case of insect-derived products, applicants must consider the potential hazards identified by EFSA,[61] which depend on the insect species, the rearing substrate, and the production method. The concentration of viable and non-viable cells must be reported for active agents and biomass-based products.

3.2.4. Finally, where relevant to support the safety of the novel food, a compositional comparison with conventional foods is recommended. However, such a comparison does not replace the need for a specific safety assessment of the novel food in question.

3.5 Information Requirements on the Stability and Specifications of a Novel Food

3.5.1. Stability Testing of a Novel Food

1. The stability of a novel food refers to its ability to maintain its characteristics and properties over time under specific storage, transportation, and usage conditions without alterations that could compromise its safety or quality. The stability of a novel food is essential not only to ensure its safety but also to ensure that the product retains its desired properties from a nutritional, sensory, and microbiological standpoint throughout its shelf life.

2. This stability is evaluated in terms of several factors, such as nutritional composition, texture, flavour, nutrient content, microbiological safety, and the absence of unwanted contaminants or substances. For novel foods, stability is a crucial aspect that must be assessed to ensure that the product is safe and suitable for human consumption throughout its lifecycle[62]. This includes:

- Nutritional stability: Ensuring that nutrient levels (e.g., vitamins, minerals, proteins) are not significantly degraded.

[61] EFSA (2015), EFSA Scientific Committee. Risk profile related to production and consumption of insects as food and feed. EFSA Journal, 13(10):4257. https://doi.org/10.2903/j.efsa.2015.4257

[62] Majid, I., Nayik, G. A., Dar, S. M., & Nanda, V. (2018). Novel food packaging technologies: Innovations and future prospective. Journal of the Saudi Society of Agricultural Sciences, 17(4), 454-462.

- Microbiological stability: Preventing the growth of pathogenic microorganisms that could compromise food safety.
- Chemical stability:[63] Preventing the formation of unwanted compounds, such as oxidation products or degradation of ingredients.
- Sensory stability:[64] Maintaining organoleptic properties, such as taste, smell, colour, and texture, to ensure consumer acceptance.

3. In its 2024 Guidance on the preparation and presentation of applications for novel food authorisation, the EFSA clearly defines the requirements for evaluating the stability of novel foods as part of the safety assessment process.[65] This evaluation is essential to ensuring that the product's compositional integrity and safety are maintained throughout its shelf life, including during storage and distribution.[66]

4. Stability testing should aim to identify potential hazards that may arise during storage, characterise degradation products, and monitor critical components or parameters that may undergo changes impacting the food's identity or safety. The selection of parameters must be scientifically justified, as should the exclusion of any considered irrelevant. These studies should address chemical, physicochemical, and microbiological stability under the proposed storage conditions, taking into account packaging, temperature, exposure to light, oxygen, and humidity.

5. Testing must be conducted on a minimum of five independent batches of the novel food,[67] covering all its intended formulations or presentations, unless a reduced requirement is scientifically justified. The duration of the stability study should at least match the proposed shelf life, with appropriate intermediate testing intervals. Results from these tests may serve to define the product's specification limits. Accelerated stability testing is acceptable when supported by

[63] Privalle, L., Bannon, G., Herman, R., Ladics, G., McCLain, S., Stagg, N., ... & Herouet-Guicheney, C. (2011). Heat stability, its measurement, and its lack of utility in the assessment of the potential allergenicity of novel proteins. Regulatory Toxicology and Pharmacology, 61(3), 292-295.

[64] Ainsa, A., Marquina, P. L., Roncalés, P., Beltrán, J. A., & Calanche M, J. B. (2021). Enriched fresh pasta with a sea bass by-product, a novel food: Fatty acid stability and sensory properties throughout shelf life. Foods, 10(2), 255.

[65] EFSA (2024). Guidance on the scientific requirements for the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA Journal 2024;22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

[66] de Boer, A., & Bast, A. (2018). Demanding safe foods–Safety testing under the novel food regulation (2015/2283). Trends in Food Science & Technology, 72, 125-133.

[67] EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck, D., Cámara, M., Bohn, T., Castenmiller, J., De Henauw, S., ... & Hirsch-Ernst, K. I. (2025). Safety of dried biomass powder of Chlamydomonas reinhardtii THN 6 as a novel food pursuant to Regulation (EU) 2015/2283. EFSA Journal, 23(4), e9413.

valid scientific extrapolation models. In addition, the presence and function of any added stabilising agents must be reported and justified.

6. When the novel food is intended to be used as an ingredient in processed food products, its stability must also be evaluated under relevant processing conditions, particularly those involving thermal or pH extremes. This includes assessing any changes to critical components, interactions with other ingredients, and the potential formation of processing-related contaminants. Studies should be conducted using realistic food matrices or validated model systems and must include appropriate controls. If the novel food is subjected to non-conventional processing methods, all potential hazards specific to those methods must be identified and characterised.

3.5.2. Information to Be Provided on the Specifications of a Novel Food

1. According to the EFSA 2024 Guidance on novel food applications, specifications play a critical role in defining the identity, quality, and safety of the novel food throughout its shelf life.[68] Specifications must describe the essential physicochemical, compositional, and microbiological characteristics of the product and establish acceptable limits to ensure batch-to-batch consistency.

2. These specifications should be based on analytical data from at least five independent and representative batches of the novel food, ideally produced under conditions reflecting industrial-scale production. Where relevant, variations linked to different forms of presentation (e.g., powdered vs. liquid) or manufacturing processes must be addressed. If multiple production processes are proposed, specifications must be supported by data from each.

3. Key elements to include in the specifications are:

- Identity and purity of the main components, including relevant markers or characteristic compounds.
- Levels of potential contaminants, such as heavy metals, mycotoxins, residual solvents, or microbial pathogens, taking into account the origin and production process of the novel food.
- Moisture content, pH, ash content, and other physicochemical parameters, as applicable.

[68] EFSA (2024). Guidance on the scientific requirements for the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA Journal 2024;22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

- Microbiological criteria, particularly for foods prone to spoilage or contamination (e.g., total aerobic count, yeast and moulds, pathogens).
- Protein content and amino acid profile, when relevant. For protein-rich novel foods, detailed information on protein structure or hydrolysis degree may be required for allergenicity assessment.

4. The specification limits should be justified with scientific evidence, supported by batch data and, where applicable, stability testing results (see section 3.5.1 above). In some cases, specifications may be adapted over time, based on ongoing monitoring or new data obtained post-market. EFSA also allows the inclusion of published data in support of the proposed specifications, provided these sources meet the required methodological standards.[69]

3.6 Information on the Intended Use of the Product, ADME, Nutritional Profile, Toxicity, and Allergenicity

1. The EFSA concludes its NDA 2024 guidance with final remarks,[70] in which the applicant must integrate and interpret the previous data. This involves providing an overall assessment that supports the novel food's safety under the proposed use conditions. The applicant must consider all the evidence presented in the application, such as compositional analyses, toxicity studies, and microbiological testing, and provide a comprehensive evaluation that assesses potential health risks. In the event that health risks are identified, a detailed analysis must be conducted, considering the anticipated daily intake and the target populations of the food. It is essential to consider that certain groups, such as children, elderly people, or individuals with pre-existing medical conditions, may be more vulnerable to specific risks.

2. Furthermore, precautionary principle should be applied in risk analysis, especially in situations where scientific uncertainties exist about the product, in accordance with the precautionary

[69] EFSA Scientific Committee, 2021. Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health. EFSA Journal 2021;19(8):6768. https://doi.org/10.2903/j.efsa.2021.6768; EFSA Scientific Committee, 2021. Scientific guidance for the submission of dossiers on food enzymes. EFSA Journal 2021;19(6):6706. https://doi.org/10.2903/j.efsa.2021.6706

[70] EFSA (European Food Safety Authority). (2024). Guidance on the scientific requirements for the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA Journal, 22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

principle set forth in Article 191 of the Treaty on the Functioning of the European Union (TFEU).[71] This principle emphasizes that, in the absence of sufficient scientific evidence, measures should be taken to protect human, animal, and environmental health.

3. The EFSA concludes its guidance with final remarks, in which the applicant must comprehensively integrate and interpret the previous data. This means providing an overall assessment that supports the safety of the novel food under the proposed conditions of use, taking into account all available scientific evidence. The evidence may include compositional food analysis, toxicological studies, microbiological testing, and other relevant data related to the product's safety. The assessment should demonstrate that no significant risks to human health arise from consuming the product in the amounts and under the conditions of use proposed.

4. If potential health risks are identified, they must be analysed considering the product's anticipated daily intake and the characteristics of the target populations. For instance, if the food is intended for consumption by children or individuals with pre-existing conditions (such as heart disease or diabetes), these groups may be more vulnerable to adverse effects, requiring more in-depth analysis in such cases.

5. Additionally, safety testing should consider different types of risks, such as chronic toxicity, genotoxicity, carcinogenicity, and allergenicity. Chronic toxicity refers to the adverse effects that may occur from prolonged food consumption over time.[72] Genotoxicity refers to the ability of a substance to damage genetic material within a cell, potentially leading to mutations or cancer. Allergenicity refers to the food's potential to trigger allergic reactions in susceptible individuals. This may occur when certain proteins in the food interact with the immune system, leading to symptoms such as skin rashes, gastrointestinal discomfort, or even severe anaphylaxis in extreme cases.[73] These tests are crucial for understanding the safety profile of novel foods, particularly those containing novel ingredients or produced through new techniques.

6. In these analyses, it is crucial to apply the precautionary principle, especially when scientific uncertainty exists about the potential effects of a novel food. The precautionary principle is

[71] Treaty on the Functioning of the European Union (2012) Official Journal of the European Union, C 326, pp. 47–390.

[72] IARC (2019). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer, World Health Organization.

[73] EFSA (2015). Food Allergy and Intolerance: Evaluation of Allergenicity in Foods. European Food Safety Authority, EFSA Journal, 13(4):4050.

enshrined in the Treaty on the Functioning of the European Union (TFEU), Article 191,[74] which states that, when there are risks of harm to human, animal, or environmental health, and insufficient scientific assessment, measures can be taken to prevent such risks.

7. Therefore, if there is insufficient scientific evidence to ensure the safety of a novel food, competent authorities may take preventive measures, such as restricting its marketing until further data is available. This is particularly relevant for innovative products, such as cell-based foods (e.g. CM/CSF) or those containing genetically modified ingredients, which require rigorous evaluation due to their novel characteristics.[75]

8. It should be noted that key findings from toxicity studies must be highlighted, specifying the methods used to identify reference points, such as the BMDL (Benchmark Dose Lower Confidence Limit) or NOAEL (No Observed Adverse Effect Level), along with any other relevant information. Furthermore, it is crucial to discuss the significance of these findings, their relevance to humans, and, if necessary, the extrapolation of animal study results to human populations. For novel foods proposed as nutrient sources, both their safety and relative bioavailability must be addressed, assessing how the nutrients from the novel food are absorbed, distributed, metabolized, and eliminated by the human body. This is critical in determining their long-term efficacy and safety.

3.6.1. Information to be Provided on Intake Estimates of a Novel Food

1. Intake estimates are essential to assess the dietary and nutritional significance of a novel food and to characterize potential risks. These estimates are based on proposed uses and usage levels, as well as actual consumption data. They help to determine whether the novel food, under normal or intended consumption conditions, might pose any risk to health or whether it will provide the expected nutritional benefits.

2. The intake estimate must specify the target population, proposed uses, and usage levels, along with any precautions and restrictions related to the novel food. This information must be cross-referenced with safety data to ensure that potential risks are properly addressed under the

[74] European Union. (2012). Treaty on the Functioning of the European Union (TFEU). Official Journal of the European Union, C 326, 47–390.

[75] Examples of Tests and Evaluations: (1) Acute Toxicity Study: To assess immediate toxicity from the consumption of the product, high doses of a product are administered to laboratory animals, and any adverse effects are observed over a short period. (2) Genotoxicity Assessment: This is carried out using in vitro tests, such as the Ames test, to determine if the food has the potential to cause genetic mutations that could lead to cancer. (3) Allergenicity Testing: If the food contains novel proteins, tests are conducted to identify potential allergic reactions in humans. This may include evaluating the ability of the proteins to trigger an immune response.

proposed conditions of use. For example, if the novel food is intended for use in infant formulas or other sensitive groups, these details must be provided, alongside supporting evidence that the intake levels are within safe limits.

3. In cases where identified risks exist, these should be adequately addressed in the context of the proposed usage. For instance, if a novel food is found to have an elevated allergenic potential or a high concentration of a potentially harmful compound, the intake estimate should be adjusted accordingly to reflect these risks and avoid overexposure.

4. The EFSA NDA guidelines[76] also specify that uncertainty factors must be applied as established by the Scientific Committee.[77] These factors help account for variability and gaps in knowledge, ensuring that the safety of the novel food is evaluated conservatively. For example, uncertainties might arise from incomplete data on long-term exposure, bioavailability, or the effects of food processing on the final product. These factors should be transparently incorporated into the risk assessment process. By thoroughly considering these elements, intake estimates serve as a fundamental component in the comprehensive safety evaluation of novel foods, helping to ensure their safe introduction into the market.

5. According to the EFSA these are key considerations to the estimation of intake:

5.1. Target Population

The intake estimate must clearly define the target population or group for which the novel food is intended. This could be the general population, specific age groups (e.g., infants, children, adults), or other subpopulations (e.g., pregnant women, individuals with specific health conditions). The intended use of the novel food in terms of the type of food product (e.g., ingredient in processed foods, meal replacement) must also be considered. If the novel food is restricted to specific groups, such as adults or infants, this should be clearly indicated.[78]

5.2. Proposed Uses and Usage Levels

[76] EFSA. (2024). Guidance on the Scientific Requirements for the Preparation and Presentation of an Application for Authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283. EFSA Journal, 22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

[77] EFSA Scientific Committee. (2012). Guidance on selected default values to be used by the EFSA scientific committee, scientific panels and units in the absence of actual measured data. EFSA Journal, 10(3), 2579.

[78] EFSA. (2024). Guidance on the Scientific Requirements for the Preparation and Presentation of an Application for Authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283. EFSA Journal, 22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

The guidance emphasizes the importance of specifying the proposed uses of the novel food, such as whether it is intended as a whole food, an ingredient, or a dietary supplement. When used as an ingredient, the following must be provided:

- Food categories: Categorize the food based on tools like FAIM or DietEx.
- Maximum usage levels per category: Provide usage levels in terms of mg/kg, mg/100g, or mg/100mL.
- Form of the food: Indicate whether it is in powder, dehydrated, or other forms.
- Justification for whole food use: If the novel food is used as a whole food, justify how it mirrors expected consumption patterns in the EU.
- For dietary supplements or other regulated products, daily intake limits for the target population should be indicated.

5. 3. Estimated Intake of the Novel Food

The chronic daily intake of the novel food (per kg body weight and total intake) should be estimated using average body weights for the population group when specific data is not available. Tools like FAIM and DietEx can help estimate average and high intake levels (e.g., 95th percentile) for different population groups. Acute intake estimates should also be considered if there are indications of potential acute effects. If the novel food is intended to replace other foods, consumption data for those existing foods should be used. A combined intake scenario should be provided, integrating the different proposed uses.[79]

5.4. The chronic daily intake of the novel food (per kg body weight and total intake) should be estimated using average body weights for the population group when specific data is not available. Tools like FAIM and DietEx can help estimate average and high intake levels (e.g., 95th percentile) for different population groups. Acute intake estimates should also be considered if there are indications of potential acute effects. If the novel food is intended to replace other foods, consumption data for those existing foods should be used. A combined intake scenario should be provided, integrating the different proposed uses.[80]

5. 5. Combined Intake from Other Sources. The intake from the novel food or its components from other sources (e.g., natural presence or use as an additive) should be considered. The potential for double-counting of compounds, such as vitamins or minerals, from the novel food and the diet

[79] EFSA. (2024). Guidance on the Scientific Requirements for the Preparation and Presentation of an Application for Authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283. EFSA Journal, 22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

[80] EFSA. (2020). Scientific Opinion on the Risks for Public Health Related to the Consumption of Novel Foods. EFSA Journal, 18(8):6154. https://doi.org/10.2903/j.efsa.2020.6154

must also be addressed. Non-dietary sources (e.g., cosmetics or pharmaceuticals) should be included if relevant.[81]

5. 6. Exposure to Risk Substances. Exposure to substances that may pose a risk, such as contaminants or metabolites, should be estimated. The intake estimate (e.g., 95th percentile) and the maximum expected concentration of the substance in the novel food should be used to calculate total exposure (from the novel food and diet) and compare it to toxicological reference values (e.g., HBGV).

5. 7. Precautions and Usage Restrictions. Precautions and restrictions should be proposed based on all available safety information, including usage instructions and specific population groups for whom consumption may not be appropriate. These should be clearly outlined to ensure the safe consumption of the novel food.[82]

5. 8. Extrapolation of Intake Data. If direct consumption data for the novel food is unavailable, EFSA advises using intake data from similar foods, considering factors such as composition and intended use. Any extrapolation should be clearly justified, explaining why the assumptions are reasonable and scientifically sound.

5. 9. Food Processing Considerations. The impact of food processing on the novel food's composition and bioavailability should also be considered. For instance, if the novel food is used as an ingredient in processed foods, any changes in its concentration or bioavailability due to processing may affect the intake estimate.[83]

5. 10. Role in Risk Assessment. The intake estimate is a critical component of the overall risk assessment. If the estimated intake exceeds safety thresholds (e.g., acceptable daily intake or tolerable upper intake levels), further safety studies, including toxicity or nutrient overload assessments, may be required. This is particularly relevant for novel foods with high concentrations of specific nutrients or bioactive compounds.[84]

[81] EFSA. (2018). Guidance on the Risk Assessment of Genetically Modified Plants and Derived Food and Feed. EFSA Journal, 16(11):5387. https://doi.org/10.2903/j.efsa.2018.5387

[82] EFSA. (2020). Scientific Opinion on the Risks for Public Health Related to the Consumption of Novel Foods. EFSA Journal, 18(8):6154. https://doi.org/10.2903/j.efsa.2020.6154

[83] EFSA. (2024). Guidance on the Scientific Requirements for the Preparation and Presentation of an Application for Authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283. EFSA Journal, 22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

[84] EFSA. (2020). Scientific Opinion on the Risks for Public Health Related to the Consumption of Novel Foods. EFSA Journal, 18(8):6154. https://doi.org/10.2903/j.efsa.2020.6154

3.6.2. The information on ADME (Absorption, Distribution, Metabolism, and Excretion)

1. The ADME (Absorption, Distribution, Metabolism, and Excretion) profile of a novel food is essential for understanding how its components interact with the body. The ADME profile offers key insights into the behaviour of the food within the body, helping to determine whether its components might accumulate in tissues or organs. This profile is essential for identifying potential health risks, ensuring that the food is safe for consumption. Thus, the ADME data not only provides a detailed understanding of the food's metabolic journey but also contributes to the overall safety assessment by evaluating any possible adverse effects.

2. This data is crucial for assessing safety and potential health risks. Here's a more detailed overview of the information that needs to be provided:

Absorption: This is the process by which the body absorbs the components of the novel food after consumption. It is important to describe how these components enter the bloodstream, including whether they are absorbed through passive diffusion, active transport, or other mechanisms. The type of absorption (e.g., gastrointestinal, systemic) and potential variations in absorption rates should also be considered.

Distribution: Once absorbed, the components of the food are transported throughout the body. Information on how these components circulate, whether through the blood or lymphatic system, and where they might accumulate (e.g., liver, fat tissue, kidneys) is important. This helps determine the bioavailability of the food's components and whether certain organs are exposed to higher concentrations that could present health risks.

Metabolism: Metabolism refers to the chemical breakdown of the food's components, primarily in the liver. This breakdown may lead to the formation of metabolites, some of which could be more or less toxic than the original substance. The metabolic pathways involved, along with the identification of key metabolites, should be detailed. This information helps evaluate whether any transformation of the food's components could pose long-term health risks.

Excretion: Excretion is the elimination of food components and metabolites from the body. This process generally occurs through the urine, faeces, or sweat. The rate and pathways of excretion are essential to understand, as components that are not efficiently excreted may accumulate in the body and potentially cause harm.

2. Based on the EFSA NDA (2024) guidance, it is necessary to provide ADME (Absorption, Distribution, Metabolism, and Excretion) data for a comprehensive safety evaluation of a novel food. This data is crucial to assess whether any food components could accumulate in the body and if they could pose any toxicity risks. If specific ADME data for the novel food are unavailable,

it is acceptable to use data from similar substances, as long as the scientific justification for such assumptions is provided.[85]

3. Prior to conducting ADME studies, it is essential to assess the novel food's chemical, physicochemical, and microbiological properties and comprehensively review the existing literature.[86] Specific studies are mandatory if the food contains new individual substances or is a mixture with toxicologically relevant components.[87] The potential effect of the food matrix on bioavailability must also be evaluated.[88]

In some cases, ADME studies may be waived if the food consists of substances commonly found in the diet or the body.[89] However, if the food serves as a source of nutrients, bioavailability must be assessed and quantified, particularly regarding issues like toxicity or allergenicity (EFSA, 2015). In cases where concerns about protein are raised, digestibility studies should be incorporated into the nutritional, toxicological, and allergenic assessments.[90] For foods containing polymers over 1000 Da that are not degraded in the gastrointestinal tract, ADME studies would not be necessary.[91] For designed nanomaterials, the EFSA's Scientific Committee guidance should be followed, including in vitro degradation studies and ADME evaluation.[92] For conventional materials with small particles (including nanoparticles), their presence and behavior should be confirmed according to Section 4 of the relevant technical guidelines.[93]

---

[85] EFSA (2024). Guidance on the Scientific Requirements for the Preparation and Presentation of an Application for Authorisation of a Novel Food in the Context of Regulation (EU) 2015/2283. EFSA Journal 2024;22(9):8961. https://doi.org/10.2903/j.efsa.2024.8961

[86] EFSA (2018). Guidance on the assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

[87] EFSA (2018). Guidance on the assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

[88] EFSA (2015). Guidance on the risk assessment of the safety of new food and feed ingredients. European Food Safety Authority. Available at: www.efsa.europa.eu

[89] EFSA (2018). Guidance on the assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

[90] EFSA (2017). Guidelines for the assessment of allergenicity of GMOs. European Food Safety Authority. Available at: www.efsa.europa.eu

[91] EFSA (2015). Guidance on the risk assessment of the safety of new food and feed ingredients. European Food Safety Authority. Available at: www.efsa.europa.eu

[92] EFSA (2018). Guidance on the assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

[93] EFSA (2017). Guidelines for the assessment of allergenicity of GMOs. European Food Safety Authority. Available at: www.efsa.europa.eu

6. EFSA has **established a tiered approach for ADME (Absorption, Distribution, Metabolism, and Excretion) studies** to ensure a stepwise evaluation process that increases in complexity depending on the factors identified during the risk assessment of a novel food.[94] This approach is designed to tailor the assessment to the specific characteristics of the food and its components, to ensure consumer safety while minimizing unnecessary animal testing. The reference guidance for this methodology is provided by the OECD Test Guideline (TG) 417.[95] The tiered approach to ADME studies established by EFSA ensures that food safety evaluations are conducted progressively, with each step increasing in complexity only when required by the evidence. This strategy allows for a more targeted risk assessment, focusing on the specific characteristics of the novel food or its components. By prioritizing in vitro methods and using animal studies only when necessary, EFSA aims to protect consumers while minimizing the use of animals in research.[96]

7. Below, the three levels of the tiered ADME approach are clarified and explained in detail.

Level I: Initial Evaluation

At the first level, the focus is on gathering and analysing existing data. This involves reviewing published studies, both in vitro and in vivo, that have investigated the novel food or its components. It is also important to consider relevant physicochemical data, such as solubility, stability, and other properties that may affect bioavailability and toxicity.[97]

Advanced in vitro models, such as Caco-2 cells (a human epithelial cell line used to study intestinal absorption) or organotypic cultures (which mimic the structure and function of human tissues), can be employed to predict absorption and metabolism. These models are particularly useful in evaluating how the food or its components might interact with the human body without the need for initial animal testing.

A crucial component of this level is comparing human and animal metabolism. This helps to identify any significant differences in the way that a substance might be processed by the body. If the food or its components are not absorbed in the small intestine, further studies using in vitro systems

[94] EFSA (2015). Guidance on the risk assessment of the safety of new food and feed ingredients. European Food Safety Authority. Available at: www.efsa.europa.eu

[95] OECD (2010). OECD Test Guideline 417: Toxicokinetics. Organisation for Economic Co-operation and Development. Available at: https://www.oecd.org

[96] EFSA (2015). Guidance on the risk assessment of the safety of new food and feed ingredients. European Food Safety Authority. Available at: www.efsa.europa.eu

[97] EFSA (2015). Guidance on the risk assessment of the safety of new food and feed ingredients. European Food Safety Authority. Available at: www.efsa.europa.eu

with human-simulated microbiota may be necessary to identify relevant metabolites that could pose a toxicological risk. [98]

Level II: Advanced In Vivo Studies

Level II is activated when evidence suggests that the substance is absorbed into the bloodstream, bioaccumulates, or forms potentially harmful metabolites. At this stage, more complex studies are necessary. These typically involve in vivo animal testing, with both single and repeated-dose studies. These studies often form part of subchronic toxicity testing (OECD TG 408), which provides data on the potential toxic effects of repeated exposure to the food or its components over a longer period.

In this stage, the focus shifts from basic absorption data to understanding how the substance behaves in the body over time, particularly if it accumulates or interacts with specific organs or tissues. The information gained in these studies helps to assess potential health risks and determine if further investigation is needed at a higher level of complexity.

Level III: Human Studies

Level III studies are required when substantial differences in ADME behaviour are observed between species, there are no suitable animal models, or there are indications of bioaccumulation from previous studies. At this point, human studies are necessary to fully characterize the ADME profile of the novel food or its components.

These studies involve the direct examination of how the food behaves in humans and may include clinical trials or controlled feeding studies. Such studies are essential for obtaining the most accurate and relevant data on how the food or its components are processed in the human body.

7. Justification for Omitting Studies. At any level of the tiered ADME approach, studies can be omitted if a scientifically sound justification is provided. For example, if it can be demonstrated that the food or its components are sufficiently similar to commonly consumed foods, or if other data (such as existing toxicological data or structural similarity to known safe substances) can be used to support safety claims, further ADME studies may not be necessary. This flexibility allows for a more efficient and tailored approach to safety evaluation.

8. Regarding new sources of nutrients, EFSA's guidance provides several clarifications. First, when the novel food serves as a source of nutrients, its bioavailability must be demonstrated. For

[98] EFSA (2015). Guidance on the risk assessment of the safety of new food and feed ingredients. European Food Safety Authority. Available at: www.efsa.europa.eu

micronutrients (vitamins, minerals), it is required to quantify the relative bioavailability, according to EFSA's 2024 guidance. As for other nutrients, their bioavailability must be evaluated and demonstrated, although quantification is not required.

3.6.3. Toxicological Information to Be Provided in the EU Novel Food Application

The guidance provided by the EFSA also details the toxicological information required for a novel food application. The primary goal of conducting toxicological studies on a novel food is to identify and characterize potential health hazards and to support the determination of safe intake levels. Before conducting these studies, applicants must first review the composition data of the food and conduct a thorough literature review on its toxicological properties, relying on existing studies and relevant case examples.[99]

> In particular, the composition data should include information on the novel food's ingredients, as well as any potential impurities or by-products generated during processing. This review serves to establish whether there is already sufficient data to assess potential risks or whether additional studies are necessary.

3.6.3.1. Key Elements for Toxicological Testing Strategy.

The key elements for developing a toxicological testing strategy include the source, production process, identity, and composition of the food, as well as any available toxicological data (including in silico, in vitro, and animal studies). If, after the review, there are significant data gaps, appropriate toxicological studies should be conducted using a test material that is representative of the food's production process. In cases where the marketed food lacks sufficient sensitivity to identify potential toxic effects, fractions of the food or concentrates may be used for testing.[100]

The decision to proceed with further studies or use alternative test materials should be based on the food's composition and the level of processing it undergoes. This ensures that the testing is as relevant as possible to the actual food product being assessed.

---

[99] EFSA (2015). Guidance on the risk assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

[100] EFSA (2015). Guidance on the risk assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

3.6.3.2. Compliance with International Guidelines and Good Laboratory Practices

All studies must be carried out in accordance with international guidelines, such as those established by the OECD (Organisation for Economic Co-operation and Development), and adhere to Good Laboratory Practice (GLP) principles.[101]

> These OECD guidelines are designed to ensure that toxicological testing is performed in a standardized, reliable, and scientifically rigorous manner. Moreover, if the novel food involves the use of nanomaterials, additional specific requirements apply to assess the potential risks associated with these materials.[102]
>
> Nanomaterials, due to their unique properties (such as small size and large surface area), can behave differently from bulk materials. Therefore, they require tailored testing strategies to accurately assess their toxicity.

3.6.3.3. Extrapolation of Toxicological Data and Threshold of Toxicological Concern (TTC).

When direct toxicological data for a novel food is limited, profiles of related substances can be used to evaluate the risk, especially for foods with similar chemical structures or compositions.[103] The concept of extrapolation is important for situations where the novel food shares significant similarities with existing food ingredients, allowing for the assumption that the toxicological behaviour might also be similar.

The Threshold of Toxicological Concern (TTC) approach can be helpful for substances with low exposure levels, such as impurities or metabolites. The TTC provides a threshold level of exposure below which no significant risk is expected.[104] This approach is particularly useful when data is sparse, but it can provide a conservative safety margin for evaluating low-exposure substances.

Furthermore, the Qualified Presumption of Safety (QPS) approach is considered when evaluating microorganisms. QPS is a framework used by EFSA to determine whether microorganisms (including bacteria or yeasts) used in novel foods can be presumed safe based on prior knowledge of similar strains or species.[105]

---

[101] OECD (2010). OECD Test Guideline 417: Toxicokinetics. Organisation for Economic Co-operation and Development. Available at: https://www.oecd.org

[102] EFSA (2018). Guidance on the assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

[103] EFSA (2015). Guidance on the risk assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

[104] EFSA (2018). Guidance on the assessment of the safety of novel foods. European Food Safety Authority. Available at: www.efsa.europa.eu

[105] EFSA (2017). Guidelines for the assessment of allergenicity of GMOs. European Food Safety Authority. Available at: www.efsa.europa.eu

3.6.3.4 EFSA's Tiered Approach for Conducting Genotoxicity and Toxicity Testing of Novel Food

EFSA outlines a tiered approach for conducting genotoxicity and repeated-dose toxicity testing. This approach ensures that studies are carried out at appropriate levels, tailored to the nature of the novel food and its potential impact on human health.

a) Genotoxicity testing. The genotoxicity testing strategy must follow a stepwise process that includes both in vitro and in vivo tests to assess the potential genotoxicity of a novel food. Initial studies can be simpler, involving basic screening methods such as bacterial mutation assays or mammalian cell assays to detect potential DNA damage. If the initial results indicate potential risks, the complexity of the studies should be increased. More advanced in vivo tests, such as micronucleus or comet assays, may be necessary to confirm whether the food or its components cause DNA damage or mutations in living organisms. If genotoxic effects are detected, further specific studies should be carried out to fully characterize the nature of the genotoxicity and to assess the risk for humans.[106]

b) Repeated-Dose Toxicity studies. Repeated-dose toxicity studies evaluate the long-term effects of consuming a novel food. These studies begin with low doses of the food, observing any adverse effects after repeated administration over a set period (typically 28 days or more). If no significant adverse effects are identified, the dose range may be gradually increased, and further observations are made to identify any potential toxic effects at higher levels. This tiered approach allows for a more accurate and gradual assessment of the potential risks, reflecting the food's characteristics and the possible cumulative effects of consumption over time. Such testing is critical for identifying any subtle or chronic effects that might not be immediately apparent.[107]

3.6.3.5. Toxicological Report

The toxicological report must provide detailed descriptions of each step in the testing process, justifying the methodology and the scientific rationale for each phase. It should also provide a clear explanation of how the testing strategy was adapted to the specific properties of the novel food. This ensures that food safety is assessed in a comprehensive, rigorous, and stepwise manner, considering all potential risks to human health. The report should conclude with a safety assessment based on the evidence collected through the tiered approach.[108]

---

[106] EFSA (2011). Scientific Opinion on the Genotoxicity of Certain Substances Used as Food Additives. European Food Safety Authority. Available at: www.efsa.europa.eu

[107] EFSA (2011). Scientific Opinion on the Genotoxicity of Certain Substances Used as Food Additives. European Food Safety Authority.

[108] EFSA (2015). Guidance on the Safety Assessment of Novel Foods. European Food Safety Authority. Available at:

3.6.4. Nutritional Information to Be Provided with the Application, with Special Attention to Potential Drawbacks Associated with the Intended Use

1. This section focuses on the nutritional information that must be included in the application for a novel food, highlighting the need to address any potential disadvantages related to its intended use. It ensures that applicants not only provide data on the food's nutritional value but also consider any possible negative impacts of the food on health when consumed under the proposed conditions.

2. We will review the guidelines established by the EFSA regarding the nutritional information that must be provided for novel foods. Specifically, we will focus on two main aspects. First, the general framework for evaluating the nutritional impact is outlined in a flowchart developed by EFSA. The information submitted should demonstrate that, at the proposed levels of intake, the novel food is unlikely to lead to excessive nutrient consumption (see 3.6.4.2). Additionally, it must show that the food will not negatively affect the consumers' nutritional status by increasing the risk of inadequate nutrient intake (see 3.6.4.3). EFSA also provides a set of additional guidelines to ensure that these criteria are met.

3.6.4.1. The Concept of Intended Use

1. The concept of "intended use" is crucial in regulatory frameworks, especially in product safety assessment and classification, including novel foods. By clearly defining the intended use, manufacturers and regulators can ensure that appropriate safety measures are implemented to protect public health and guide informed decision-making. In the context of novel foods, this means evaluating the specific purpose of the food and the conditions under which it will be consumed, which directly impacts its safety assessment and regulatory requirements.[109]

2. According to the U.S. Food and Drug Administration (FDA), "intended use" refers to the general purpose of a product as determined by the manufacturer or distributor. This intent is typically conveyed through labelling, the design or composition of the product, or the distribution circumstances. For instance, the intended use of a blood glucose monitor is to help individuals with diabetes monitor their blood glucose levels, which aids in managing their condition and making informed decisions regarding diet and medication.[110] This definition is also applicable in

[109] EFSA (2024). Scientific Opinion on the Nutritional Safety of Novel Foods. European Food Safety Authority.

[110] FDA (2021). Guidance for Industry: Intended Use of Products. U.S. Food and Drug Administration.

food regulation, where understanding the intended use of a novel food helps determine the appropriate safety assessments and regulations.

3. In the case of novel foods, the intended use is particularly important in determining the appropriate safety evaluations. The EFSA stresses that the safety assessment of a novel food should take its intended use into account, as this influences the potential exposure to and health risks associated with its consumption. The proposed conditions of use, such as the quantity and frequency of consumption, are critical in assessing whether the food could have harmful effects on health.[111]

3. The EU regulation on novel foods requires that any potential nutritional disadvantages associated with the product be disclosed during the authorization process. To this end, a flowchart has been established to assess the potential impact of the novel food under the proposed conditions of use. It is essential to investigate whether the new food could pose a nutritional disadvantage for consumers based on the intended consumption conditions. This framework for evaluating the nutritional impact, as outlined in the EFSA guidance, mandates that the provided information demonstrate that, at the expected levels of intake, the novel food is unlikely to lead to excessive nutrient consumption or negatively affect the nutritional status of consumers. This includes ensuring that the food does not increase the risk of inadequate nutrient intake.[112]

3.6.4.2. Excessive Nutrient Intake

1. A novel food is considered nutritionally disadvantageous if, under the proposed conditions of use, it has the potential to cause excessive nutrient intake in one or more population groups. In other words, it is considered a risk if it exceeds the tolerable upper intake levels (UL) for any given nutrient. When no UL is available for a specific nutrient, other reference values should be used, such as the Health-Based Guidance Values (HBGV), which include values like the Acceptable Daily Intake (ADI) for nutrients such as copper.[113]

2. According to the EFSA guidelines, the estimated nutrient intake for the relevant population groups must be calculated, considering the proposed maximum levels of specification and usage (see above, 3.6.2). This calculation should focus on the target population groups (see above,

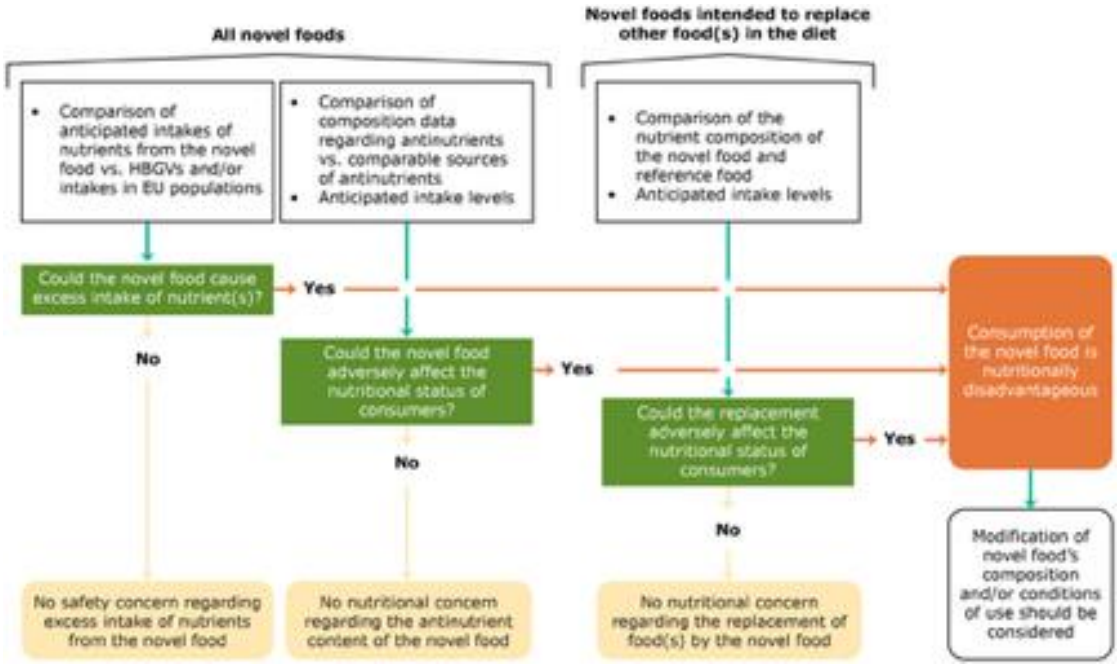
[111] EFSA (2015). Guidance on the Safety Assessment of Novel Foods. European Food Safety Authority. Available at: EFSA Website

[112] EFSA (2015). Guidance on the Safety Assessment of Novel Foods. European Food Safety Authority.

[113] EFSA Scientific Committee. (2023). Guidance on the Risk Assessment of Novel Foods. European Food Safety Authority.

3.6.1). Additionally, the applicant is required to consider the combined sources of nutrients, such as the baseline diet and the novel food (Section 6.4). The intake estimates must be compared to the applicable HBGV. In cases where no such value exists, the applicant must justify how the novel food could increase nutrient intake compared to the baseline diet.

Here (below) the flowchart for investigating a potential adverse nutritional impact of the novel food under the proposed conditions of use. Source: EFSA, 2024.[114]



3.6.4.3. Inadequate Intake of Essential Nutrients and Evaluation of Its Possible Risks

1. Inadequate Intake of Essential Nutrients refers to the insufficient consumption of nutrients are vital for maintaining normal bodily functions and health. These nutrients include vitamins, minerals, amino acids, and fatty acids that the body cannot produce on its own, or cannot produce in sufficient quantities, and therefore must be obtained through diet. Inadequate intake

[114] Flowchart for investigating a potential adverse nutritional impact of the novel food under the proposed conditions of use. Source: EFSA, 2024.

occurs when the amount of these essential nutrients consumed falls below the recommended dietary levels, potentially leading to nutrient deficiencies and associated health risks. The definition of "inadequate intake" is typically based on established dietary reference values, such as the Recommended Dietary Allowances (RDAs) or Adequate Intakes (AIs).[115]

2. Novel food is considered nutritionally disadvantageous if, under the proposed conditions of use, it may negatively affect the nutritional status of consumers by increasing the risk of inadequate intake of essential nutrients. Particular attention should be paid to those nutrients whose intake is below the recommended levels in the European population.[116]

3. Evaluation of Potential Risks of Inadequate Intake of Essential Nutrients. The evaluation of potential risks of inadequate intake of essential nutrients should be based on compositional data (see above) and comparisons with other foods. This includes assessing both the nutritional profile of the novel food and its impact on the consumer's overall diet, considering the potential for deficiencies or excesses in key nutrients.

3.1 Antinutrients Content. Antinutrients are compounds that can interfere with the absorption of essential nutrients. These substances, such as tannins, lectins, trypsin inhibitors, phytic acid, and phytates, can reduce the bioavailability of vital nutrients, particularly minerals like iron, zinc, and calcium. Novel foods may contain these compounds, and it is crucial to assess their levels to evaluate any potential nutritional disadvantages. Depending on the origin of the novel food, the applicant must provide information on the content of antinutrients and compare it to similar foods (e.g., hydrolysed barley or rice proteins). This comparison helps in understanding the potential effects of antinutrients on nutrient absorption and their contribution to the overall diet.[117]

3.2 Potential Replacement of a Conventional Food. When a novel food replaces a conventional food (e.g., UV-treated milk versus conventional milk), the applicant must demonstrate that the nutritional composition of the novel food is not detrimental to consumers. This includes evaluating whether the novel food can meet the nutritional needs typically provided by the conventional food it replaces. Special attention should be given to the impact of new production processes on the nutritional profile of the final product. Moreover, the applicant should provide detailed information about the nutritional composition of the conventional food, focusing on those nutrients that are a significant source of the diet. This comparison

[115] World Health Organization (WHO). (2004). Vitamin and mineral requirements in human nutrition (2nd ed.). Geneva: WHO Press; U.S. National Academies of Sciences, Engineering, and Medicine. (2020). Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press. https://doi.org/10.17226/13050

[116] EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). (2022). Scientific Opinion on the update of the EU population nutrient intake recommendations.

[117] EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). (2023). Scientific Opinion on the safety of novel foods. European Food Safety Authority.

ensures that the new food does not create imbalances in nutrient intake, especially for nutrients that are typically consumed in high quantities, such as proteins, vitamins, and minerals.[118]

3.6.4.4. Additional Considerations on New Sources of Nutrients and Proteins

When evaluating novel foods, the EFSA emphasizes the importance of providing comprehensive nutritional information, particularly when the food in question introduces new sources of nutrients or proteins. In these cases, special attention must be paid to ensure that the nutritional composition of the novel food meets the necessary safety and quality standards for human health. Below are the key areas of focus:

a. New Sources of Micronutrients. For novel foods acting as sources of micronutrients (such as vitamins and minerals) in food or supplements, applicants are required to follow EFSA's guidelines on safety assessment and bioavailability evaluation.[119] These guidelines outline how to assess and quantify the bioavailability of micronutrients from new sources. This is essential because the bioavailability of nutrients can vary depending on the food matrix and processing methods, which can influence the efficiency with which nutrients are absorbed by the body. These considerations help ensure that novel foods provide the intended nutritional benefits without posing risks to consumer health.

b. New Sources of Proteins. When a novel food could significantly contribute to the protein requirements of the target population, especially when replacing a conventional protein source, the quality of the protein must be evaluated. This is particularly important if the novel food is expected to be a major dietary protein source. The protein quality should be assessed using the Digestible Indispensable Amino Acid Score (DIAAS) method, as recommended by the Food and Agriculture Organization (FAO/ IAEA).[120] DIAAS takes into account the ileal digestibility of amino acids and compares them to an appropriate reference pattern, ensuring that the protein from the novel food can effectively support human nutritional needs.

c. Additional Nutritional Information on Novel Foods. In certain cases, additional studies may be necessary to assess the interaction of the novel food with the diet and other nutrients. These studies can be conducted in vitro, in silico, in animal models, or even in

[118] EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). (2023). Scientific Opinion on the safety of novel foods. European Food Safety Authority.

[119] EFSA NDA Panel (2024). Guidance on the evaluation of the bioavailability of micronutrients from novel food sources.

[120] FAO (2013). Dietary protein quality evaluation in human nutrition. FAO Food and Nutrition Paper No. 92. Food and Agriculture Organization of the United Nations; FAO and IAEA (2024). Assessment of protein quality and digestibility in foods. Food and Agriculture Organization of the United Nations and International Atomic Energy Agency.

humans, depending on novel food's composition, origin, and production process. The need for such studies is determined by the specific characteristics of the novel food, its intended use, and how it will be handled and consumed. These additional investigations help to ensure that the novel food does not cause any unintended nutritional imbalances or adverse health effects when consumed as part of a typical diet.[121]

3.6.5. Information on Allergenicity to be Provided in a Novel Food Application

1. Allergenic potential is an essential aspect of the safety assessment of novel foods, as some ingredients may trigger allergic reactions in susceptible individuals. The EFSA provides comprehensive guidelines to evaluate the allergenic potential of novel foods, considering both the food's inherent properties and its interaction with the human immune system. Identifying allergens in food products is vital for public health and forms part of the broader safety evaluation process required for novel food authorization within the European Union (EU). According to Regulation (EU) No. 1169/2011, all food products, including novel foods, must be appropriately labelled to indicate potential allergens to inform consumers, especially those with known food allergies.

2. The EFSA's 2024[122] guidance specifies the data requirements necessary to investigate the allergenic potential of novel foods. This is crucial for supporting regulatory decisions, including allergen labelling. These data requirements are tailored to the nature of the novel food, its production process, and its classification under the EU food labelling regulations. Based on this, the categorization of the novel food and the relevant allergenic data needed for its evaluation will vary.

3. The guidelines outline the data requirements for investigating the allergenic potential of novel foods. This data is essential to support regulatory decisions, including allergen labelling. The requirements vary depending on the nature of the food, the production process, and its classification under Regulation (EU) No. 1169/2011 on allergen labelling.

[121] EFSA NDA Panel (2024). Guidance on the evaluation of the bioavailability of micronutrients from novel food sources.

[122] EFSA NDA Panel (2024). Guidance on the evaluation of the bioavailability of micronutrients from novel food sources.

3.6.5.1. Categories that Help Determine the Necessity of Allergenic Testing and Labelling

The allergenic potential of novel foods is a critical consideration in their safety assessment and regulatory approval. The EFSA's 2024 guidance[123] provides a detailed framework for evaluating the allergenicity of novel foods, with specific data requirements depending on the food's source, production process, and whether it is derived from known allergenic ingredients. The guidance outlines **several categories that help determine the necessity of allergenic testing and labelling**:

a) Novel Foods Without Proteins Derived from the Production Process. For novel foods that do not contain proteins, glycoproteins, or peptides—such as those produced by chemical synthesis or derived from mineral sources—there are no specific allergenicity data requirements. These foods are generally considered to pose no risk of causing allergic reactions since they lack the protein components that typically trigger allergic responses. An example of this category could include mineral-based supplements or synthetically produced food additives that do not contain protein structures.

b) Novel Foods Derived from Allergenic Foods Subject to Mandatory Labelling. Foods that are derived from allergenic sources listed in the EU's mandatory allergen labelling regulations (Regulation (EU) No. 1169/2011, Annex II)[124] are assumed to retain the allergenic potential of their source. These foods are therefore subject to mandatory allergen labelling to ensure that consumers are informed of the potential risks. An example could be a new food ingredient derived from peanuts, which are classified as a major food allergen in the EU. If these novel foods contain proteins from non-labelled sources, further allergenicity testing is required to identify and assess their potential to cause allergic reactions.

c) Novel Foods Derived from Allergenic Foods Not Subject to Mandatory Labelling. If the novel food is derived from a known allergenic source, but this source is not listed in Annex II of the EU Regulation (i.e., it is not subject to mandatory allergen labelling), it is assumed to retain its allergenic potential. In this case, the applicant must provide information on the prevalence of allergies to the source, common symptoms associated with allergic reactions, the allergenic potency of the food, and the identification of relevant allergenic proteins. An example of this could include a food derived from a source like mustard, which is a common allergen but not part of the mandatory allergen labelling list under EU regulations. The applicant would need to provide comprehensive data on the allergenic risks associated with mustard-derived ingredients.

d) Novel Foods with Unknown Allergenic Potential. For novel foods with unknown allergenic potential, a thorough bibliographic review is required, including in silico, in vitro, in vivo, and human studies. These studies should evaluate cross-reactivity and protein digestibility to assess

[123] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2024). Scientific Opinion on the Assessment of Allergenicity of Novel Foods.

[124] European Commission. (2011). Regulation (EU) No. 1169/2011 on the provision of food information to consumers.

potential risks. If cross-reactivity is observed, additional testing should be conducted to fully understand the allergenic risk. An example could be a novel protein source derived from a lesser-known plant or microorganism, for which there is little existing research on its allergenic potential. In this case, extensive testing would be needed to ensure the safety of the food before it is marketed.

3.6.5.2. Stepwise Approach to Allergenicity Assessment of Novel Foods

1. The stepwise approach to assessing allergenicity in novel foods follows a series of progressive steps, increasing in complexity depending on the results obtained at each stage. This approach ensures that foods are adequately evaluated for allergenic safety, starting with simpler methods of assessment and advancing to more complex ones if necessary, based on the potential risk detected.

2. Below is a detailed description of this stepwise approach to the allergenicity evaluation of novel foods, focusing on how this process is applied in the context of novel foods.

1. Initial Assessment: Food Characteristics. The first step in the stepwise approach is to evaluate the characteristics of the novel food, particularly if it contains proteins or compounds known to be allergenic. At this stage, applicants must provide detailed information about the food's source, production process, and any relevant protein data. If the novel food comes from a source known for its allergenic potential (e.g., nuts or soy), a preliminary risk assessment is carried out based on its origin.[125]

2. In Silico Assessment: Computational Analysis. At this stage, computational models (in silico) are used to predict the likelihood that the proteins in the novel food may trigger allergic reactions. These models are based on existing data about known allergenic proteins and their ability to provoke immune responses. This analysis is especially useful when experimental data is not available.[126]

3. In Vitro Testing: Protein Reactivity Assessment. If the in silico assessment suggests potential risk, the next step is to conduct in vitro tests. These tests are performed in laboratory settings using cells or tissues and allow the evaluation of the reactivity of proteins from the novel food. Common tests include assessing the ability of proteins to bind to specific antibodies involved in food allergies.[127]

[125] Example: If a new ingredient is derived from a legume, its allergenic potential must be evaluated, as legumes are a common source of food allergies.

[126] Example: In silico tools can predict whether a protein derived from a novel food shares structural similarities with known allergenic proteins, such as Ara h 1, an allergenic protein in peanuts.

[127] Example: An ELISA (Enzyme-Linked Immunosorbent Assay) test can be used to measure how the proteins from the novel food interact with antibodies specific to food allergies.

4. In Vivo Testing: Animal Model Studies. If in vitro tests suggest the potential for allergic reactivity, in vivo testing in animal models (e.g., mice) is required. These studies provide more detailed information on the immune response to proteins in the novel food and their ability to induce a complete allergic reaction.[128]

5. Human Studies: Clinical Trials. In the most critical cases, if in vivo testing shows promising results, human studies can be conducted. These studies help assess the impact of consuming the novel food in individuals with known allergies and verify whether the food could trigger allergic reactions. Such studies must comply with strict ethical protocols and be supervised by experts in the field.[129]

3. For novel foods that contain **individual proteins or simple protein blends**, a stepwise approach must be followed.[130][131] Level I involves a literature review to gather existing data on the allergenic potential of the proteins present in the novel food. Level II consists of bioinformatic analyses to assess the potential for cross-reactivity with known allergens. These analyses use databases to compare the novel food's proteins with those from known allergenic sources. Level III involves human serum testing on confirmed allergic individuals to identify if there is any immune reactivity to the novel food proteins. If results suggest a potential risk, Level IV includes oral food challenge tests and skin prick tests to assess the clinical reactivity of the novel food in allergic individuals. These tests help to confirm whether the food induces a true allergic response.[132]

4. **For novel foods involving complex protein mixtures and whole foods**,[133] the stepwise approach is similarly applied but begins with a phylogenetic analysis to assess the relationships between the proteins

[128] Example: Mice can be sensitized to proteins from the novel food and then evaluated for allergic symptoms such as skin rashes or gastrointestinal issues.

[129] Example: Human trials may involve food tolerance testing, where participants consume small amounts of the novel food under medical supervision to assess potential adverse reactions.

[130] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2024). Scientific Opinion on the Assessment of Allergenicity of Novel Foods. EFSA Journal.

[131] If a novel food contains a protein from a legume, a Level I review would examine available data on legume allergies, followed by bioinformatic analysis (Level II) to check for similarity to allergens like those in peanuts. If no cross-reactivity is detected, testing on allergic individuals (Level III) would be conducted, and if any reactions occur, oral food challenges (Level IV) would be necessary.

[132] If a novel food contains a protein from a legume, a Level I review would examine available data on legume allergies, followed by bioinformatic analysis (Level II) to check for similarity to allergens like those in peanuts. If no cross-reactivity is detected, testing on allergic individuals (Level III) would be conducted, and if any reactions occur, oral food challenges (Level IV) would be necessary.

[133] If a novel food is derived from a complex mixture such as a whole grain or a plant-based protein blend, a phylogenetic analysis (Level I) would be conducted to determine its evolutionary relationship with known allergens. If the results indicate potential cross-reactivity with common allergens like soy or wheat, bioinformatics (Level II) and additional in vitro tests (Level III) may be employed to assess human relevance.

in the novel food and known allergens.[134] If any relationship is identified, bioinformatic tools are used to evaluate the potential for cross-reactivity (Level II). If the results suggest a higher likelihood of an allergic reaction, further cross-reactivity tests are conducted. In cases where cross-reactivity is confirmed, clinical human testing is performed to determine whether the novel food triggers allergic reactions in sensitive individuals (Level III and IV).

4. Some Clarifications on Decision-Making Bodies, Competencies, and Key Instruments in Relation to Novel Foods

4.1 Institutions Involved at the EU Level in the Assessment and Management of Risks Associated with Novel Foods and Their Functions

1. Within the European Union's General Food Law framework, the distinction between risk assessment, risk communication, and risk management is clearly established in Regulation (EC) No. 178/2002. This principle of functional separation is essential to ensure scientific objectivity and independence in food safety decision-making.[135]

2. In line with this framework, several institutions at the EU level are entrusted with distinct yet complementary responsibilities in the assessment, management, and communication of risks related to novel foods. These bodies operate under the principle of functional separation to collectively ensure the safety, transparency, and regulatory compliance of novel foods placed on the EU market.

3. The EFSA is the body responsible for the scientific risk assessment of novel foods, in accordance with Article 22(2)(a) of Regulation (EC) No. 178/2002. This provision explicitly mandates EFSA to "provide scientific advice and scientific and technical support in all areas which have a direct or

[134] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2024). Scientific Opinion on the Assessment of Allergenicity of Novel Foods. EFSA Journal.

[135] European Parliament and Council. (2002). Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Official Journal of the European Communities, L31, 1–24.

indirect impact on food safety".[136] Furthermore, Article 23 elaborates on EFSA's functions, including risk assessment and communication, in cooperation with the European Commission, Member States, and relevant stakeholders.

4. By contrast, risk management—that is, the adoption of specific measures such as legislative or administrative decisions to prevent, reduce, or eliminate risks—falls under the responsibility of the European Commission and the Member States, as outlined in Article 6(3) of the same Regulation. According to this provision, risk management must be based on the scientific assessment provided by EFSA, while also considering other legitimate factors, such as social, economic, or environmental aspects, and applying the precautionary principle where appropriate (Art. 7).

5. As a result, while EFSA acts as an independent scientific body tasked with delivering objective and transparent advice, binding and executive decisions—such as the authorisation, restriction, or prohibition of a food product, including genetically modified foods—are the competence of the European Commission, supported by Standing Committees composed of representatives from the Member States.

6. This institutional framework ensures that food safety decisions are adopted in a balanced manner, grounded in scientific evidence but also sensitive to broader societal, political, and ethical considerations, which rightly fall within the remit of risk managers.

4.2 The Role of the Commission and Member States in the SCoPAFF

4.2.1. Risk Managers in the Novel Food Framework: The European Commission and the Member States

1. In the context of the EU's novel food regulation, risk management responsibilities are primarily assigned to the European Commission and the Member States. These institutions play a central role in the decision-making process regarding the inclusion of new foods in the Union list, as stipulated in Article 9 of Regulation (EU) 2015/2283. While the EFSA is tasked with the scientific risk assessment, the final risk management decisions rest with the Commission and the Member

[136] European Parliament and Council. (2002). Regulation (EC) No. 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Official Journal of the European Communities, L 31/1.

States, ensuring a clear separation of roles in line with the principles of the General Food Law (Regulation (EC) No. 178/2002, Articles 6–7).

2. Functions of the Commission. The Commission is the main actor responsible for initiating and managing the authorization process of novel foods across the EU. Its duties include:

- Requesting scientific opinions from EFSA on the safety of novel foods when necessary (Article 10, Regulation (EU) 2015/2283).
- Preparing draft implementing acts to authorize the marketing of a novel food, taking into account EFSA's opinion as well as other legitimate factors such as societal, ethical, or environmental considerations (Articles 10 and 9).
- Maintaining and updating the Union list of authorized novel foods, ensuring that only foods assessed and approved under the conditions of use can be marketed or incorporated into other products (Article 6).

Through these tasks, the Commission ensures the consistent application of food safety rules and the functioning of the internal market.

3. Functions of the Member States. Member States also play a crucial role in the risk management process, acting both at the national level and through their participation in EU decision-making structures such as the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee). Their responsibilities include:

- Assessing the validity of applications submitted by food business operators, ensuring that the dossiers are complete and meet the requirements for risk assessment (Article 10.2).
- Collaborating with EFSA and the Commission by providing supplementary information or clarifications during the assessment process.
- Implementing and enforcing the Commission's authorization decisions, including the application of specific labelling, traceability, or post-market monitoring obligations.

This shared governance model between the Commission and Member States enables a harmonized yet flexible approach to the management of risks associated with novel foods, while safeguarding public health and consumer interests.[137]

[137] European Food Safety Authority (EFSA). (2021). Guidance on the preparation and presentation of applications for authorisation of novel foods. EFSA Journal, 19(3), 6552;). Regulation (EU) 2015/2283 on novel foods.

4.2.2 On Decision-Making within the Standing Committee on the Food Chain in Relation to Novel Foods

1. The Standing Committee on Food Chain and Animal Health (SCFCAH) —currently known as the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF)— is a technical body of the European Commission that plays a key role in risk management within the areas of food safety, animal and plant health, and feed regulation in the European Union.[138]

2. The SCoPAFF is integral to the development and implementation of EU laws related to food safety, animal health, plant health, and animal feed, overseeing the compliance of EU member states with established safety standards and ensuring that food products meet the health protection criteria established by European legislation. It operates in close collaboration with the EFSA, providing a platform for experts to discuss and assess scientific data relevant to the safety of food products, animal health, plant protection, and feed safety. The committee contributes to the adoption of legislation on various aspects of the food chain, including new food products, food additives, genetically modified organisms (GMOs), pesticides, and contaminants in food.

3. Key Regulatory Frameworks and References regarding the ScoPAFF:

1) Regulation (EC) No. 178/2002 of the European Parliament and of the Council, establishing the European Food Safety Authority (EFSA) and laying down procedures in the field of food safety. This regulation provides the basis for SCoPAFF's role in assessing the risks posed by food products and ensuring that only safe food reaches the market.
2) Regulation (EC) No. 1829/2003 on genetically modified food and feed: This regulation governs the approval and safety assessment of GM food and feed products within the EU, with SCoPAFF playing a key role in evaluating these products and their compliance with EU safety standards.
3) Regulation (EC) No. 1830/2003 on the traceability and labelling of genetically modified organisms and food and feed products produced from GMOs: SCoPAFF is involved in ensuring that GM products are accurately labelled, traced through the food chain, and meet the necessary safety criteria.
4) Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms: This directive outlines the procedures for the environmental risk assessment and approval of GMOs, with SCoPAFF providing input into the regulatory framework.
5) Regulation (EU) No. 2015/2283 on novel foods: This regulation covers the safety and approval process for new foods in the EU, and SCoPAFF is responsible for evaluating their safety of these foods before they can be marketed in the EU.

[138] European Commission. (2021). Standing Committee on Plants, Animals, Food and Feed (SCoPAFF). Retrieved from https://ec.europa.eu/food/committees/scoff_en

4. Through these frameworks and others, the ScoPAFF Committee plays a key role in ensuring that technical decisions in sensitive areas such as food, health, and the environment are not solely in the hands of the European Commission, but also reflect the active involvement of Member States.[139] This engagement ensures regulatory coherence across the Union and channels national concerns within the single market framework. Specifically, in the context of novel foods, it guarantees that Member States directly participate in decisions regarding their authorization, particularly when factors such as social sensitivity, risk perception, or consumer preferences are involved. Therefore, risk management is not only a technical process based on EFSA's scientific assessment, but also a political and deliberative one. As highlighted above, the involvement of both the Commission and Member States is vital for balancing scientific evidence with political and social considerations (Regulation (EC) No. 178/2002).

5. Concerning decision-making within this Committee, it is important to recall that it was established by Decision 1999/468/EC[140] and is now governed by Regulation (EU) 182/2011,[141] which outlines the procedure for the exercising implementing powers delegated to the Commission (comitology). The Committee comprises representatives from the Member States and is chaired by a representative of the European Commission. It is organized into several specialized sections, such as those dealing with genetically modified organisms (GMOs), food hygiene, and food contact materials, among others.

Its primary function is to issue opinions on draft implementing acts proposed by the Commission in technical areas where the Commission exercises executive powers (e.g., the authorization of a novel food or GM food, emergency measures, hygiene standards, etc.). The Committee acts as a risk management forum, where Member States can express their positions and vote on the Commission's proposals.

6. The general procedure for decision-making within this Committee follows the rules of comitology, as established in Regulation (EU) 182/2011, specifically the examination procedure, which applies to decisions with significant public health or internal market implications, such as those related to novel foods or GMOs.

---

[139] European Commission. (2020). The Role of Member States in the EU's Food Safety System

[140] Decision 1999/468/EC of the European Parliament and of the Council, laying down the procedures for the exercise of implementing powers conferred on the Commission. Official Journal of the European Union, L184, 23-30.

[141] Regulation (EU) No. 182/2011 of the European Parliament and of the Council, laying down rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers.

The quorum and voting result are determined by Qualified Majority Voting (QMV).[142] For a proposal to be adopted, it needs the support of at least 55% of the Member States (which means at least 15 out of 27 countries), and these countries must also represent at least 65% of the total EU population.

- If the Committee issues a favourable opinion, the Commission adopts the implementing act.
- If no qualified majority is reached either in favour or against (a "no opinion" outcome), the Commission may decide whether to proceed. However, it typically consults with Member States or refers the decision to an Appeals Committee. In these decisions, both political and technical contexts play a significant role.
- If the Committee rejects the act by qualified majority, the Commission cannot adopt it.

7. Once EFSA has issued a favourable opinion on the safety of a novel food, the European Commission prepares a draft implementing act to authorize its inclusion in the EU list of authorized novel foods (Article 10.1 and 10.2 of Regulation 2015/2283). This draft must be examined by the Standing Committee, which:

- Reviews the draft authorization proposed by the Commission.
- Votes on whether to support the authorization by qualified majority of Member States.
- Issues an opinion within the framework of the examination procedure outlined in Regulation 182/2011.

4.2.3. Temporary Restrictions that a Member State Can Apply to Novel Foods under Article 18 of the NF Regulation

1. The legal basis for a European Union (EU) Member State to impose restrictions or conditions on novel foods authorized at the EU level, restrictions that would only apply within its national territory, is found in Article 18 of Regulation (EU) 2015/2283 on novel foods.

2. Legal Framework for National Restrictions: Article 18 allows a Member State to adopt national protective measures if it has sufficient grounds to consider that the marketing of a novel food within its territory poses a risk to human health, animal health, or the environment. In such cases, the Member State can implement temporary restrictions, while conducting a more thorough risk

[142] A "qualified minority" refers to the minimum number of countries needed to prevent the adoption of a decision under this system. To block a proposal, at least four Member States representing more than 35% of the EU population must vote against it. This threshold is important because it ensures that a small number of large countries cannot block decisions alone, and neither can a large number of small countries. It's a balance between population size and the number of states.

assessment. If deemed necessary to protect public health, the Member State may even prohibit using a novel food.

3. Notification and Approval Process: Any measures adopted under this provision must be notified to the European Commission and the other EU Member States. These restrictions can only remain in force if they are subsequently approved at the EU level after a more detailed risk evaluation. This ensures that the decisions made by Member States are subject to scrutiny and consistent with EU-wide standards.

4. Contextualization of the Procedure: This process allows Member States to manage specific risks that may arise due to national circumstances or unique risk factors, while ensuring alignment with the broader European regulatory framework. The system provides flexibility for addressing localized risks while maintaining the integrity and uniformity of the EU's single market for novel foods.

5. This approach reflects the EU's commitment to public health and safety, while also acknowledging the importance of maintaining flexibility for national authorities in response to emerging risks or specific conditions within their territories. The overarching goal is to balance national protection with EU-wide consistency and collaboration.

4.2.4. European Regulation on the Designation of Novel Foods and the Prerogatives of Member States and the European Commission in this Area

1. The designation of a food refers to the name or labelling given to a food product that reflects its nature, composition, and intended use. In the context of novel foods, **the designation ensures that the product is accurately described, helping consumers understand what they are purchasing and its potential impacts on health**. It is a critical aspect of food regulation, as misleading or unclear designations can lead to consumer confusion, misinformed choices, and even potential health risks. Proper designation also ensures that foods comply with legal standards and transparency requirements, allowing for effective risk management and consumer protection.

2. The legal framework that empowers European Union (EU) Member States to make decisions regarding the designation of novel foods, with the aim of protecting consumers, is outlined in Article 24 of Regulation (EU) 2015/2283 on novel foods. This regulation establishes guidelines for the approval, safety assessment, and market authorization of novel foods across the EU.

3. Article 24 stipulates that the designation of a novel food **must be clear and not misleading regarding its nature or characteristics**. If a Member State deems that the designation of a novel food is misleading or may confuse consumers, it may adopt national measures concerning the

product's name to protect consumers within its territory. Such action is consistent with the broader consumer protection mandate recognized by the CJEU. However, these measures must be justified with evidence demonstrating that the designation is indeed misleading or confusing, must comply with the principle of proportionality, and should not create arbitrary or unjustifiable barriers to the internal market. Moreover, even if national decisions diverge from EU-level assessments, they must remain compatible with the fundamental principles of EU law as interpreted across various sectors.

These measures ensure that food products are properly identified and that consumers are not misled about what they are purchasing, thereby safeguarding public health and consumer rights.

3. Furthermore, the European Commission is responsible for establishing the criteria and guidelines for the designation of novel foods. However, if a Member State believes that a novel food's designation could potentially mislead or confuse consumers, it may intervene to ensure that the food is properly named. This intervention helps to ensure that the food's name provides clear and accurate information, preventing any potential risks of consumer confusion or deception. The Commission may review the designation if needed, in line with the regulatory framework established at the EU level.

4. In conclusion, Article 24 empowers EU Member States to regulate the designation of novel foods to protect consumers, ensuring that food names are accurate and transparent. This aligns with the broader EU regulatory framework that aims to maintain consistency and consumer safety in the internal market while giving individual Member States the ability to take national action when necessary.

4.3. EFSA

1. EFSA was established in 2002 and is the main risk assessment institution for food safety in the European Union. It is the primary "consumer" of the product from the European Commission's authority, which makes changes to legislative acts based on the results of studies conducted and risk assessments carried out.

2. Its legal basis is Regulation (EC) No. 178/2002 of the European Parliament and Council, which sets out the principles and general requirements of food law, creates the EFSA, and establishes procedures related to food safety.

3. Chapter III of Regulation No. 178/2002 outlines the functions, structure, and basic principles of EFSA's activities in relation to the provision of scientific information, as well as its obligations for independence, transparency, and confidentiality.

4. Through cooperation with national institutions and other organizations in the food sector, EFSA provides scientific advice to the institutions of the European Union and its Member States on matters that directly or indirectly affect food and feed safety, as well as areas such as animal health and welfare and plant protection. EFSA's main responsibilities are risk assessment and notification. In particular, EFSA's functions include providing scientific justification to risk managers (the European Commission, European Parliament, and Council) for the development of legislation and the drafting of regulations.

5. Regarding novel food, it is important to clarify the specific tasks and limitations of the EFSA in the context of novel food regulation, as its role is often misinterpreted. EFSA's primary function is to conduct independent scientific assessments and provide risk-based advice regarding the safety of novel foods. However, EFSA does not have decision-making power regarding the approval or market authorization of novel foods (see above 2.3.7). This decision lies within the jurisdiction of the European Commission, in consultation with EU Member States.

4.4. On the Monitoring of Novel Food Evaluation and Authorization Processes (Transparency)

1. Transparency is a cornerstone of democratic governance and is crucial in building public trust in the European Union (EU) decision-making processes. The EU's credibility, particularly in areas such as food safety, hinges on the perception that decisions are made in an open, accountable, and well-informed manner. Transparency in regulatory processes, especially in food safety, is vital to ensure that decisions are based on sound scientific evidence, with due consideration of public health and consumer interests. It provides citizens and stakeholders with access to information, fosters greater participation, and supports public trust in the effectiveness of regulatory frameworks. In the food context, transparency helps assure consumers that their safety is a priority and that they have a voice in the policies that affect them. Furthermore, it

promotes the credibility of EU institutions by reducing the potential for conflicts of interest and increasing the visibility of decision-making processes.[143][144]

2. The transparency in the novel food approval process within the European Union is governed by various provisions in Regulation (EU) 2015/2283 on novel foods. These provisions are designed to ensure that the process is clear, accessible, and understandable to consumers and other stakeholders, thus allowing them to track and comprehend the decisions made at each stage of the approval process. Regulation (EU) 2015/2283 aims to enhance the credibility of the decision-making process by providing stakeholders with clear and timely access to critical information.[145]

3. Key Elements of Transparency in the Novel Food Approval Process:

3.1. Publication of Applications and Evaluations. Article 12 of Regulation (EU) 2015/2283 mandates that the European Commission must publicly disclose the list of novel food applications under evaluation. Additionally, the EFSA, which is responsible for evaluating the safety of novel foods, is required to make its scientific assessment of the safety of the foods in question publicly available. EFSA's reports must include detailed information on the methods used and the scientific reasoning behind the conclusions drawn, ensuring that stakeholders can scrutinize the basis of these decisions.

3.2. Public Consultations. The European Commission and EFSA must ensure that public consultation mechanisms are in place for cases involving novel food applications that may raise safety concerns or trigger public debate. These consultations offer stakeholders, including consumers and industry representatives, an opportunity to express concerns or support, fostering an informed discussion of potential risks and benefits. This process also allows for the inclusion of diverse perspectives, which may improve the decision-making process and help address concerns from all affected parties.[146]

3.3. Access to Information. The Regulation stipulates that the outcomes of scientific evaluations and authorization decisions must be made publicly available. This includes access to EFSA's opinions and detailed information regarding the decision-making process. Providing this information helps ensure that the public and relevant stakeholders can access the rationale behind decisions and hold decision-makers accountable.

---

[143] Ecker, U. K. H., & von Alvensleben, R. (2020). Public Trust in European Food Safety: An Analysis of Transparency and Participation. Journal of Risk Research, 23(5), 589-609. https://doi.org/10.1080/13669877.2020.1805937

[144] uropean Commission. (2020). European Food Safety: A Transparent Approach.

[145] European Commission. (2020). European Food Safety: A Transparent Approach. European Commission.

[146] European Commission. (2020). European Food Safety: A Transparent Approach. European Commission.

3.4. Public Review of Applications. Member States have the right to submit comments on novel food applications during the evaluation process. Furthermore, the involvement of other stakeholders, including the general public, is encouraged, allowing for a broader dialogue on the potential implications of novel food authorizations. This collaborative approach enhances the legitimacy of the process and ensures that diverse concerns are addressed, contributing to more balanced decision-making.

3.5. Implementing Acts. Adopting implementing acts, which authorize or reject the commercialization of novel foods, must also be conducted transparently. Member States have the right to object to these acts, ensuring room for debate and revision. This ensures that the process remains open to scrutiny and that decisions are not made unilaterally, maintaining a fair and inclusive process for all parties involved.

5.- Some Notes on the Evaluation and Authorization Process for Novel Foods Based on GM or Containing GM Ingredients

1. The evaluation and authorization process for novel foods, particularly those that are genetically modified (GM) or contain GM ingredients, follows a rigorous and scientifically grounded procedure within the European Union. This process ensures that any food products authorized for sale in the EU meet high safety standards. Below are some key aspects of the process.

2. The legal framework governing the evaluation of GM novel foods is primarily outlined in Regulation (EU) 2015/2283 on Novel Foods and Regulation (EC) No. 1829/2003 on GM food and feed. These regulations establish the procedures for the approval of GM novel foods, prioritizing safety and the protection of public health and the environment. Foods that are genetically modified or contain GM ingredients must undergo a detailed evaluation process to assess potential risks.

3. The procedure for the authorization of genetically modified (GM) foods within the European Union is structured around several clearly defined stages, underpinned by a regulatory framework that ensures the protection of human, animal, and environmental health, while also guaranteeing transparency and traceability throughout the process. At its core, the process relies on a thorough scientific evaluation by the EFSA, followed by a formal decision made by the European Commission. The procedure also includes specific requirements for labelling,

traceability, and post-market monitoring, all of which are critical for ensuring consumer confidence and the integrity of the authorization system.

4. The process begins when an applicant (typically a producer or company) submits an authorization request to the European Commission to market a GM food. As outlined in Article 4 of Regulation 1829/2003, the application must provide detailed scientific data regarding the food's safety and potential risks.

5. Risk Assessment by EFSA: One of the pivotal steps in the process is the risk assessment conducted by EFSA. EFSA evaluates the potential risks that GM novel foods may pose to human health, animal health, and the environment, in line with Articles 6 and 18 of Regulation 1829/2003. This evaluation includes an in-depth analysis of food safety, potential allergens, effects on health and the environment, and the product's behavior under real consumption conditions. EFSA's comprehensive scientific assessment takes into account the genetic modification, compositional analysis, nutritional aspects, and any potential allergenicity of the GM ingredients.

6. After the application is submitted, EFSA conducts its risk assessment and provides an opinion based on the available scientific data (see Article 4 of Regulation 1829/2003). This opinion is central to the decision-making process and guides the European Commission and member states in deciding whether to approve the food. The opinion is made publicly available to ensure transparency and to enable stakeholders to review the scientific basis for the decision.

7. Public Consultation and Transparency: In line with the EU's commitment to transparency, public consultation is an integral part of the evaluation process for GM novel foods. As stipulated in Article 7 of Regulation 1829/2003, EFSA must issue its opinion within six months of receiving the application. The opinion is based on scientific evidence and follows the precautionary principle. The European Commission and EFSA ensure that the public and relevant stakeholders are informed about GM novel food applications. The consultation provides an opportunity for interested parties to submit their comments, concerns, and suggestions before a final decision is made. This process enhances transparency, builds public trust, and ensures that all relevant perspectives are considered.

8. After EFSA issues its scientific opinion, the European Commission and member states will decide whether to authorize the GM food for commercialization, as specified in Article 12 of Regulation 1829/2003. If the food is deemed safe, it will be authorized for sale within the EU. This decision is based on the EFSA opinion and takes into account concerns raised during the public consultation. If necessary, further studies or additional assessments may be requested before final approval is granted. This ensures that any remaining concerns are addressed, and that the food product is safe for public consumption.

9. Post-Market Monitoring: Once a GM novel food is authorized, it is subject to post-market monitoring to ensure that it continues to meet safety standards, as stipulated in Article 8 of Regulation 1829/2003. This monitoring includes periodic evaluations of the food's composition and additional studies to assess its long-term effects on human health, animal health, and the environment. Ongoing monitoring is essential to maintain the integrity of the food safety system and to incorporate new data into future regulatory decisions.

10. Labelling and Traceability: As part of the authorization process for GM novel foods, specific requirements for labelling, traceability, and post-market monitoring are outlined in Article 13 of Regulation 1829/2003. These requirements are crucial to ensuring consumer confidence and maintaining a robust authorization system. Clear labelling provides consumers with accurate information about the food they are purchasing, while traceability guarantees that the origin and safety of the food can be tracked throughout the supply chain.

11. Periodic Review and Reassessment: The authorization for a GM food may be reviewed periodically, depending on new scientific data or discoveries. As stated in Article 20 of Regulation 1829/2003, the European Commission can reassess the authorizations and market conditions based on evolving scientific knowledge or any new risks associated with the product. Moreover, if new risks are identified post-commercialization, manufacturers are required to report them, and the authorization may be modified or revoked as necessary, according to Article 23 of the same regulation.

6. The Legislative Review of NGTs in the EU: Will It Affect GMO Novel Foods?

1. Since 2021, the European Union, driven by the European Commission and at the request of the Council, has intensified its efforts to establish a specific regulatory framework for certain plants modified through genetic editing techniques. This new legislation, currently in an advanced stage of development, proposes to exclude plants modified solely through cisgenesis, intragenesis, or targeted mutagenesis (provided no foreign DNA is incorporated) from the scope of the current regulation on genetically modified organisms (GMOs)—based on Directive

2001/18/EC. These plants would instead be regulated under a distinct framework. However, any technique that introduces foreign DNA will remain subject to the existing GMO legislation.[147]

2. In this context, the term New Genomic Techniques (NGT) is introduced to refer to this group of plants, which is further subdivided into two categories: NGT1 and NGT2, depending on the extent of the genetic modifications.

3. At present, there is a disagreement between the European Commission, the European Parliament, and the Council regarding the criteria that should define this division, and it is expected that the upcoming trialogues will help reach a consensus. Furthermore, there are differences in the regulatory treatment of food products derived from these plants, particularly with regard to NGT2. The Council proposes full application of Regulations 1829/2003 and 1830/2003, which govern genetically modified food and feed, to NGT2 products.

4. Food products using NGT1 plants would no longer be classified as GM foods, should the legislation pass in one of the three versions currently under discussion. However, it appears (based on the Council's position) that NGT2 plants will still fall under the GM food classification.

7. Concluding remarks

1. At present, the likelihood that EU Member States will reach an agreement on a dedicated ad hoc regulatory framework for cultivated meat and cell-based food (CM/CSF) products appears highly unlikely. The current legislation on novel foods—particularly its applicability to cell-based products—provides a sufficiently comprehensive legal basis for accommodating the applications currently under review. It is worth noting that, to date, only one cell-based product of plant origin has been authorised, and only two applications involving products of animal origin are under evaluation. Under these circumstances, there is no compelling justification at this stage for developing a separate regulatory framework or for creating additional subcategories within the novel food regulation.

2. Nevertheless, areas of regulatory uncertainty remain, particularly concerning the life cycle assessment (LCA) of certain production models. This is especially relevant for on-farm production systems, where food safety risk assessment may need to be complemented by a more targeted

[147] Escajedo San-Epifanio L, Filibi I, Lasa Lopez A, Puigdomènech P and Uncetabarrenechea Larrabe J (2023) Possible EU futures for CRISPR-edited plants: Little margin for optimism?. Front. Plant Sci. 14:1141455. doi: 10.3389/fpls.2023.1141455; Escajedo San-Epifanio, L., I. Filibi, J. Uncetabarrenechea, and A. Lasa-López (2024) Genome editing in Plants and EU provisions for coexistence with organic farming, in Back to the future: Sustainable innovations foe ethical food production and consumption, Brill, 135-141.

evaluation of veterinary risks, which are not fully addressed under the existing novel food procedures.

3. Additionally, while the 2024 updated EFSA guidance on novel foods provides a detailed technical framework for the scientific assessment of CM/CSF products, the subsequent phase of risk management remains open to interpretation. There is currently limited clarity on how the European Commission and Member States will exercise their respective competences regarding risk management decisions, including the possibility of introducing specific conditions or restrictions at either the EU or national level.

4. In conclusion, the EU regulatory framework for CM/CSF offers a clear and technically robust structure for risk assessment and the allocation of institutional responsibilities. However, important uncertainties persist regarding regulatory decision-making and the practical implementation of such decisions in the authorisation and market placement of these innovative products.

5. As the number of applications increases and production models diversify, it may become necessary to revisit certain aspects of the framework to ensure consistency, legal certainty, and public trust.

Annexes

Annex 1 – EFSA's structure[148]

ANNEX 2 – EFSA Scientific Panels

The European Food Safety Authority (EFSA) has several specialized scientific panels that address different areas of food safety. The main panels are:

a) Panel on Food Additives and Flavourings (EFSA FAF Panel) (formerly ANS Panel): Assesses the safety of food additives, colorants, preservatives, sweeteners, flavourings, and materials intended to come into contact with food.

b) Panel on Contaminants in the Food Chain (EFSA CONTAM Panel): Evaluates chemical contaminants in the food chain, such as heavy metals, pesticides, mycotoxins, and other toxic substances.

c) Panel on Nutrition, Novel Foods and Food Allergens (EFSA NDA Panel): Focuses on the assessment of human nutrition, the safety of novel foods, food ingredients, and food allergens.

d) Panel on Animal Health and Welfare (EFSA AHAW Panel): Assesses risks to animal health and animal welfare in the context of food safety, including zoonoses (diseases transmissible from animals to humans).

e) Panel on Plant Protection Products and their Residues (EFSA PPR Panel): Evaluates the risks associated with the use of pesticides in agriculture, considering their safety in food and environmental impact.

f) Panel on Genetically Modified Organisms (EFSA GMO Panel): Responsible for assessing the safety of genetically modified organisms (GMOs) and their derived products, as well as the environmental impact of such technologies.

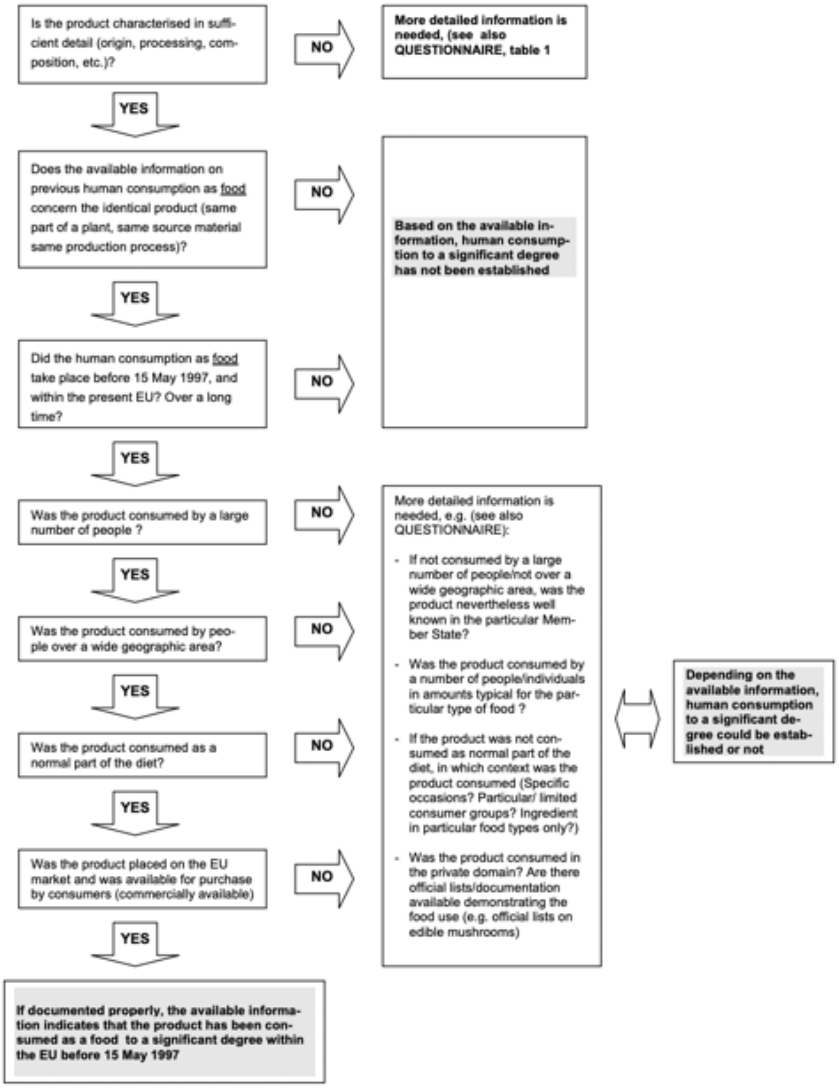
g) Panel on Additives and Products or Substances used in Animal Feed (EFSA FEEDAP Panel): Examines the safety of feed and feed additives, and their potential effects on both animal and human health.

h) Panel on Emerging Risks and New Technologies (EFSA ERNT Panel): Assesses risks associated with emerging technologies and novel products that may impact public health or the environment.

These panels operate independently and are composed of experts from diverse scientific disciplines. Their work aims to provide objective, evidence-based advice to regulatory authorities and policymakers in the European Union.

[148] Imagen obtenida de: Marco Silano, Vittorio Silano, "The fifth anniversary of the European Food Safety Authority (EFSA): Mission, organization, functioning and main results", Fitoterapia, Volume 79, Issue 3, 2008: 149-160, https://doi.org/10.1016/j.fitote.2007.11.018.

Annex 3 - Decision tree[149] (Information and Guidance Document "Human Consumption to a Significant Degree")



[149] Information and Guidance Document "Human Consumption to a Significant Degree", ttps://food.ec.europa.eu/document/download/7d4bba03-4e60-4a2a-be97-76db96d47974_en?filename=novel-food_guidance_human-consumption_en.pdf

FEASTS
Fostering European Cellular Agriculture for Sustainable Transition Solutions
Funded by the European Union

Annex 4 – Categories of Novel Foods under repealed Regulation (EC) No. 258/97.

* This Regulation remained in force until 1 January 2018, when it was repealed and replaced by Regulation (EU) 2015/2283 on novel foods.

According to Article 3(2) of Regulation (EC) No. 258/97, a "novel food" is defined as any food that has not been consumed to a significant degree within the Community before 15 May 1997 and that falls into one of the following categories:

(a) Foods based on genetically modified organisms or products derived from them.

(b) Foods whose composition or manufacturing process has been substantially modified.

(c) Foods that contain or result from new substances not previously used within the Community.

(d) Foods produced from new food sources or from raw materials that have not been significantly used before.

(e) Foods based on new combinations of ingredients or food substances not previously used.

(f) Foods produced by means of a new production process that had not been significantly used within the Community prior to 1997.

(g) Foods with characteristics that had not previously been used, or whose nutritional or sensory composition has been altered.

(h) Foods containing new protein sources, such as proteins obtained from new raw material sources or from processes not previously used.

(i) Food products whose function in the human diet is new, or which introduce new forms of food consumption.

(j) Foods whose ingredients or components have been specifically modified in a way that affects how the product interacts with human health.

Annex 5 – Art. 3(2)(a) Regulation (EU) 2015/2283, novel food categories:

A **"novel food"** is defined as any food that had not been used for human consumption to a significant degree within the Union before 15 May 1997, irrespective of the dates of accession of Member States, and that falls under at least one of the following categories:

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

(b) Food consisting of, isolated from, or produced from microorganisms, fungi or algae;

(c) Food consisting of, isolated from, or produced from material of mineral origin;

(d) Food consisting of, isolated from, or produced from plants or parts of plants, except when the food has a history of safe food use within the Union and is derived from a plant or a variety of the same species obtained through:
– traditional propagating practices used for food production within the Union before 15 May 1997; or
– non-traditional propagating practices not used for food production in the Union before that date, provided that those practices do not result in significant changes in the composition or structure of the food affecting its nutritional value, metabolism, or levels of undesirable substances;

(e) Food consisting of, isolated from, or produced from animals or their parts, except for animals obtained through traditional breeding practices used for food production in the Union before 15 May 1997, and provided that foods derived from those animals have a history of safe food use within the Union;

(f) Food consisting of, isolated from, or produced from cell cultures or tissue cultures derived from animals, plants, microorganisms, fungi, or algae;

(g) Food resulting from a production process not previously used for food production within the Union before 15 May 1997, where that process results in significant changes in the composition or structure of a food, affecting its nutritional value, metabolism, or levels of undesirable substances;

(h) Food consisting of engineered nanomaterials, as defined in Article 3(2)(f) of Regulation (EU) 2015/2283;

(i) 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); or
– the substances contain or consist of engineered nanomaterials;

(j) Food used exclusively in food supplements within the Union before 15 May 1997, where it is now intended for use in foods other than food supplements as defined in Article 2(a) of Directive 2002/46/EC.

FEASTS

Fostering European Cellular Agriculture
for Sustainable Transition Solutions

Funded by
the European Union