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Novel foods in the European Union: Scientific requirements and challenges of the risk assessment process by the European Food Safety Authority

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ABSTRACT

The European Food Safety Authority (EFSA) has been involved in the risk assessment of novel foods since 2003. The implementation of the current novel food regulation in 2018 rendered EFSA the sole entity of the European Union responsible for such safety evaluations. The risk assessment is based on the data submitted by applicants in line with the scientific requirements described in the respective EFSA guidance document.

The present work aims to elaborate on the rationale behind the scientific questions raised during the risk assessment of novel foods, with a focus on complex mixtures and whole foods. Novel foods received by EFSA in 2003–2019 were screened and clustered by nature and complexity. The requests for additional or supplementary information raised by EFSA during all risk assessments were analyzed for identifying reoccurring issues.

In brief, it is shown that applications concern mainly novel foods derived from plants, microorganisms, fungi, algae, and animals. A plethora of requests relates to the production process, the compositional characterization of the novel food, and the evaluation of the product's toxicological profile. Recurring issues related to specific novel food categories were noted.

The heterogeneous nature and the variable complexity of novel foods emphasize the challenge to tailor aspects of the evaluation approach to the characteristics of each individual product. Importantly, the scientific requirements for novel food applications set by EFSA are interrelated, and only a rigorous and cross-cutting approach adopted by the applicants when preparing the respective application dossiers can lead to scientifically sound dossiers. This is the first time that an in-depth analysis of the experience gained by EFSA in the risk assessment of novel foods and of the reasoning behind the most frequent scientific requests by EFSA to applicants is made.

1. Introduction

With innovation and globalization, an increasing number of foodstuffs tries entering the European Union (EU) market, aspiring to meet the evolving interest of consumers towards new products, new dietary alternatives, and environmentally sustainable choices. Foodstuff produced with new technologies, derived from new sources, new substances, and traditional foods consumed in non- EU countries, not consumed to a significant degree within the EU before 15 May 1997, are considered as "novel foods" in Regulation (EU) 2015/2283 (2015). This regulation, into force since 1 January 2018, requires food business operators to seek premarket authorization by the European Commission (EC) for their novel foodstuffs.

For almost 20 years, the European Food Safety Authority (EFSA) has

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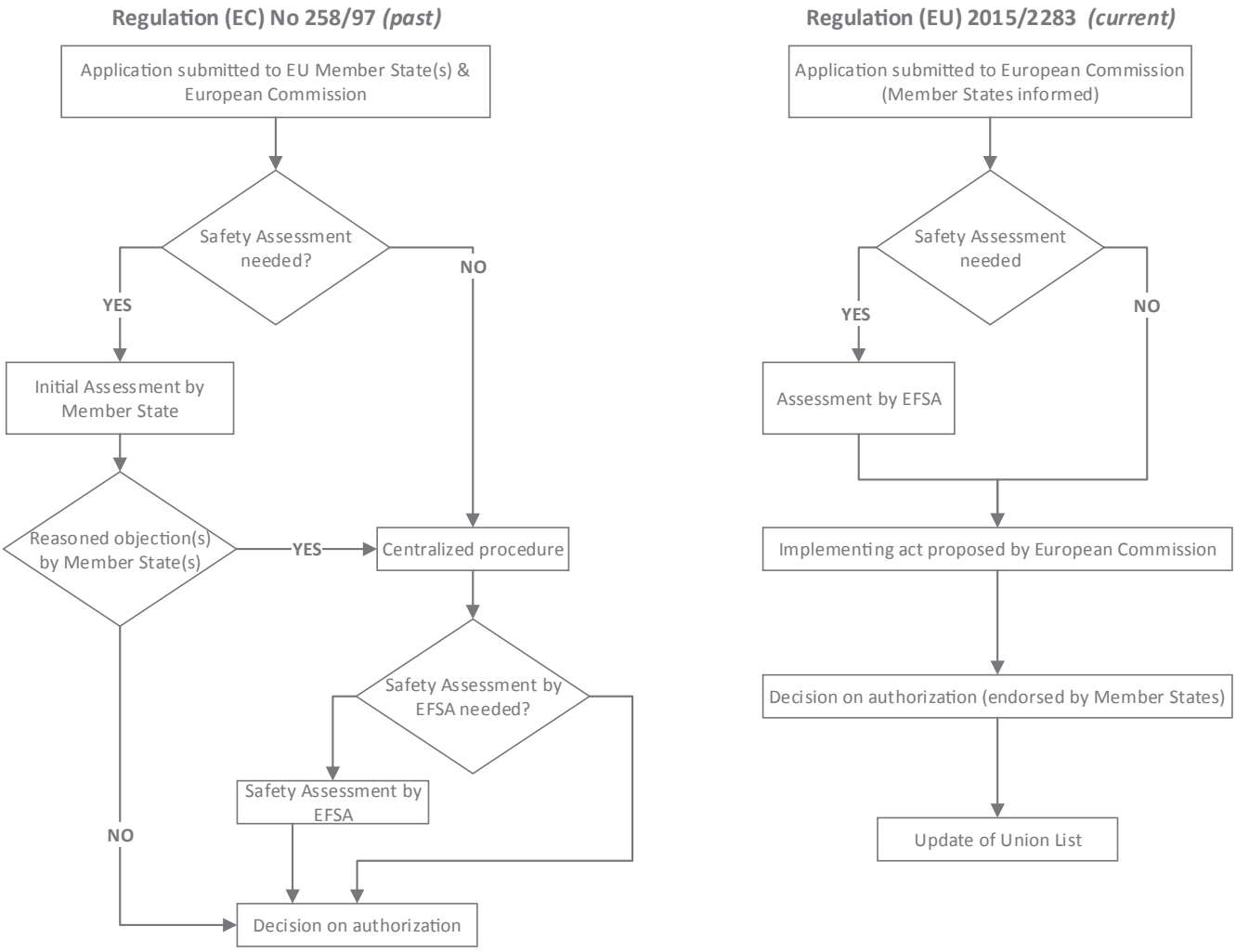

Fig. 1. Main steps of the past and current EU novel food regulations.

built up experience in the field of novel foods, combining interdisciplinary knowledge of e.g. chemistry, microbiology, food technology, toxicology, and human nutrition under a common assessment methodology. EFSA's role is identifying and characterizing any hazards linked to the consumption of novel foods, and assessing the risk associated to their consumption under the proposed conditions of use. Since it became operational in 2003, EFSA has performed risk assessment of novel foods when EU Member States raised concerns on their safety. In 2018, the implementation of Regulation (EU) 2015/2283 [repealing and replacing Regulation (EC) No 258/97)] shifted the role of EFSA, which became the sole EU entity responsible for carrying out such risk assessments. A comparison between the main steps of the two regulations is provided (Fig. 1) to facilitate the reader. Analysis of the two regulatory frameworks has been reported elsewhere (de Boer & Bast, 2018; Pisanello & Caruso, 2018; Zarbà et al., 2020) and is out of scope of the present work.

The main scientific requirements for a novel food application are outlined in the EFSA's "Guidance on the preparation and presentation of an application for authorization of a novel food in the context of Regulation (EU) 2015/2283" (EFSA NDA Panel, 2016a). It should be acknowledged that the guidance document aims both to be self-explanatory and to provide flexibility to the applicants when designing their research strategy, given the diversity of novel foods. During the risk assessment under the current or past novel food regulatory frameworks, EFSA has requested additional information to the applicants, for validating or supporting the submitted data, or for clarifying scientific issues as per the administrative guidance for the processing of applications for regulated products (EFSA, 2019).

The main objectives of the current work are to identify the scientific issues most commonly addressed during risk assessment, and to stress the importance of certain scientific requirements linked to the nature of the novel food and/or its source by providing practical examples from published outputs. All novel foods received by EFSA have been clustered by their source, in order to draw further attention to the highly heterogeneous profile of these regulated products. Novel foods have been grouped into single substances, simple mixtures, complex mixtures, and whole foods, as per the respective definitions provided by EFSA's novel food Guidance document (EFSA NDA Panel, 2016a). Since the evaluation process of single substances and simple mixtures has been well established in other cross-cutting areas such as those of food additives (EFSA ANS Panel, 2012), nutrient sources (EFSA ANS Panel, 2018) and feed additives (EFSA FEEDAP Panel, 2019), the current work focuses on aspects related to novel complex mixtures and whole foods. For identifying the scientific issues most commonly addressed, all requests raised by EFSA to applicants during the evaluation process were screened, for all novel food applications received by EFSA until the end of 2019. Elaboration on the rationale behind the most frequent requests and correlation of them to specific novel food categories thought practical examples will help to facilitate the use of the existing EFSA guidance documents.

All novel food applications received by EFSA, and all the published scientific outputs on the risk assessment of these products are publicly

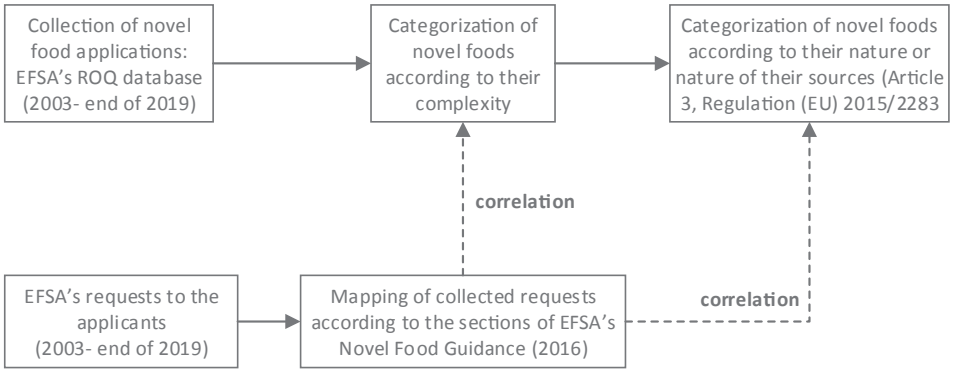

Fig. 2. Flowchart of the data collection methodology.

available via the EFSA Register of Questions (ROQ) database (EFSA, 2020a) and EFSA's website (2020b), respectively. To the knowledge of the authors, this is the first in-depth analysis of the experience built up in the novel food risk assessment by EFSA. The results of this work are expected to further inform stakeholders including consumers, academia, regulatory agencies and industry on EFSA's risk assessment process, and to increase awareness of applicants towards specific data requirements for future dossiers. The experience gained from analyzing the reoccurring issues contributes to identify improvements in the tailored applicability of the existing EFSA guidance documents.

2. Materials & methods

All novel food applications received by EFSA from January 2003 till the end of 2019 were retrieved from the EFSA ROQ database (EFSA, 2020a). Thus, only applications assessed by EFSA were considered (ongoing and completed assessments, including applications withdrawn by applicants).

Following a tiered approach (Fig. 2), all novel foods were initially categorized as single substances, simple mixtures, complex mixtures or whole foods. Mixtures are simple when all their components can be chemically characterized, contrary to complex mixtures (e.g. extracts, protein hydrolysates) and whole foods (e.g. novel seeds or fruits) (EFSA NDA Panel, 2016a). Subsequently, the novel foods were grouped according to their nature or the nature of their sources, following the most recent classification described in Regulation (EU) 2015/2283(2015), which covers the categories of Regulation (EC) No 258/97 (1997) (Fig. 4).

All requests for additional or supplementary information sent to the applicants during the evaluation process were screened. Requests were clustered according to the sections outlined in EFSA's guidance document (i.e. identity of the novel food, production process, compositional data, specifications, proposed uses and use levels and anticipated intake of the novel food, history of use of the novel food and/or of its source, ADME, nutritional information, toxicological information and allergenicity) (EFSA NDA Panel, 2016a).

3. Results

The maximum yearly number of novel food applications received by EFSA between 2003 and 2017 was 10 (in 2016), with an average of 5 applications per year (Fig. 3). In 2018, with the implementation of the new regulation, it peaked to 40 in 2018 and 39 in 2019.

Complex mixtures represent a considerable proportion of the novel foods assessed by EFSA, irrespective of the regulation in place (Fig. 4). The proportion of novel whole foods has increased since the implementation of the new regulation, whereas the proportion of novel single substances has decreased.

Fig. 5 reports the categorization of novel foods by their nature or the nature of their sources. In the current novel food regulation, new food categories have been added to the already existing ones. These new categories are foods consisting of engineered nanomaterials, derived from material of mineral origin, derived from cell culture or tissue cultures, or used exclusively as food supplements in EU before 15th of May 1997, and vitamins, minerals and other substances falling under the remit of the new regulation. The current regulation does not apply any more to genetically modified foodstuffs [Regulation (EC) No 1829/2003]. The categories more represented in 2018–2019 include products derived from plants, animals, microorganisms, fungi or algae. Notably, in 2019, EFSA received 9 novel foods with modified molecular structure (mainly oligosaccharides). So far, no application on novel foods consisting of engineered nanomaterials has been received.

In Fig. 6, the clustering of requests by EFSA during evaluation shows that many relate to the production process and the compositional characterization. Regarding the toxicological profile of the novel food, a plethora of requests are related to the inadequate or lack of implementation of the tiered approach proposed by EFSA or to the representativeness of the testing material used in the toxicological studies. Requests on the intake estimates concern the methodology applied and ambiguous information regarding the intended uses. Several other requests relate to the specifications of the product, the history of use of the novel food and/or its source, human studies and allergenicity testing. It should be highlighted, that Fig. 6 includes only information on the requests sent to applicants by EFSA and not by Member States under the previous regulatory framework as, to the knowledge of the authors, a database of all Member States' comments is unavailable.

4. Discussion

The implementation of the new novel food regulation in 2018 led to a significant increase in the numbers of novel food applications entering EFSA's risk assessment process (Fig. 3). The centralization of the procedure can be assumed as one of the main reasons for this change; since the new regulation came into force, all new novel food applications are assessed solely by EFSA, whereas in the past the assessment was also done by the competent authorities of EU Member States.

The present analysis of novel food applications received by EFSA from 2003 to 2017 (81) is a partial depiction of those for which a premarket authorization was requested during this period (information on applications assessed by the EU Member States not available). The number of novel foods authorized in the EU from 2003 to the end of 2017, as presented in the "Union list of novel foods" established by the Commission Implementing Regulation (EU) (2017)/2470, (2017), provides a better overview of the situation. Under the past regulation (more than 15 years), 125 novel foods were authorized (safety assessed by the Member States or by EFSA). Within 2 years since the new regulation came into force, EFSA has received around 80 new novel food applications. The provisions of the new regulation were expected to increase the interest of the industry in the novel food area, since they provide harmonized legal and technical procedures to the applicants,

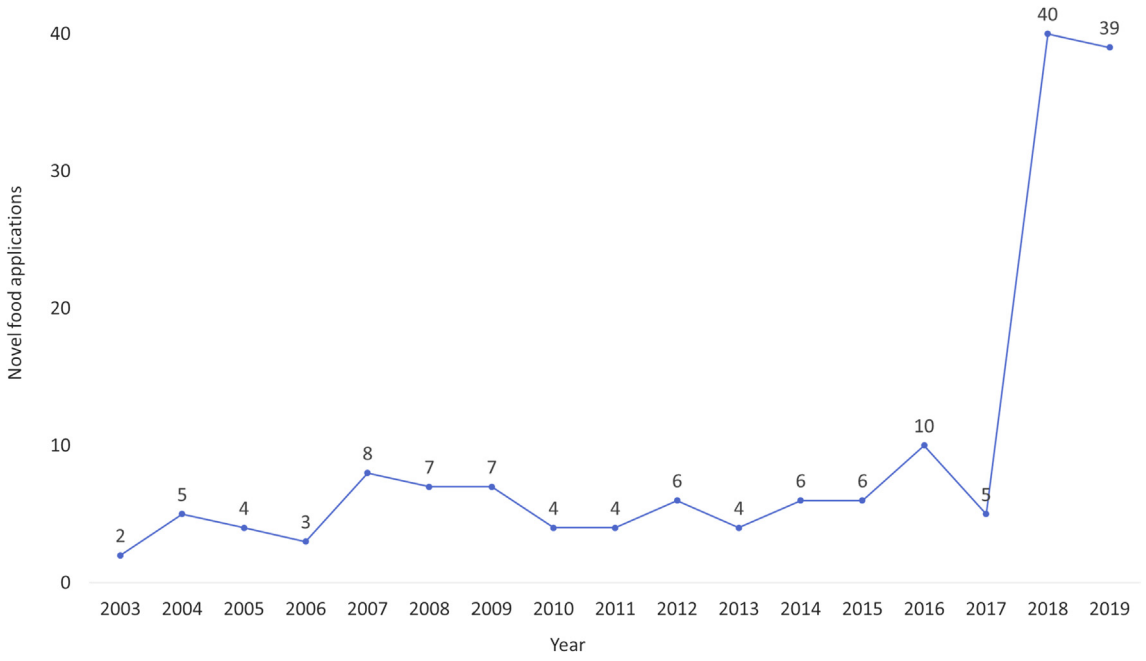

Fig. 3. Novel food applications that entered EFSA's risk assessment, from January 2003 up to December 2019.
Source: EFSA ROQ database.

and reduce bureaucracy. The possibility for applicants to request data confidentiality, and to be granted five-years EU market exclusivity for their product could be another attractive element in the area of novel foods (Zarbà et al., 2020).

The categorization of novel foods by their nature or the nature of their sources (Fig. 5) shows that botanical preparations, food of animal origin (mainly insects and products thereof) and foods derived from microorganisms, fungi or algae are among the main areas of interest. Such results are in line with the growing interest of consumers, policy makers and industry towards new food sources and more environmentally sustainable dietary options (Aiking & de Boer, 2018; Fasolin et al., 2019).

In the following sections, a thorough discussion on the issues encountered during the risk assessment of novel foods is done. Practical examples from the screening of novel food applications are given, aiming to explain in depth the necessity of scientific requests for the risk assessment of specific products or food categories. Particular focus is given to novel complex mixtures or whole foods, since the classical risk assessment approach cannot be always readily implemented. The purpose of this work is not to provide an update of the scientific literature in support of the guidance document, but rather to increase the awareness of stakeholders about the scientific requirements in the risk assessment of novel foods by EFSA.

4.1. Production process

The production process can significantly impact the composition and, consequently, the safety of a novel food, and should be precisely described. However, details on production conditions are often not initially provided by the applicants, triggering requests for clarifications.

For whole foods, impact of the production process on safety should be addressed by thorough chemical and physicochemical characterization of the product. Thermal treatments (e.g. blanching, pasteurization, sterilization, roasting) are commonly used to ensure microbial stability of foods and may contribute to reduce the presence of antinutrients or toxic components. Also, thermal treatment practices may result in the formation of process contaminants (e.g. acrylamide).

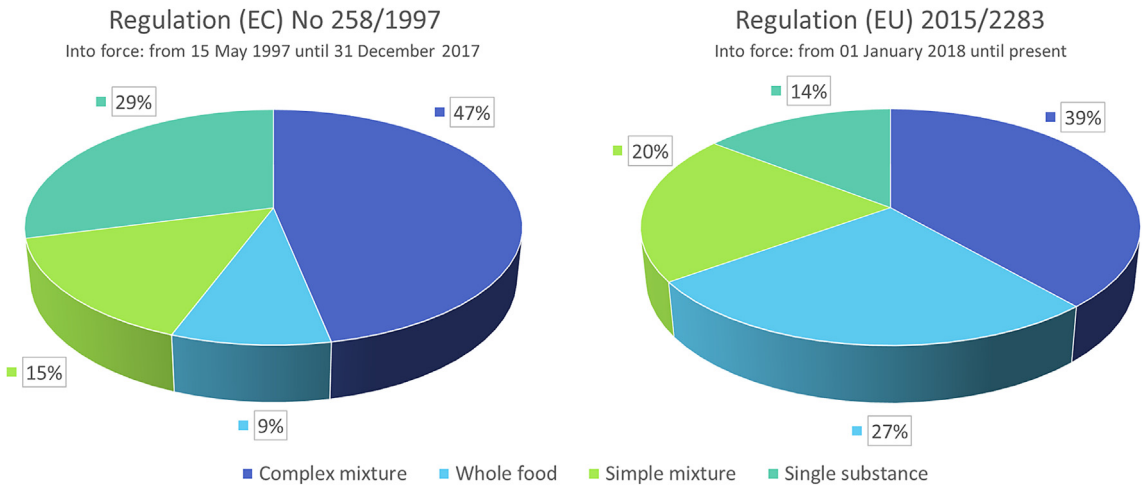

Fig. 4. The type of novel foods that entered EFSA's risk assessment (% of the novel food applications).

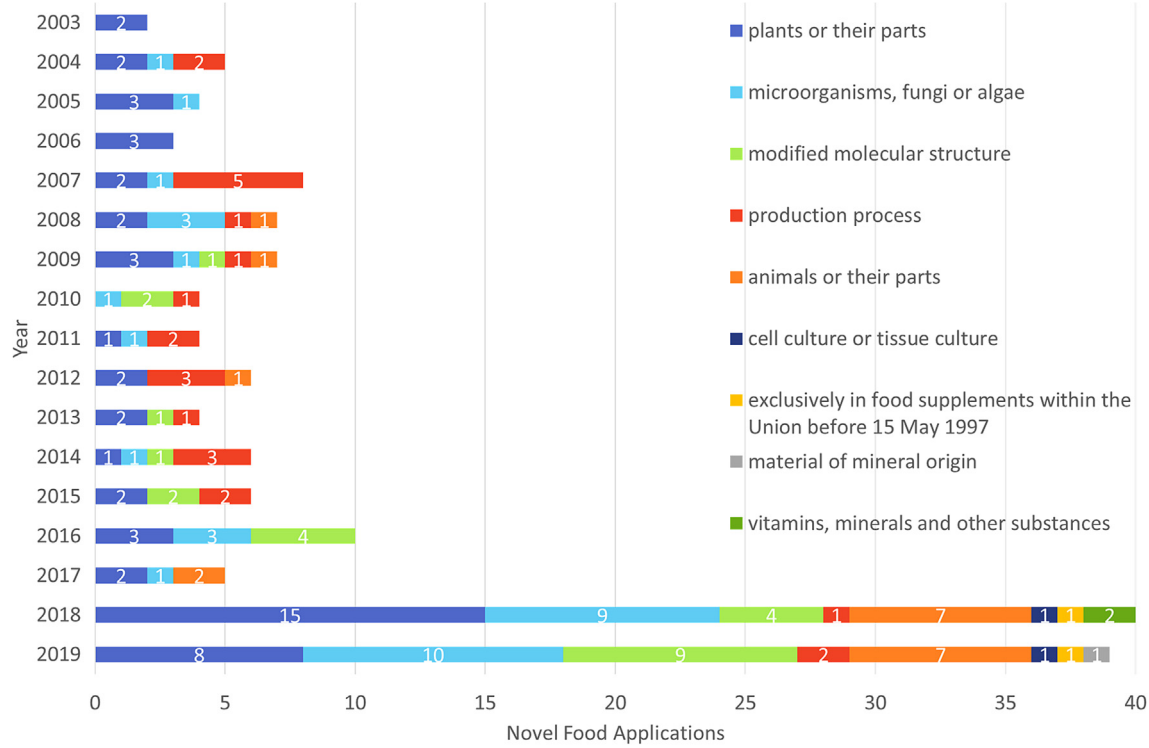

Fig. 5. The nature of novel foods that entered EFSA's risk assessment.

Moreover, extraction techniques (e.g. solvent extraction, acidic/alkaline treatment) can substantially affect the composition of the extract, either by selectively separating certain components of the initial material, as in herbal extracts (EFSA NDA Panel, 2016b) or by degrading chemically labile compounds.

Technological and scientific advances in food production may provide specific desirable properties to foodstuff and ensure a standardized production. Nevertheless, possible undesired effects of such practices on the product should be addressed. For example, the application of UV-irradiation to cow's milk to enhance its vitamin D_3 content triggered questions regarding the possible impact of the process on riboflavin and vitamin B_{12} contents of the milk (EFSA NDA Panel, 2016c). EFSA has also requested information on the production yield, i.e. the resulting amount of a novel food from its source expressed in weight, such as for fermented black beans extract (EFSA NDA Panel, 2011a), cranberry extract (EFSA NDA Panel, 2017a), sardine peptides (EFSA NDA Panel 2010a), and UV-treated mushroom powder (EFSA NDA Panel, 2020). EFSA considered the production yield as supportive information where the estimated exposure to components in the novel food did not exceed the exposure to these components from the dietary consumption of the presumed safe source (black beans, cranberry juice, sardines, and mushrooms, respectively).

4.2. Compositional data and specifications

Chemical, physicochemical and microbiological data provide crucial information both for the preparation of the dossier by applicants, and for the risk assessment. Compositional characterization of novel foods triggers the largest variety of requests for information to applicants (Fig. 6), particularly for complex mixtures and whole foods. Compositional data may be collected by the applicants from experimental analyses on the product, and further substantiated by data from the scientific literature (EFSA NDA Panel, 2016a), following the methodology developed by EFSA for literature search (EFSA, 2010). Either scientific literature is usually overlooked by applicants or the extrapolation of the retrieved data to the novel food is often challenging due to its nature and quality. Applicants should ensure the liability and robustness of the experimental compositional data collected, by considering the principles of representative sampling, and by implementing analytical methods with suitable limits of detection and quantification.

Complex mixtures and whole foods may comprise hundreds, or even thousands of substances, making thus their comprehensive analysis impossible. Applicants have to provide qualitative and quantitative data on the main constituents and, in particular for whole foods, perform proximate analyses. The percentage of unidentified substances in the novel food needs to be reduced as much as possible. When the product is characterized mainly by a specific class of components (e.g. phenolic compounds, peptides, fatty acids), a comprehensive characterization of this fraction should be provided. For example, for the risk assessment of a shrimp peptide concentrate, its peptides needed to be thoroughly analyzed (e.g. *de novo* sequencing, molecular weight) to characterize the product (EFSA NDA Panel, 2018a).

Qualitative and quantitative analytical data on inherent substances hazardous to human health should also be provided. For example, applicants should investigate in the novel food the presence and occurrence levels of endogenously produced repellent compounds by insects in insect-derived foodstuffs (EFSA Scientific Committee, 2015) or of secondary metabolites such as pyrrolizidine alkaloids in plant-derived foodstuffs (EFSA CONTAM Panel, 2011). The relationship between the analytical results of these compounds and possible adverse health effects should be critically appraised.

Besides the chemical and microbiological characterization of a foodstuff at the end of its production, data on its stability under the proposed storage conditions, covering at least the intended shelf life, should be provided. According to the nature of the novel food, the experimental requirements may differ. For example, regarding novel foods with high fat content such as the coriander seed oil (EFSA NDA Panel, 2013a) and the Antarctic krill oil (EFSA NDA Panel, 2009a), studies on the lipid oxidation were considered essential to assess the risk of formation of hazardous compounds during storage due to fat deterioration. When the novel food is prone to microbiological deterioration, such as the Noni fruit puree and concentrate (EFSA NDA

Fig. 6. Mapping of requests for additional or supplementary information sent by EFSA.

Panel, 2009b), its microbiological stability during the shelf life must be tested. When the novel food is expected to be used as ingredient added in foodstuff, its stability in the intended food matrices should be assessed, considering possible matrix effects and impact of further processing. For example, when insects (EFSA Scientific Committee, 2015) or novel seeds (EFSA NDA Panel, 2019a) are used as ingredients in the production of e.g. bakery products, the presence of process contaminants such as acrylamide, and further growth of thermostable bacteria, should be investigated.

Finally, the analytical data on the composition and stability of the novel food are key to establish the specification parameters. Specifications can be considered as the scientific and legal identity card of the novel food, that characterizes and substantiates its identity, defines the respective limits of compositional parameters, particularly those of safety relevance, and aims to ensure a consistent production process. However, often, specification parameters initially suggested by applicants did not sufficiently address the identity and safety of the product or exceeded existing legal limits, and thus needed amendments.

4.3. History of use of the novel food and/or its source

The definition of a "novel" food, i.e. no significant human consumption within the EU before 15 May 1997, implies that risk managers consider that foods significantly consumed within the EU prior 1997 are safe. The historical consumption of a novel food or its source should be documented through a comprehensive literature search and an overview on existing data provided by the applicants. Whilst data on the history of use of the novel food or its source cannot generally offset the need for toxicological studies on the product, they can still contribute to the risk assessment. History of use could be an important asset, particularly for whole foods on which repeated-dose toxicological studies may be challenging. For example, in the assessment of the cranberry extract powder, the history of consumption of the source (cranberry juice) within and outside the EU, alongside the thorough compositional analysis and human studies, allowed EFSA to conclude that the novel food does not raise any safety concerns under the proposed conditions of use (EFSA NDA Panel, 2017a). For oligosaccharides added in infant and follow-on formulae, EFSA considered their natural occurrence levels in human milk (EFSA NDA Panel, 2019b, EFSA NDA Panel, 2019d).

4.4. Proposes uses, use levels and anticipated intake

Requests for information mainly relate to the description of the intended uses, the estimation of the intake and the target population. Novel foods can be either used as ingredients in foodstuff, consumed as such (e.g. fruit pulp, seeds) or consumed as food supplements (Directive 2002/46/EC). Estimation of the chronic intake (average and high percentiles) is generally considered in the risk assessment, as well as acute intake when acute effects may be of concern. Different tools are available to applicants (e.g. EFSA Food Additive Intake Model). To harmonize intake estimation, EFSA is using the data available in its Comprehensive European Food Consumption Database (EFSA, 2011). When novel foods are to be consumed as such (e.g. whole foods), anticipating the consumption can be challenging but could be done by

identifying a comparable product already on the EU market which the novel food can potentially replace, as for the "novel chewing gum base" (EFSA NDA Panel, 2011b). For novel foods used as food supplements, e.g. phenylcapsaicin (EFSA NDA Panel, 2019c), the intake is directly derived from the maximum daily use levels proposed by the applicant. When constituent(s) of the novel food come also from other sources, their combined intake is considered by aggregating all the intended uses proposed by the applicant (ingredient, whole food, and food supplement) and including the intake from natural sources (i.e. from the background diet) and from any other food sources (e.g. food additives), as for lycopene derived from the fungus *Blakeslea trispora* (EFSA NDA Panel, 2005). If the novel food is used as an ingredient or is a whole food, the target population cannot be restricted to a specific group, but all age groups of the general population (from infants to adults) must be considered by applicants (Commission Implementing Regulation (EU) (2017)/2469, (2017)). Specific population groups can be targeted in cases of food supplements and foods for special medical purposes. EFSA has developed dedicated guidelines for foods for infants below 16 weeks of age (EFSA Scientific Committee, 2017), to be used to estimate the intake of novel foods intended to be added to those products.

4.5. Absorption, distribution, metabolism and excretion (ADME)

The risk assessment requires an evaluation of the level of absorption of the novel food itself or its breakdown products. If there is evidence for no or negligible absorption, further toxicological studies may not be needed. The complexity of the studies to investigate the ADME characteristics of the novel food depends on its chemical and physicochemical characteristics. *In silico, in vitro,* and *in vivo* studies can be considered for investigating the kinetic profile of specific substances, following the tiered approach proposed by EFSA. It comprises three steps: computational considerations, evaluation of physicochemical properties and subsequent experimental tests (EFSA NDA Panel, 2016a; EFSA ANS Panel, 2012; EFSA Scientific committee, 2018). In the case of whole foods and complex mixtures, characterization of the ADME of their individual toxicologically and nutritionally relevant constituents (e.g. secondary metabolites in botanical extracts) are needed, as conventional toxicokinetic studies may not be feasible. A common limitation in dossiers is the lack of rationale for extrapolating results from *in silico* or *in vitro* studies to the *in vivo* situation, limiting their value for the assessment. Furthermore, considering the nature of complex mixtures and whole foods, one of the main challenges for applicants is the proper selection of specific compounds to be investigated.

4.6. Nutritional information

The purpose of the nutritional assessment is to demonstrate that the novel food is not nutritionally disadvantageous under the proposed conditions of use (EFSA NDA Panel, 2016a). Nutritional assessment covers both nutrient and antinutrient occurrence and bioavailability, and considers the effect of the production process, storage conditions and further processing prior consumption. The levels of nutrients and antinutrients are considered alongside the intake estimate (see Section 4.4) and the potential replacement by the novel food of another food in the diet. A novel food may be nutritionally disadvantageous for the consumers, if the tolerable upper intake levels (ULs) for nutrients are exceeded under the proposed use levels, or if its consumption may significantly impact the nutrient supply of consumers (EFSA NDA Panel, 2016a).

When ULs for specific nutrients exist (EFSA NDA Panel, 2018b), the risk of excess intake is characterized by comparing the values to the total intake of the nutrients, estimated from the consumption of the novel food and the usual intake from the background diet. This approach was applied for e.g. evaluating the risk of vitamin D_2 excess intake in the assessment of a UV-treated mushroom powder (EFSA NDA Panel, 2020). The highest vitamin D_2 estimated intakes were found to be below the ULs for all age groups of the target population. Also, EFSA concluded that the intake of iron through the addition of a novel ingredient composed of lactoferrin, an iron-binding glycoprotein, to infant formulae did not raise concerns regarding excess iron intake in infants, considering the low contribution expected from this novel ingredient to the total intake of iron (EFSA NDA Panel, 2012).

For novel foods expected to replace a relevant source of nutrients in the diet, the applicant should demonstrate that the substitution does not raise concern regarding the nutrient supply of consumers. For instance, the UV-irradiation of milk to increase its vitamin D content was found not to significantly impact the macro-and micronutrient composition of the milk (EFSA NDA Panel, 2016c). The substitution of conventional milk by the UV-treated milk was considered not to be nutritionally disadvantageous.

To address concerns regarding antinutritional compounds, their levels in the novel food can be compared with those in foods with a similar role in the diet, or with relevant health-based guidance values, when available (EFSA NDA Panel, 2016a). For example, the content of phytic acid in a novel rapeseed protein isolate was found to be similar to those in soybeans and thus, not a cause of concern in the context of the assessment (EFSA NDA Panel, 2013b).

4.7. Toxicological information

Collecting toxicological information is a multifaced process, in which applicants have to carefully consider e.g. the composition of the novel food, the intended uses and use levels, studies available from literature, and the toxicity testing strategy proposed by EFSA (EFSA NDA Panel, 2016a).

The toxicity testing strategy presents a tiered approach in order to limit the use of animals and resources (EFSA ANS Panel, 2012; EFSA NDA Panel, 2016a, EFSA Scientific Committee, 2018). *In silico* data, *in vitro,* and *in vivo* toxicity studies may provide insight on kinetics (see Section 4.5), genotoxicity, sub-chronic/chronic toxicity, and reproductive and developmental toxicity, as appropriate. The need for *in vivo* studies should be decided according to the characteristics of the novel food or information already available (e.g. *in silico* data, similarity with other substances in a "read-across" approach). In the case of mushroom powder with enhanced vitamin D_2 levels, EFSA considered studies from literature as sufficient to address toxicological aspects (EFSA NDA Panel, 2020). For the risk assessment of UV-treated bread, EFSA considered that toxicological studies were unnecessary since occurrence levels of reaction products formed during the novel production process (UV-irradiation) were expected to be lower than those formed during the traditional baking process.

Studies shall be conducted following international guidelines (e.g. OECD) and Good Laboratory Practices. The set of studies generally required (tier 1) consists of two *in vitro* genotoxicity studies and a sub-chronic 90-day oral toxicity study that aims to identify possible adverse effects following repeated exposure of rodents to the novel food via gavage or the diet, over a prolonged period of time. Results of these studies, conducted by the applicant and/or found in the literature, may trigger the need for further testing following the respective EFSA guidance documents. Additional studies (tier 2 and 3) may address carcinogenicity, reproductive and developmental toxicity or specific endpoint(s) e.g. immunotoxicity, neurotoxicity or endocrine activity. Toxicity testing for novel foods to be consumed by infants below 16 weeks of age shall be aligned with the requirements provided in the EFSA's Guidance document on the risk assessment of substances present in such food (EFSA Scientific Committee, 2017).

The main reason triggering requests for additional toxicological information is that applicants do not consider the tiered approach described above, often without even providing any justifications. Overlooking the tiered approach has sometimes led applicants to even conduct toxicological studies unnecessary for the risk assessment. Additionally, toxicological studies were sometimes conducted with a

test material not representative of the novel food (Fig. 6). For whole foods, the above-mentioned testing strategy can be challenging, and case-by-case considerations should be made. With regard to the sub-chronic/chronic toxicity testing, difficulties may be encountered if the doses of the novel food needed to be administered to allow an acceptable margin of exposure (EFSA Scientific Committee, 2012) are so high that they cannot be fed or may cause nutritional imbalances to the animals. If the available body of evidence cannot rule out the need to perform such studies, specific guidance is provided (EFSA Scientific Committee, 2011a).

The evaluation of genotoxicity of a novel food is related to its characteristics and origin and follows the existing EFSA guidance and statements (EFSA Scientific Committee, 2011b, 2017; 2019). For novel foods which are mixtures, the genotoxicity assessment should follow the recent EFSA statement (EFSA Scientific Committee, 2019). In particular, the mixture should be chemically characterized as much as possible. If the mixture is "fully characterized" and one or more substances are genotoxic, the mixture raises concern for genotoxicity. If the mixture contains uncharacterized components (e.g. oils or botanical preparations), experimental testing of the unidentified fraction should be considered firstly. If not feasible, the whole mixture should be tested, and the testing limitations highlighted. Whether the novel food is a single substance or a mixture, the testing strategy should follow the stepwise approach outlined in the respective EFSA guidance document (EFSA Scientific Committee, 2011a,b). The expected approach consists of an *in vitro* test battery that in principle includes a bacterial reverse mutation test and an *in vitro* micronucleus assay. If the *in vitro* testing provides clearly negative results, the novel food does not raise genotoxicity concerns. If at least one *in vitro* test is positive, an *in vivo* assay is required. The *in vivo* assay consists of either micronucleus assay, comet assay or the Transgenic Rodent Mutation assay, depending on the positive endpoints found in the *in vitro* battery. The most occurring requests for information in this area are related to deviations from the approach described above, e.g. performing *in vivo* genotoxicity studies without having already provided results from *in vitro* genotoxicity studies or submitting *in vivo* genotoxicity studies with novel foods for which the results of the *in vitro* genotoxicity testing were negative. Regarding mixtures, if the outcomes of the *in vivo* studies are negative, the possible limitations of the *in vivo* testing should be weighted in an uncertainty analysis, before concluding that there is no concern regarding genotoxicity. Whole foods per se can usually not be subject to the classical genotoxicity tests but testing of their fractions could be performed instead. For the mushroom powder with enhanced vitamin D_2, a whole food, EFSA considered that there was no need for the applicant to conduct genotoxicity studies, given the source, nature, and intended uses of the product (EFSA NDA Panel, 2020).

Human studies are not required by default for the risk assessment of novel foods (EFSA NDA Panel, 2016a). However, such studies, if available, should be submitted, when they contain information relevant for the risk assessment. Of note, the assessment of novel foods is limited to safety and the evaluation of potential beneficial physiological effect related to the consumption of the foods is out of the scope of the assessment. The evaluation of beneficial effects falls under the framework Regulation (EC) No 1924/2006 (2006) on nutrition and health claims made on food. Human studies may be needed e.g. to address adverse effects observed in toxicological studies. Similarly, when the novel food may exert pharmacodynamic effects, specific studies may be required to demonstrate that its proposed consumption and use do not raise safety concerns. Other studies potentially relevant include, e.g., immunotoxicity, hypersensitivity and food intolerance, neurotoxicity, endocrine activity and mode of action, which may need to be studied in humans. Regarding ADME, human studies can provide information on the (toxico-) kinetics of specific substances of the novel food or of the novel food per se, which would facilitate the assessment of the relevance of effects observed in animals for humans.

Although human trials conducted with the novel food may not be specifically designed to assess safety, they may contain data relevant for the risk assessment such as reports of physical examination, blood chemistry, hematology, urine analysis, blood pressure, body weight gain (in the case of infants) and organ function tests and/or monitoring of adverse reactions (e.g. headache, insomnia, rash, symptomatic neurological deterioration, or mortality). Information on safety related parameters was sometimes considered supportive evidence and contributed to demonstrate the safety of the novel food, e.g. synthetic *trans*-resveratrol, sardine peptides, bovine lactoferrin and shrimp peptides (EFSA NDA Panel, 2016d, 2010a, 2012; 2018a). Relevant human data may also be derived from the use of the novel food for medical purposes, as in the case of citicoline (EFSA NDA Panel, 2013c). Human data was sometimes pivotal to the risk assessment. For instance, a safe intake level for the use of betaine as a novel ingredient was derived from the safe intake levels observed in human studies (EFSA NDA Panel, 2017b). For the evaluation of conjugated linoleic acid (CLA) as a novel ingredient (EFSA NDA Panel, 2010b), potential adverse effects regarding insulin resistance and cardiovascular risk were identified in rodent studies. This animal model having limited value for such endpoints, human studies addressing the parameters affected in animals were needed to evaluate the safety of the novel food for human consumption.

To conclude, the diversity of novel foods is also reflected in the different use and weight of human studies in the risk assessment. The safe consumption of many novel foods could be established in the absence of human data. Occasionally, however, human studies were used as supportive evidence and, rarely, were even required for the risk assessment.

4.8. Allergenicity

The allergenicity assessment investigates the possible occurrence of immune-mediated adverse reactions in sensitive individuals upon the consumption of the novel food, under the proposed uses and use levels. Assessment of food intolerance (non-immune mediated) is not considered. The mechanisms underlying immune-mediated adverse reactions, such as allergy, are not completely understood, and therefore predicting whether proteins in the novel food have the potential to induce an adverse response is challenging.

As no single method on its own enables predicting the allergenic potential of a protein, a cumulative body of evidence, in a so-called weight-of-evidence approach, is in place to reduce uncertainty and improve the reliability of predictions (Codex Alimentarius, 2009; EFSA NDA Panel, 2016a; EFSA GMO Panel, 2017). Nevertheless, these methods are designed for the assessment of individual proteins and are not easily applicable to complex mixtures and whole foods that may contain many different proteins. Furthermore, no threshold values applicable to allergens are currently available for risk assessment purposes (EFSA NDA Panel, 2014). In practice, the assessment of the allergenic potential of a novel food is often limited to its content of protein and to a comprehensive literature search regarding information available on sensitization and allergic reactions to the novel food proteins under question. For example, when the source of a novel food is a recognized allergenic food subject to mandatory labelling (listed in Annex II of Regulation (EU) No (1169)/2011, 2011), the product is considered potentially allergenic and mandatory labelling is applicable, e.g. fermented soybean extract, egg membrane hydrolysate, whey basic protein isolate (EFSA NDA Panel, 2016e, 2018c). When the novel food is not derived from the aforementioned regulated sources but contains proteins, the novel food's allergenic potential is framed in the context of the available information, e.g. rapeseed protein isolate, chia seeds (EFSA NDA Panel, 2013b; EFSA NDA Panel, 2019a). Triggering adverse allergic reactions can be considered highly unlikely to occur for novel foods with no detectable protein e.g. phenylcapsaicin (EFSA NDA Panel, 2019c).

To this end, there is a need to develop more robust approaches

appropriately designed for risk assessment purposes when testing the allergenic potential of novel proteins. In particular, efforts should be invested to develop stronger bioinformatic approaches, more refined *in vitro* protein digestion protocols and more predictive cell-based/*in vivo* approaches (Fernandez et al., 2019,2020; Verhoeckx et al., 2020).

5. Conclusions

The number of novel food applications assessed by EFSA has increased since the implementation of the new novel food regulation in 2018. The centralization of the process is one of the main reasons for increasing of EFSA's workload in the novel food area. The current legal framework harmonized at EU level, provisions enhancing fair competition, and the constantly changing societal needs can be considered as additional factors boosting the activity in this sector.

The data collected from the screening of all novel food applications received by EFSA, and the clustering and critical appraisal of the requests sent by EFSA to applicants showcase that requests for additional information mainly occur due to the unjustifiable incompliance of the applicants' strategy with the recommended EFSA approach. Indubitably, the guidance document needs to permit some flexibility to applicants when preparing an application, considering the diversity of novel foods.

Novel food applications comprise numerous complex mixtures and whole foods. Because of their heterogeneity, experience has shown that there is no one-size-fits-all risk assessment approach for novel foods. Still, common principles must apply as described in the respective EFSA Guidance document to ensure a harmonized and transparent assessment of applications. While the toxicological assessment of complex mixtures can follow the same principles as the general tiered approach applied in other regulated areas, case-by-case approaches appear more appropriate for the assessment of whole foods. Importantly, EFSA proposed a general approach but deviations from it can be accepted if scientifically justified.

The experience gained from the reoccurring issues analyzed in this work is expected to further inform consumers, academia, regulatory agencies, and industry on EFSA's risk assessment process and increase awareness of applicants toward specific data requirements for future applications.

Credit Author Statement

All authors have equally contributed to the work.

Disclaimer

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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