



Grey Area Novel Foods: An Investigation into Criteria with Clear Boundaries

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Author's contribution

Author HV initiated and supervised the project. Authors RVDB, SI, KDM, EP, SSB and HVDV are MSc students at Wageningen University, who performed the research and wrote the initial project report. Author HVK did early development work. Author CS performed additional research. Author BVDM supervised students from the Wageningen facility and contributed to the legal aspects. Authors CS, HVK, HVL, BVDM and HV wrote the paper on the basis of the work performed by the students.

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ABSTRACT

In the European Union novel foods are defined by the Novel Foods Regulation as food products and food ingredients that have not been consumed to a significant degree in the European Union before May 1997. However, there are new foods for some reason not considered as novel foods, although it may not be excluded that they differ from conventional foods to such an extent that an assessment of their safety prior to their entry to the market would be called for. Previously, we reported that this 'grey area' of novel foods exists and comprises: (1) food products or ingredients for which the current Novel Foods Regulation leaves too much space for different interpretations and (2) food products or ingredients that are not novel according to the current Novel Foods Regulation,

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because it contains gaps. This paper focuses on how to handle these interpretation differences and gaps and provides recommendations to improve these pitfalls of the current Novel Foods Regulation. To this end, we propose criteria with clear boundaries as part of an assessment tool to reduce the uncertainties in interpretation with respect to consumption to a significant degree in the European Union, which take into account the commercial availability, length, extent and frequency of use of the particular food/ingredient. In addition, biological relevant boundaries for the criteria regarding changes in the nutritional value, metabolism (better all aspects of absorption, distribution, metabolism and excretion), and levels of undesirable substances are proposed for significant changes in the composition of foods due to changes in the production process. In addition, criteria are proposed to cover ambiguities and gaps in the Novel Foods Regulation dealing with food products and food ingredients obtained from 1) animals on a new feeding regime, 2) new varieties of organisms, 3) other growth stages of crops. Finally, a criterion that takes into account the total ingredient intake rather than single product intake is added to deal with the risk of overexposure to substances. Taken together, the proposed boundaries and criteria may contribute to diminishing the interpretation issues regarding the Novel Foods Regulation and thus to reducing the extent of the grey area of novel foods.

Keywords: Novel foods; EU regulation 258/97; food safety; grey area.

1. EUROPEAN FOOD LAW

Cornerstone of European food law is the general principle that food shall not be placed on the market if it is unsafe (Article 14(1) Regulation 178/2002 [1,2]). The safety of food encompasses both the inherent properties of the substance and its condition. For example, a toxic substance can be considered inherently unsafe; a food that is not toxic by nature may become unsafe due to spoilage or contamination. Food businesses are responsible for the safety of the food they place on the market. However, the European legislator plays an important role as well. The legislator may set limits distinguishing acceptable and unacceptable levels of contamination. The current paper focusses on the involvement of the legislator with the inherent safety of products. In the EU, it is assumed that conventional foods are categorically safe unless evidence shows otherwise. Roughly speaking, conventional foods are foods that have a history of safe use in the EU. For a gradually increasing number of non-conventional foods, the European legislator requires authorization. This means that these foods are considered hazardous unless they are authorized based on risk analysis [3]. Among these foods and food ingredients are food additives (Regulation 1333/2008) including sweeteners, colorants and other ('miscellaneous') additives [4], extraction solvents (Directive 2009/32) [5], flavourings (Regulation 1334/2008) [6], infant formulae (Directive 2006/141) [7] and some other foods for particular nutritional uses (Directive 2009/39) [8], food supplements (Directive 2002/46) [9], novel foods (Regulation 258/97) [10], genetically modified foods (Regulation 1829/2003) [11], novel food contact materials (Regulation 1935/2004) [12] and decontaminants (Article 3(2) Regulation 853/2004) [13].

Among these categories of non-conventional foods, novel foods form the most general category. In case of an innovative product that does not belong to any of the specific categories [4-9,11-13], as a consequence for the applicability of a market access

requirement based on risk analysis it is important to establish whether (or not) the product qualifies as a novel food.

1.1 Novel Food Law

In 1997, in the European Union (EU) Regulation (EC) 258/97 concerning novel foods was introduced [10]. According to this Novel Foods Regulation, novel foods are food products and food ingredients that have not been used for human consumption to a significant degree within the European Union before 15 May 1997, and fit into one of the four categories below (quoted from Regulation 258/97) [10]:

- (c) 'foods and food ingredients with a new or intentionally modified primary molecular structure;
- (d) foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae;
- (e) foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditionally propagating or breeding practices and having a history of safe use;
- (f) foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances'.

1.1.1 Food products and ingredients excluded from Regulation 258/97

To several foods and ingredients, Regulations other than the Novel Foods Regulation apply. For being a novel food, the product first has to be a food; therefore, it has to fall under the definition of food provided in Regulation 178/2002: 'any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans' [1]. The food products or food ingredients listed in Table 1 is excluded from Regulation 258/97 since they have their own legal settings.

1.1.2 Modifications of the Novel foods Regulation

Since its introduction in 1997, the Novel Foods Regulations has been modified only in 2003. Initially, genetically modified organisms (GMOs) were included in the Novel Foods Regulation. However, the application of the novel foods regime to GMOs turned out to be problematic. In 2003, a separate regime was designed for GMOs (Regulation 1892/2003 [11]) and therefore they no longer fall under the scope of the Novel Foods Regulation.

In 2008, a proposal for revision of Regulation 258/97 was published [15], but this proposal failed to gain support of the European Parliament. A new proposal has been published recently [16].

Table 1. Food products or food ingredients excluded from Regulation 258/97

Food product or food ingredient	Definition	Legal setting
Food additives	'any substance not normally consumed as a food in itself and not normally used as a characteristic ingredient of food, whether or not it has nutritive value, the intentional addition of which to food for a technological purpose in the manufacture, processing, preparation, treatment, packaging, transport or storage of such food results, or may be reasonably expected to result, in it or its by-products becoming directly or indirectly a component of such foods'	Regulation 1333/2008 [4]
Flavourings	substances 'used to improve or modify the odour and/or taste of foods for the benefit of the consumer'[6]	Regulation 1334/2008 [6]
Food enzymes	'a product obtained from plants, animals or micro-organisms or products thereof including a product obtained by a fermentation process using micro-organisms: 1) containing one or more enzymes capable of catalysing a specific biochemical reaction; and 2) added to food for a technological purpose at any stage of the manufacturing, processing, preparation, treatment, packaging, transport or storage of foods' [19].	Regulation 1332/2008 [14]
Extraction solvents	solvent which is used in an extraction procedure during the processing of raw materials, of foodstuffs, or of components or ingredients of these products and which is removed but which may result in the unintentional, but technically unavoidable, presence of residues or derivatives in the foodstuff or food ingredient [5].	Directive 2009/32/EC [5]
Genetically modified organism (GMO)	genetically modified organism (GMO) means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.	Regulation 1829/2003 [11]

1.2 Grey Area Novel Foods

As stated above, the EU system is designed to ensure that all foods legally on the EU market belong to a category that can be considered inherently safe, either based on past experience or on the basis of scientific risk assessment. There are, however, flaws in this design and its application. Verhagen et al. [17] identified a 'grey area' consisting of foods that are too new to be considered safe on the basis of past experience but that may escape safety assessment due to flaws in the text and the application of the Novel Foods Regulation. The most critical flaw is in the openness or vagueness of concepts used. Normally vague legal concepts acquire precision through interpretation by the competent authorities and courts of justice in the application in individual cases or through interpretative documents such as guidelines. In the case of the Novel Foods Regulation, however, authorities have largely failed to make their interpretations explicit in the substantiation of their decisions and have been scarce in providing guidance. Consequently, the vagueness of the concepts in the Novel Foods Regulation is uncommonly persistent.

Verhagen et al. [17] identified two main groups within the 'grey area':

- (i) Food products or food ingredients for which the current Novel Foods Regulation leaves (too) much space for interpretations:

- a. Due to vagueness of the term 'significant degree' related to consumption before 15 May 1997;
 - b. Due to the term 'significant changes' related to change in production process;
 - c. Animal feed related to changed composition of foods;
 - d. New varieties of organisms resulting in a changed composition of foods.
- (ii) Foods treated as not novel due to gaps in the current Novel Foods Regulation.
- a. Because of safety of foods is not assessed for new target groups;
 - b. Foods obtained from different growth stages of crops resulting in a changed composition of the particular foods;
 - c. The regulation covers the application of a new product and do not take into account the total consumption of a specific ingredient.

After the recognition of the 'Grey area novel foods' in 2009, hardly any systematic approaches have been performed to solve these issues. Currently, the EU and the Health Council of the Netherlands point out that implementation of the current Novel Foods Regulation sometimes gives problems and may not always identify all new food products that possibly pose a health risk. To reduce the 'grey area' novel foods and thereby to better protect the consumer, improved definitions of novel foods are needed. In addition, assessment tools with clearly defined criteria and univocal boundaries are useful instruments to assess the novelty of a food. Currently, a few assessment tools are available, these are depicted in Section 2.

The present paper aims to set out criteria with clear boundaries, which could be used as an assessment tool for delineating between novel foods and conventional foods. In addition, this paper presents some additional criteria not covered by Regulation 258/97. This is described in Section 3.

2. AVAILABLE ASSESSMENT TOOLS FOR NOVEL FOODS

Assessment tools can reduce interpretation differences and are thereby of help in the decision of foods to be novel or not. At present, assessment tools for novel foods are available to only a limited extent. In Australia and New Zealand, where a comparable system applies, a two-step questionnaire-based decision process was created for the advisory Committee on Novel Foods to assist in deciding on the status of a product as novel food. The first step determines whether a food is conventional or non-conventional (thus, a novel food) using lower and upper limits on a linear scale, the second step gives guidance whether a safety assessment is required in case the food is considered novel[18]. With respect to the determination of the novelty of a food, the guidance tool identifies four main criteria: length of use, extent of use, quantity (level of intake) of use and purpose or context of use, all provided with indicated boundaries. For example, for the length of use, the upper limit is set as five years or less, while the lower limit is set at two to three generations or more. Regarding the requirement of the safety assessment, six aspects that needs to be considered have been defined: the potential for adverse effects in humans, the composition of the structure of the food; the process by which the food has been prepared, the source from which it is derived, patterns and levels of consumption of the food, and any relevant matters not covered by these aspects. Depending on the information of each of these six aspects, a safety assessment could be required. For example, for DHA extracted from *Schizochytrium* sp (microalgae) it was concluded that based on the source from which the DHA is derived, which give rise to potential safety issues to the potential for undesirable

substances such as toxins and pathogens, a safety assessment is required. No boundaries are provided for these aspects.

Canada requires prior authorisation of novel foods. To assess a product's status, Canada wields extensive guidelines, in which a small decision tree is present. The decision tree, constructed with consecutive questions to be answered with 'yes' or 'no', guides the petitioner to consider whether a food might be regarded as a novel food, and where to find the most appropriate guidelines for submitting the notification of that food [19]. The Canadian guidance tool contains useful definition for the history of safe use: 'A substance may be considered to have a history of safe use as a food if it has been an ongoing part of the diet for a number of generations in a large, genetically diverse human population where it has been used in ways and at levels that are similar to those expected or intended in Canada'. The Canadian guidance does not provide boundaries for these criteria.

Recently, the EU has published an information and guidance document, which focuses on the criterion 'consumption to a significant degree' within the EU before 15 May 1997 [20]. This guidance document aims to assist competent authorities and interested stakeholders to interpret and apply Regulation 258/97 in a uniform way. To achieve this, a decision tree and an accompanying questionnaire were prepared. Although the questions in the tree can be consecutively answered with 'yes' or 'no', it is clearly indicated that the criteria listed should not be taken as a ranking, instead each food has to be assessed on a case by case basis. The guidance document defines useful aspects and criteria of 'consumption to a significant degree', including geographical aspects, quantity of use, use by specific population groups, context of use, availability and duration of use. Clear boundaries, however, are not provided.

Since no currently available assessment tools cover all sources of 'grey area' novel foods, and boundaries for criteria were only available to limited extent, we propose criteria with clear boundaries as part of an assessment tool for the delineation between novel foods and conventional foods. The objective of this tool is to serve as an instrument for stakeholders dealing with the current Novel Foods Regulation to more effectively implement it. Our main objective is not to systematically recommend changes to the regulation as such. However, as our research inevitably highlights flaws in the current legal design and the European Commission is considering a review, we have indicated possibilities to improve the law.

3. CRITERIA WITH BOUNDARIES FOR NOVEL FOODS

To determine criteria with boundaries as part of an assessment tool for novel foods, the criteria and definitions of the Novel Foods Regulation are reviewed below and, wherever possible, criteria with boundaries are proposed. In case criteria are lacking for proper assessment on the novelty of foods, additional criteria are proposed and their rationales discussed. All criteria and boundaries can be summarized into a decision tree. Fig. 1 shows the proposed decision tree. The first two criteria addresses issues described in Section 1.1.1 'Food products and ingredients excluded from Regulation 258/97'. The other criteria will be addressed in the following sections.

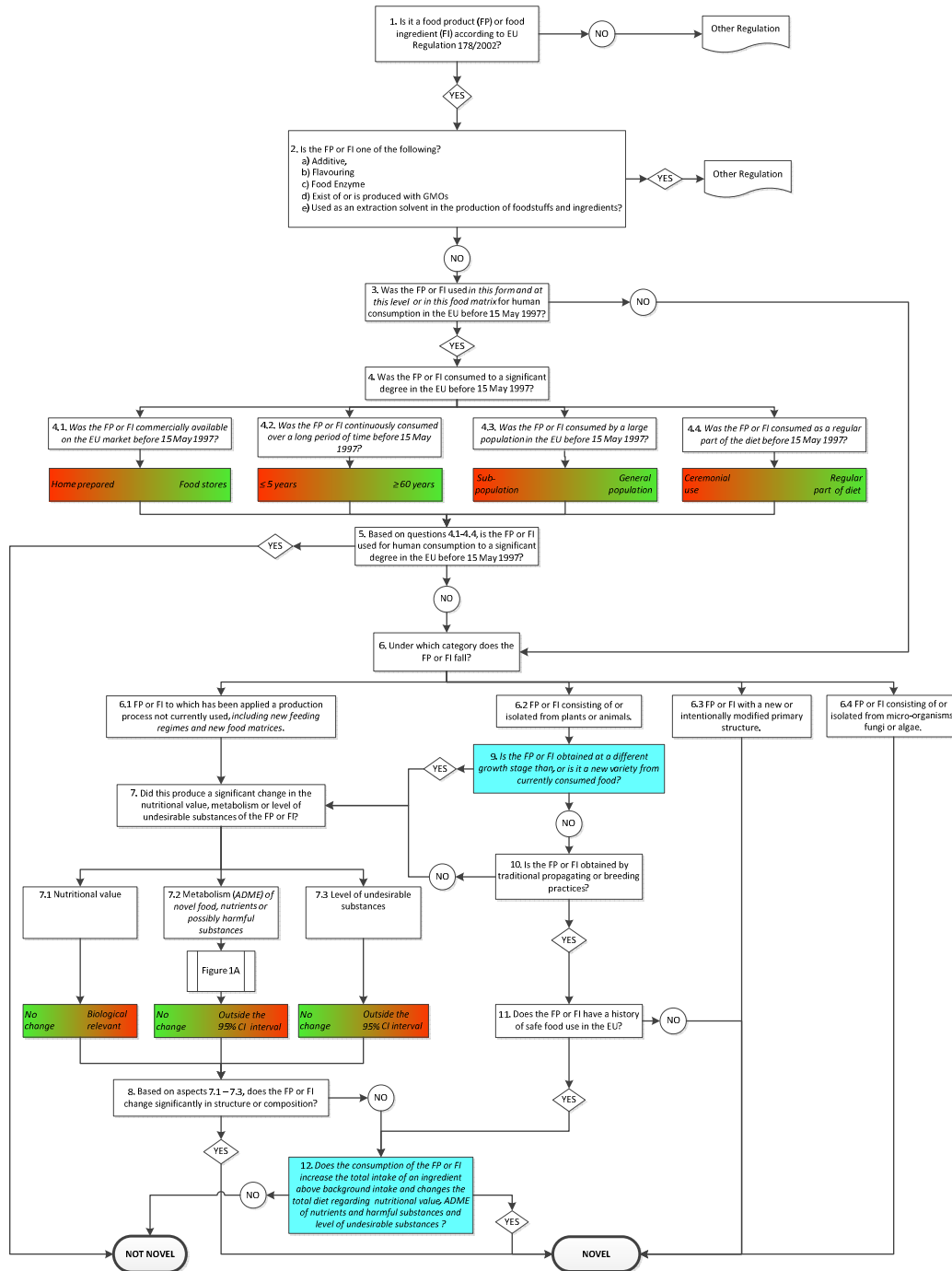


Fig. 1. Decision tree as an assessment tool for the novelty of foods

The decision tree includes criteria obtained from Regulation 258/97 on novel foods and proposed new criteria (in italics). Blue boxes indicate newly added full criteria. Details regarding the criteria are elaborated in the corresponding sections in current publication. ADME means absorption, distribution, metabolism and excretion of nutrients

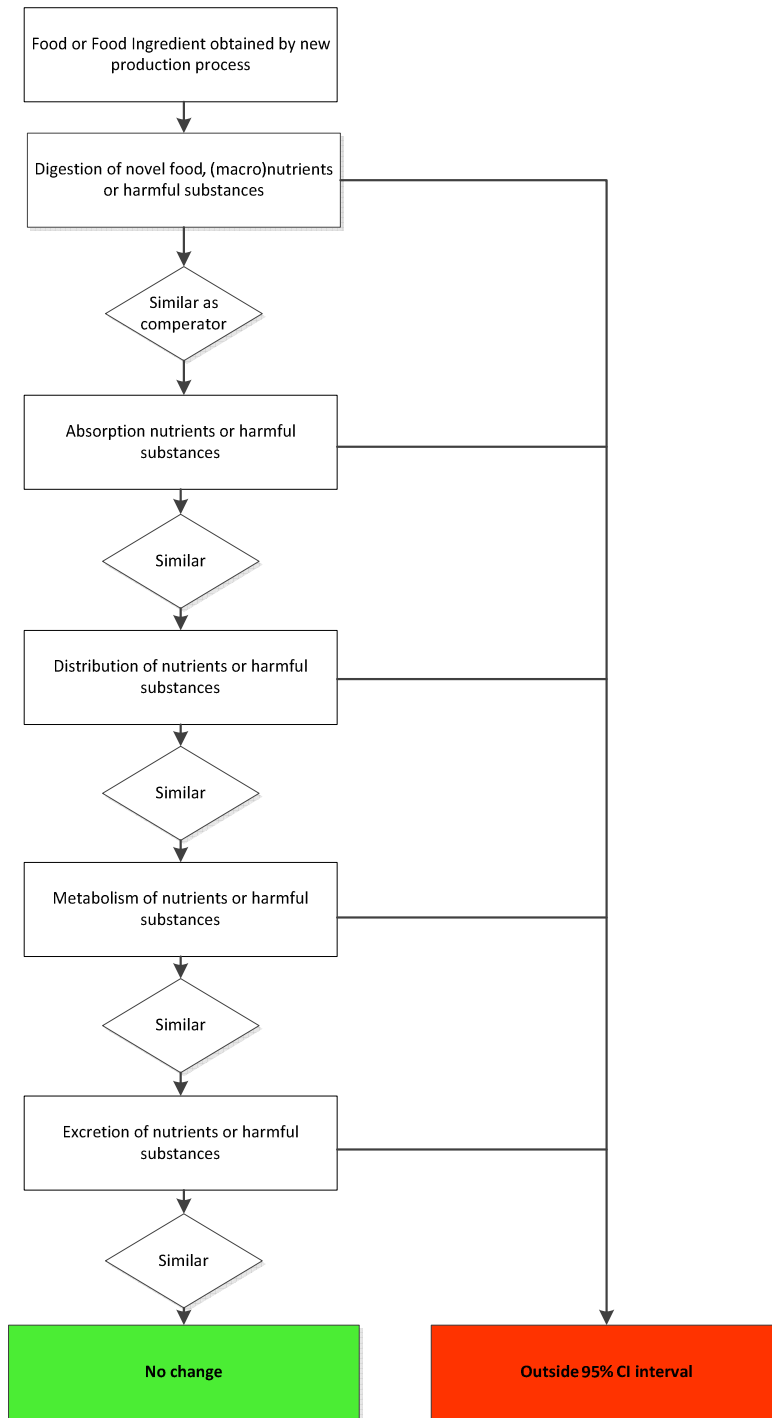


Fig. 1A. Subpart of the decision tree for novel foods to determine the effect of a food or food ingredient on absorption, distribution, metabolism and excretion (ADME) of nutrients
95% confidence interval (CI) is defined as the CI of the comparator food.

3.1 Consumption to a Significant Degree before 15 May 1997

Regulation 258/97 applies to food products and food ingredients that have not been used for human consumption to a significant degree within the Community before 15 May 1997 [10] (Fig. 1; Criterion 4). An established history of food use to a significant degree in at least one EU Member state is sufficient to exclude the food from the scope of Regulation 258/97 [20]. For example, the blood cholesterol lowering ingredients phytosterols were introduced in the EU when Finland became a member in 1995. As a result, these ingredients were consumed in an EU member state. In case Finland would not have entered the EU prior to 1997, these ingredients would have had to be authorized as novel foods [17].

'Consumption to a significant degree' is mentioned in Regulation 258/97. However, for establishing the novelty of foods and food ingredients, consumption to a significant degree should also be regarded in terms of biological relevance. In this respect, 'significant' is a vague term and leaves (too) much space for different interpretations. Verhagen et al. [17] identified some 'grey area' novel foods, of which the consumption to a significant degree within the EU before May 1997 may be an issue, such as camel milk, the acai berry, argan oil and pitaya [17]. After reviewing the New Zealand Guidance Tool [18] and the EU Guidance document [20], four criteria were deduced which may serve to determine biological relevant consumption to a significant degree: commercial availability, length of use, extent of use and the frequency of use. For each criterion, boundaries with lower and upper values were set to establish the consumption to a significant degree. These boundaries are shown in Fig. 1, with lower and upper limits in green and red, respectively. Intermediate values have an intermediate color. For each food product or food ingredient, all four criteria must be addressed. Section 3.1.6 describes how to handle the outcome of the four criteria.

3.1.1 Commercial availability (Fig. 1; Criterion 4.1)

The EC argues that human consumption to a significant degree within the European Union can be demonstrated by the general availability of a food within the Community [20]. Commercial availability can be used as a criterion for general availability, since a commercially available food is accessible to the whole population. For foods sold in supermarkets and/or common food stores, like a bakery and butchery, it is accessible to the whole population [20]. Foods used in the private domain only (e.g. mushrooms or berries picked from the forest by individuals) cannot be regarded as generally available. It should be noted that the EU Guidance document mentions that these foods may be on the market in certain geographical areas, e.g. local farmer's markets. This could be regarded as consumed to a significant degree, even if the commercial value is limited [20]. However, this cannot be taken as a clear criterion, and this is most likely to be determined on a case-by-case basis. Therefore an upper boundary is set at home-prepared only (low access to the food) and a lower boundary is set at available in food stores (high availability).

3.1.2 Length of use (Fig. 1; Criterion 4.2)

The length of use is also important in establishing consumption to a significant degree. Foods continuously consumed for a long time without showing any harmful effect can be regarded as having a history of safe use. Using this criterion, foods that are consumed during a specific limited time in history only, e.g. during famine, are excluded. Another example excluded by this criterion is a food product once presented on a trade fair before 1997 [20]. According to the New Zealand Guidance Tool, use of a food for less than five years is considered as a short period of use. On the other hand, two or more generations is

considered to be a long period of use [18]. By defining generation as a period of 30 years, continuous consumption for more than 60 years counted backwards from 1997 is a long period of use, while excluding the use of food products or food ingredients in ancient times. According to Engel et al. [21], continued use for at least 25 years is a criterion for the length of use. Life-long exposure is relevant for certain diseases that reveal in middle aged and elderly subjects, such as cardiovascular disease and certain cancers. Since sixty years reflect life-long exposure better than 25 years, the lower boundary is set at more than 60 years counted backwards from 1997. The upper boundary is set at less than five years counted backwards from 1997.

3.1.3 Extent of use (Fig. 1; Criterion 4.3)

In the assessment of a food used for human consumption to a significant degree, the extent of use has to be taken into consideration [20]. If the general population in one of the Member States consumes the food, it is considered extensive consumption in the EU. In contrast, the consumption of the food by one isolated sub-population in one of the Member States is considered as limited use. Consumption by several sub-populations might be sufficient as extensive consumption, depending on the size and number of sub-populations [18,20]. Therefore, the upper boundary is set at one sub-population in one Member State and the lower boundary is set at the general population.

3.1.4 Frequency of use (Fig. 1; Criterion 4.4)

The consumption frequency of the food is relevant for establishing consumption to a significant degree. Since the quantity of the food consumed depends on the type of food, (e.g., herbs are eaten in smaller quantities than food products made from cereals, such as pasta and bread), the frequency of consumption is a better criterion than quantity. Foods consumed on a regular basis are considered as frequently used food products. Foods only consumed during particular ceremonies, festivities or famine, are considered non-frequent consumed foods [18,20]. Therefore, the upper boundary is set at "ceremonial use" (non-frequently consumed foods) and the lower boundary is set at regular part of the diet, where seasonal foods are considered as being regular part of the diet.

3.1.5 Evidence consumption to a significant degree

According to the EU guidance, the evidence proving the consumption to a significant degree should be based on robust, reliable information and data taken from referenced sources and relate to foods that have been legally on the Community market [20]. Written documentation is preferred, since it is the most convincing evidence for demonstrating the history of use in the EU [18]. However, all data and information, both written and in other formats, available for establishing significant consumption should be taken into account [18]. National nutritional guidelines, data from national food consumption records, and data from databases on food product launches, such as the INNOVA (<http://new.innovadatabase.com>) and Mintel (<http://www.mintel.com>) database, can serve as evidence. This type of evidence proves the length, extent and frequency of use of a food. Use in food supplements is not regarded as consumption to a significant degree [22]. According to the Health Council of the Netherlands, by use in food supplements, consumption is limited to a subpopulation not representative for the whole population [22]. Moreover, supplements containing poorly defined ingredients with limited data on safety are on the market [22]. Additional data could be obtained from consumption questionnaires and interviews. Sales figures and invoices from food companies and food stores, menus, food advertisements in magazines, flyers,

television and radio commercials can prove the commercial availability of a food [20,23]. Regarding the frequency of consumption of the food, documents on rituals and ceremonies can prove when and how often the food was consumed [18].

3.1.6 Decision (Fig. 1; Criterion 5)

The overall consideration is based on the weighed outputs of the four different criteria: availability, length, extent and frequency of use of the food. Together, they can be used to determine whether the consumption has been to a significant degree. When a food was available in food stores in one of the EU member states before 15 May 1997, and consumed for over 60 years by the general population as a regular part of the diet, it is clearly not a novel food. In contrast, if a home-prepared food was consumed for less than 5 years before 15 May 1997 by a subpopulation during ceremonies, a strong argument can be made that it is a novel food. In case one or more criteria fall within these boundaries, all components in this determination must be considered to be of equal importance, and the output of one component must be weighed against the output of the other components [18]. As an example: the assessed food product was, based on advertisements and discount flyers, available in the supermarkets. The food product was introduced in 1982, the introduction date to the EU market was available, and the food was consumed from that time onwards. Based on the outcomes of the national food consumption records, it shows that the food product was frequently consumed by the general population. The overall consideration would be that even though the food product does not have a long period of use, the outcomes of the other three components balance this output and therefore the consumption of this food product can be considered as consumption to a significant degree. As such, the assessment of the significant consumption of a food is done on a case-by-case basis, and based on the best available information [18].

3.2 Food and Food Ingredients Applied by a Production Process not Currently Used (Fig. 1, criterion 6.1)

Regulation 258/97 applies to the 'group of foods to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods which affect their nutritional value, metabolism or level of undesirable substances' [10]. For this group of foods, the following uncertainties are established: 1) a production process not currently used (Fig. 1, criterion 6.1) and 2) significant changes in the composition or structure affecting nutritional value, metabolism or level of undesirable substances.

The term 'production process not currently used', leaves room for different interpretations. It is not clear whether this term refers to production processes not currently used for the specific food product, or, more in general, to a production process not currently used in food production. According to the Commission Recommendation [24] a production process not currently used is 'a process not currently used in food production', Examples of processes not currently used in food production are: new types of heat processing, new processes to chill or freeze products, non-thermal preservation methods, application of new processes catalysed by enzymes, and processes to dehydrate products [21]. According to Verhagen et al. [17], an ambiguity in the definition 'a production process not currently used' is the combination of two commonly used production processes in the food industry, which results in a new way of producing food. Examples are Quart and Valess, which are produced by a combination of existing production processes. In this respect, a new combination of two commonly used production processes in the food industry must be regarded as a production

process not currently used. Another ambiguity forms the new combination of a known process applied to a known food. For example, a known fermentation process of a particular food is applied using other raw material. Since this may give rise to changes in the nutritional value, metabolism (better 'ADME', see section 3.2.2) or level of undesirable substances, it can be a novel food. In this respect, the term 'production process not currently used', must be regarded as a process not currently used for this food. Section 3.6.1 describes a gap in the Novel Food Regulation, related to a new animal feeding regime, which can be regarded as a production process not currently used. The inclusion of a short description of the production process in the specification in the Commission approval helps to judge on the novelty of the production process.

Some novel foods ingredients are only approved for use in certain foods and need to go through a new evaluation before they can be used in other food matrices. The food matrix may affect the nutritional value and metabolism (better 'ADME', see section 3.2.2) of a novel food. For example, the effect of phytosterols on blood cholesterol depends on the food matrix to which the phytosterols were added [25]. Since the use in a new food matrix can be regarded as a production process not currently used, the phrase 'and new food matrices' has been added to criterion 6.1 (Fig. 1).

Another uncertainty is the term 'significant changes', which is not quantified or defined specifically, which leaves (too) much space for debate [17]. With respect to the toxicological aspects of novel foods, the Commission Recommendation uses the term 'substantial equivalence' in the comparison of the novel food with an accepted traditional food or food ingredient [24]. Jonas et al. [26] defined substantial equivalence as the biochemical identity within the limits of natural diversity of the traditional counterpart. According to Constable et al. [27], a novel food should be rigorously analysed and compared with its traditional food comparator. Thus, the nutritional value, metabolism and level of undesirable substances of the novel food or food ingredient obtained from a new production process should be compared with those obtained from a traditional production process. For each of the three effects, i.e. nutritional value, 'metabolism' (better 'ADME' – see hereafter) and level of undesirable substances, setting boundaries improves the establishment of their significance.

3.2.1 Nutritional value (Fig. 1; Criterion 7.1)

Assessing the change in the nutritional value of novel foods is relevant since it may have an impact on the total nutritional value of the diet. At present, it is not clear which criteria should be used. By comparing the nutritional value of foods based on chemical analysis of e.g. the protein, vitamin and mineral compound, statistical significance compared with the traditional food could be used as a boundary. However, a statistically significant change does not necessarily imply a biologically relevant effect. According to Lyyra et al. [28], when a production process changes the nutritional value of a food and its consumption changes the intake of a particular nutrient with 15% of the RDA (Recommended Dietary Allowance), it is considered nutritionally relevant. Regulation 1924/2006 on nutrition and health claims also uses the 15% of RDA criterion for the definition of 'source of vitamins and minerals' [29]. However, Regulation 1169/2011 defines significant amounts of vitamins and minerals as 7.5% of nutrient reference values (e.g. RDA) for beverages and 15% of nutrient reference values for products other than beverages [30]. The annex of Regulation 1924/2006 also depicts other definitions for the nutritional values of foods. Therefore, these definitions can be used for setting the upper boundary. Thus, if the consumption of a food changes the intake of a particular nutrient to the extent defined in Annex of Regulation 1924/2006 or Regulation 1169/2011, it is regarded as a biological relevant change. This criterion is

proposed as the upper boundary. The lower boundary is set as no change in nutritional value.

3.2.2 Metabolism (Fig. 1. Criterion 7.2)

The Novel Foods Regulation has 'metabolism' in its text, but the term 'metabolism' leaves room for interpretation issues, since it might be interpreted as chemical conversion of nutrients instead covering all aspects of absorption, distribution, metabolism and excretion (ADME). By using the term 'ADME', this criterion becomes more clear (Fig. 1, Criterion 7.2). However, these data may not always be available. A change in the ADME of nutrients and other compounds may lead to harmful effects and must therefore be considered in the assessment on the novelty of a food. Whereas for the example of iron nanoparticles mentioned here below, the bioavailability of iron itself might be increased, for other novel foods or novel food ingredients the effect may be on the ADME of other food components, such as nutrients, non-nutrients and harmful substances. Examples of naturally existing components affecting the ADME of nutrients are protease inhibitors, tannins and phytate [31]. Production processes may affect the level or activity of these compounds rather than their own metabolism, as has been shown for heat-sensitive trypsin-inhibitors in legumes [31]. Therefore, the effect of a new production process on the ADME of the food or food ingredient itself may be too limited as a criterion and should include the effect on the general ADME of nutrients, non-nutrients and harmful substances. This is obtained by adding the phrase 'their metabolism and those of nutrients, non-nutrients and harmful substances'.

The Novel Foods Regulation does not provide criteria for estimating the effect on 'ADME'. The EFSA Scientific Summary Report [32] on novel foods proposed a tiered approach for nanomaterials. If at any stage the ADME of the new nanomaterial differs from the comparator, the nanomaterial should be subjected to a special risk assessment other than for the comparator material. The paradigm proposed in this EFSA Scientific Summary Report can be adapted for the assessment of the novelty of a food (Fig. 1A). If at any stage the ADME is affected by a food or ingredient obtained by a new production process, it can be considered as a novel food. In the EFSA opinion on α -cyclodextrin, a statistically significant change in reduction in blood plasma α -tocopherol levels as measure of tocopherol bioavailability, was not regarded as biologically relevant, since values were still within the normal range [33]. Therefore, boundaries on biological relevant effects should be set rather than statistically significant changes. Setting biological-relevant boundaries for all criteria in Fig. 1A is currently not possible because of lack of good quality data [32]. For nutrients that can be monitored in blood or urine, the normal range of values can be considered as a boundary, as has been used as a criterion in the EFSA opinion on α -cyclodextrin [33]. Obviously, this should be the normal range of non-deficient subjects (e.g. mean \pm 2SD). In addition, a scientific discussion should be initiated to define boundaries. Until these biologically relevant boundaries can be set, the criteria of statistical significance should be used to indicate a possible effect on metabolism. The upper boundary we propose is set at outside the 95% confidence interval range of the comparator food, whereas the lower boundary is set at no change (Fig. 1, Criterion 7.2; Fig. 1A). On a case-by-case basis, this can be followed by evaluation of the biological relevant effects.

3.2.3 Level of undesirable substances (Fig. 1. Criterion 7.3)

New production processes in foods may result in the formation of new compounds, which may have an impact on health. For instance, soy beans subjected to chemical hydrolysis to obtain vegetable proteins may result in the formation of high concentrations of chlorinated

propranolol, a compound that has carcinogenic effect in animals [34]. Alternatively, new production processes may yield higher amounts of possible harmful substances compared with traditional ones. An example of undesirable substances influenced by the production process, are anthraquinones in noni juice. Although the juice is made from the fruit, parts of the branches and leaves can contaminate the juice. These parts of the noni tree contain anthraquinones, with adverse effects [35]. The current manual production process ensures that these parts do not contaminate the juice. A new mechanical production process may increase the level of anthraquinones.

For food products with limits for compounds with health risks, such as pesticides (Regulation 396/2005) [36] or contaminants (Regulation 1881/2006) [37], it is obvious that these limits should not be exceeded. However, it is not clear which criteria should be used if such limits have not been established. Therefore, a scientific discussion must be initiated to set clear boundaries that aid the decision whether the tolerable level of undesirable substances is exceeded. These boundaries may take into account the range of these compounds in conventional food. Until such boundaries are available, the criteria of statistical significance can be used as an indication. Therefore, the lower boundary we propose is set at no change, whereas the upper boundary is set as outside the 95% confidence interval range of the comparator food.

3.2.4 Nanomaterials

Nanotechnology is an example of a novel production process that may lead to grey area novel food (ingredients). The term 'alter of structure or composition of the food' leads to indistinctness on how to interpret foods and food ingredients obtained by nanotechnology. From a chemical point of view, nanomaterials do not alter the structure or composition of the food, which may lead to the conclusion that foods or food ingredients produced by nanotechnology are not novel. However, nanostructured compounds do have a different particle size and surface area of the compounds than the comparator compound. Hence, these nanosized compounds may have profound effect on absorption, distribution, metabolism, and/or excretion (ADME). For example, nanoparticles of iron or zinc are explored as ingredients with high bioavailability [38]. Therefore, nanomaterials do qualify for novel foods or novel food ingredients.

A solution for this ambiguity is to read the fourth category in the Novel Foods Regulation from "foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances" as "foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in their nutritional value, metabolism or level of undesirable substances in the food", and where 'metabolism' is better replaced by all ADME terms.

3.2.5 Allergenic potential

Different types of food processing may have an impact on allergenicity. Often this may result in reduction of allergenicity, but the reverse also occurs, for example by roasting of peanuts. Differences in conformational structure of proteins have an impact on their allergenicity [39,40]. Regulation 258/97 does not explicitly mention the allergenic potential of food and food ingredients, and novel foods cannot be disapproved because of potential allergenicity. The EFSA Scientific Colloquium Summary Reports [32] states that 'allergenicity should not

be a reason for negative outcome, in fact it may be addressed by labelling at the risk management level' However, information on potential allergenicity is required. Commission Recommendation 97/618 addresses the allergic potential of novel foods and provides solutions to test the allergic potential, such as screening novel proteins for sequence epitope homology with known allergens, heat stability, sensitivity to pH and digestibility by gastrointestinal proteases or by testing in vitro immunological reactivity of individuals who react to the conventional food counter parts or in vivo challenges, such as a skin prick test.

3.3 Food and Food Ingredients with a New or Intentionally Modified Primary Structure (Fig. 1. Criterion 6.3)

The primary structure of a biological molecule is the exact specification of its atomic composition and the chemical bonds connecting those atoms. Changes in the primary structure of biomolecules can significantly alter their functions and/or activity. For example, changing an α -glycosidic bound into a β -glycosidic bound alters digestible carbohydrates into non-digestible ones. Another example is cyclodextrins. Whereas digestive enzymes easily digest linear dextrins, the cyclic form of the molecule is resistant to digestive enzymes [33]. At present, each food with a new or intentionally modified primary structure is a novel food, which leaves no room for interpretation issues.

3.4 Food and Food Ingredients consisting of or Isolated from Microorganisms, Fungi or Algae (Fig. 1. Criterion 6.4)

Microorganisms, fungi, algae, or their constituents can serve as nutritious food sources [41-44]. The main concerns on new food products harbouring microorganisms are containment, potential pathogenicity and/ or toxigenicity and the potential of microorganisms to colonize the gut [24]. Because a large amount of fungal species are toxic, food products or food ingredients obtained from fungal species not previously used for human consumption may need to be well-characterized regarding their safety. Algae are widely and commonly consumed in forms of seaweed in many Asian countries as well as North America and Northern Europe. In the last few decades, consumption of seaweed and algae products in Europe has increased. With respect to the safety of microorganisms, the European QPS (Qualified Presumption of Safety) approach for assessing the safety of micro-organism in food and feed and its frequent/annual updates is applicable [45]. In the QPS system, the safety assessment of a defined taxonomic group (e.g. genus or species) is based on four pillars: establishing identity, body of knowledge, possible pathogenicity and end use. Other sources of safety of microorganisms are available, such as the GRAS (generally recognised as safe) system of the FDA [46].

A specific case of microorganisms that could fall within the scope of the Regulation 258/97 are the so called probiotics [19]. In part, this may be due to the lacking scientific consensus to assess adequately their history of use [47]. All food and food ingredients consisting of or isolated from microorganisms, fungi or algae that have not been consumed to a significant degree before 15 May 1997 are considered as novel. Microorganisms intended to promote health are applied by the food industry, and newer subspecies may be used and end up in food products. These may have other effects, both as presumed beneficial effects for which they are intended, as well as adverse effects. Any new variant should be considered as novel, and thus fall under the Novel Foods Regulation.

3.5 Food and Food Ingredients consisting of or Isolated from Plants or Animals (Fig. 1. Criterion 6.2)

Foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating (Fig. 1, Criterion 10) or breeding practices and having a safe history of use (Fig. 1; Criterion 11) forms the fourth category of novel foods (Fig. 1. Criterion 6.2). The reason for inclusion of the criterion on non-traditional propagation and breeding practices was genetic modification. Nowadays, genetically modified organisms are regulated separately via Regulation 1829/2003 [11]. By maintaining this criterion, inclusion of all other possible forms of non-traditional propagation and breeding practices is secured. When evaluating food obtained from non-traditional propagation and breeding practices, the criteria 'nutritional value', 'metabolism' ('ADME') and 'level of undesirable substances' as discussed above under 'a production process not currently used' can be applied.

This novel food category comprises species that are uncommon food sources or have lost their former importance for human consumption in the European Union, such as minor cereals, grain and legumes, exotic fruits, camels, yaks and lama's, even though a history of safe use is established in third countries. A food may have a history of safe use within a third country, because of its processing methods or consumption patterns [27]. Introducing this food in Europe does not necessarily mean that consumption is safe because of possibly different consumption patterns and processing methods, and also because of possible genetic differences in metabolism. Well-known examples of genetic differences in metabolism are lactose intolerance in many populations and the lower capacity of alcohol metabolism in East-Asian populations compared with Caucasians. When considering foods from third countries as novel, possibly unknown harmful effects are excluded. The EU established a novel food catalogue listing animal and plant food that might be regarded as novel [48]. This list is non-exhaustive and serves as an orientation on the novelty of plant and animal food.

Regulation 258/97 only includes food ingredients obtained from animals and does not include foods consisting of whole animals. An example is whether 'scorpion vodka' could be considered an extract of the animal, and thus covered by the Novel Food Regulation, or a whole animal and thus not covered by the Regulation. This can be solved by using the phrase 'food and food ingredients consisting of or isolated from plants or animals'.

Discussion exists on naturally occurring components used in concentrated forms [25]. An example of this category of novel foods is isolated bovine lactoferrin, a milk protein naturally present in low amounts in milk. Bovine lactoferrin was recognized as a novel food [49], because of a new method of production. The intended use of bovine lactoferrin increases the intake 30–60 times above background intake from natural sources [49]. In addition, lactoferrin intended as novel food might be consumed as a native protein, whereas the lactoferrin in milk and milk products may also be present in the denaturated form, because of heating [49]. The unclarity in the Novel Foods Regulation with respect to naturally occurring components in concentrated forms may be solved by adding the phrase 'in this form and at this level' to the text of the definition or to its interpretation, i.e. 'foods and food ingredients which have not hitherto been used in this form and at this level for human consumption to a significant degree' (Fig. 1. Criterion 3).

3.6 Additional Criteria Needed to Cover Gaps in the Novel Foods Regulation

According to Verhagen et al. [17], a number of issues need to be addressed in order to reduce the 'grey area' of novel foods. These issues are: 1) animal feed related to changed composition of foods, 2) new varieties of organisms, 3) growth stage of crops, 4) safety not assessed for new target groups and 5) single product intake versus total ingredient intake. These additional criteria are shown in Fig. 1 as a blue box when a completely new criterion was added or in italics when a criterion was included in an already existing criterion.

3.6.1 Animal feed related to changed composition of foods

An interpretation issue related to Regulation 258/97 arises when the composition of a food has changed significantly due to a change in (the composition of) the animal feed. An example of a food product, which changed due to the use of different animal feed, is the Aurora cheese. This cheese was obtained from cow's milk, which were given special feed, resulting in a cheese that 'contains higher levels of conjugated linoleic acid and n-3 fatty acids than normal cheese' [17]. Depending on the change of the concentration and nature of the components, food products resulting from a change in feeding are regarded as novel [24]. Therefore the new type of animal feed used in the production chain can be seen as a different production process in the decision tree and therefore has been placed in the first part of the category of 'production process not currently used' and those food products will be assessed on their significant changes due to the production process. Therefore, the phrase 'including new feeding regimes' is added to the new production process criterion (Fig. 1. Criterion 6.1).

3.6.2 New varieties of organisms (Fig. 1. Criterion 10)

For products consisting of or isolated from new plants or animals that are the result of traditional propagating and breeding methods, the criterion whether or not to consider a product as novel food is not clear [17]. The Health Council of the Netherlands, uses the species boundary [24]. When belonging to the same species, a food is not considered as novel. However, in some cases, new varieties of foods belonging to the same species can differ in their composition and structure [17], such as potato varieties differing in glycoalkaloid content, the golden kiwi differing in its allergen profile from the green kiwi, and the purple asparagus containing 3-[3''-(O-β-d-glucopyranosyl)-6''-(O-α-l-rhamnopyranosyl)-O-β-d-glucopyranoside] [50]. This problem can be solved by assessing 'food products or ingredients consisting of or isolated from plants' on the variety line instead of the species line (Fig. 1; Criterion 9). With this respect, the criteria 'nutritional value', 'metabolism' ('ADME') and 'level of undesirable substances' as discussed under 'a production process not currently used' could be used (Fig. 1. Criteria 7.1 to 7.3).

3.6.3 Different growth stage (Fig. 1. Criterion 9)

Plants may have different composition during different growth stages of crops. Consuming crops in a different growth stage than normally consumed may have unknown health effects. An example is BroccoCress, which is broccoli harvested in an early stage [17]. Compared to the mature broccoli, the sprouts of the broccoli contain much more glucoraphanin, the glucosinate of sulforaphane [51]. A solution to cover this gap is to add a separate criterion that deals with the issue whether the food was obtained during a growth stage different from the traditional growth stage within the food category 'Food or food ingredient consisting of or isolated from plants or animals'(Fig. 1, Criterion 9). In turn, this could be followed by the

criteria with respect to 'Nutritional value', 'Metabolism' ('ADME') and 'Level of undesirable substances' (Fig. 1, Criteria 7.1 to 7.3).

3.6.4 Single product vs total ingredient intake (Fig. 1, Criterion 12)

The Novel Foods Regulation covers the application of a new product or ingredients, or the new application of existing foods, but does not take into account the total consumption of a specific ingredient [17]. This is not a problem itself, but it may become a problem when the food is consumed in a diet already containing a high amount of the same ingredient or component. For example, introduction of novel foods with high n-3 fatty acid content may cause an overconsumption of these fatty acids, because of the consumer's increased awareness of its possible role in the reduction of coronary heart disease. Over consumption could possibly result in negative health effects [52]. A solution to cover this gap in Regulation 258/97 is to add a final criterion to the novel food decision tree, which takes into account the upper intake of the novel food or food ingredients and its effect on total nutrient intake, ADME of nutrients, non-nutrients and harmful substances and exposure to undesirable substances. At present, no such boundaries exist. A provisional increase with 20% above background intake of the 95th percentile, or in case of nutrients, values 20% below the background intake of the 5th percentile could be taken as a boundary (but also other percentages can be argued). Obviously, this expected intake should not exceed safety recommendations, such as tolerable intake levels, acceptable daily intake and margins of safety.

4. CONCLUSION

To reduce gaps and interpretation issues of the Novel Foods Regulation, we defined additional criteria and provided biological relevant boundaries for these new as well as existing criteria. To decide on the consumption to a significant degree, four criteria with boundaries that determine commercial availability, length, extent and frequency of use are provided. To determine the effect on 'nutritional value', 'metabolism' ('ADME') and 'level of undesirable substances', the use of biological relevant criteria are proposed. At present, such criteria can be given for the 'nutritional value', but not for 'metabolism' ('ADME') and the 'level of undesirable substances'. In these cases, a list with unwanted substances or effects may be prepared, followed by a scientific discussion on what changes can be regarded as a biological relevant change. Until then, statistical significance can be used as a criterion. Additional criteria are provided for foods obtained from a new growth stage, from new varieties of organisms and as a result from new animal feed. The need for a final criterion that takes into account the total intake rather than single product intake is emphasized. The proposed criteria and boundaries may contribute to diminish the interpretation issues of Regulation 258/97 and thereby to reduce the extent of the grey area of novel foods.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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