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Review

Demanding safe foods – Safety testing under the novel food regulation (2015/2283)

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ABSTRACT

Background: A legal framework cannot ensure that a food will never pose a risk to any consumer. Risk management procedures are put in place to control potential risks occurring from food consumption. In the EU, this is translated into premarket authorisation decisions to allow novel food products on the market, laid down in the Novel Food Regulation (NFR).

Scope and approach: In the authorisation decision under the NFR, the scientific dossier dealing with the food product's safety is key. Various adjustments were made in updating the 1997 NFR to the new NFR (Regulation 2015/2283), but scientific dossier requirements seem comparable between both versions. This paper aims to optimise the crosstalk between the two corner stones of the NFR, science and regulation, and therefore reviews methodological requirements to establish food safety.

Key findings and conclusions: For novel foods, the scientific dossier must provide evidence that no adverse effects are elicited by consuming the product and consequently, kinetics, toxicology, nutritional information and allergenicity must be analysed. Methodological developments within these fields and specifically in toxicology will reduce required resources as well as the need for large numbers of experimental animals in conducting risk assessments. New methods should be embraced throughout the EU by promoting their (of course critical) use in safety assessments of foods.

1. Introduction

Following a second round of discussions and proposals for a new regulation, *Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods* was adopted in November 2015 as an update of *Regulation (EC) No 258/97 concerning novel foods and novel food ingredients*, which it will repeal (Commission of the European Communities, 2008; European Parliament and Council of the European Union, 2015). In 1997, Regulation (EC) No 258/97, known as the Novel Food Regulation (NFR), was adopted to harmonise national procedures for bringing new products or ingredients intended for human consumption to the European market (European Parliament and Council of the European Union, 1997). Next to harmonising legislation throughout the European Union, one of the goals of this legislative act was to ensure that novel products were safe for consumers' health (European Parliament and Council of the European Union, 1997). This is in line with the overall aim of European food law as described in Article 14(1) of the General Food Law (GFL), stating that *'food shall not be placed on the market if it is unsafe'* (European Parliament and Council of the European Union, 2002).

Ensuring that consumers are protected from unsafe products is again one of the key objectives of the 2015 NFR (European Parliament and Council of the European Union, 2015). The decision of the European Commission (EC) to allow a new food product or ingredient to be placed on the market is therefore based on the risk assessment conducted by the European Food Safety Authority (EFSA). Within this risk assessment, EFSA reviews the dossier that is delivered by the food business operator who requests authorisation for their product, in which health risks of the product are evaluated (European Parliament and Council of the European Union, 2015; Turck et al., 2016a). This premarket authorisation is not only required for novel foods, but is also a prerequisite to place other foodstuffs on the market (such as food improvement agents) or before being able to use health claims on food labels (Alie de Boer, Vos, & Bast, 2014; European Parliament and Council of the European Union, 2006, 2008). The new NFR describes a new – and theoretically faster – procedure for this risk assessment.

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Whether newly developed methodologies in nutritional science to establish safety can be used in the scientific dossier, however, still remains uncertain in the revised legislative act.

In contrast to nutritional science, which thrives with ongoing discussions and continuous methodological improvements, law and subsequent guidelines usually use unambiguous specific requirements for safety assessments. These regulatory acts are therefore always based on dated scientific concepts and not on the most recent advancements (Bast & Hanekamp, 2017b; Silano, 2009; Zwietering, 2015). This review aims to optimise the crosstalk between science and law by analysing the legal concept of food safety and discussing the methodological requirement to assess safety. Whereas other publications (Ballke, 2014; Coppens, 2013; Finardi & Derrien, 2016) already addressed the development of the new novel food regulation, this article focusses on bridging the gap by increasing the mutual understanding of both nutritional science and food law. This paper first discusses the concept of food safety in food law, subsequently the adjustments made to the NFR are evaluated and the safety assessment requirements under the 2015 NFR are explored.

1.1. Food safety and risk management policies

As previously described in literature, it is impossible to ensure that a food will never pose a risk to any consumer (Blaauboer et al., 2016). Policies regarding food safety are therefore developed to establish, as described by the Organisation for Economic Co-operation and Development (OECD) in 1993, *'a reasonable certainty that no harm will result from the intended uses'* (OECD, 1993). With this definition, the OECD recognises that a food may contain (natural) toxins, but they are considered to be safe based on long-term experience how to prepare and use these foods (OECD, 1993). To control potential risks arising from food consumption, risk analysis procedures are put in place, in which risks are evaluated and management decisions are made based on this scientific evaluation of the potential risk (FAO/WHO, 1997).

In Europe, risk assessment procedures were established when food legislation was reformed in response to various food scares such as the BSE crisis in the 1990s (Vos, 2000). Prior to these food scares, the primary focus of European legislation on foodstuffs was to ensure that national legislation of different member states of the EU would be harmonised, to create one internal market without barriers to trade. The need to protect consumers from safety hazards and from being mislead through legislation was identified by these food scandals, which resulted in the development of a new framework regulation for European food law, known as the General Food Law (GFL) (Szajkowska, 2009). Article 6 of the GFL emphasises the need for scientific evidence to analyse the risk that a food poses, to guarantee a high level of health protection (European Parliament and Council of the European Union, 2002; Szajkowska, 2009). This scientific risk assessment is conducted independently and transparently by EFSA. The results from this risk assessment feed directly into the EC's risk management decision, determining whether the product can be brought to market (Alie de Boer et al., 2014; European Parliament and Council of the European Union, 2002).

Although the GFL does not provide a definition for food safety, Article 14, describing food safety requirements, emphasises that unsafe foods '*shall not be placed on the market*' (European Parliament and Council of the European Union, 2002). This unsafety is classified into a food being either '*injurious to health'* or that it is *'unfit for human consumption'* (European Parliament and Council of the European Union, 2002). When a food affects short- or long term health of the person consuming it or that of subsequent generations, when toxic effects could accumulate or when the specific target group of the food may be sensitive to the product, a food can be recognised as injurious to health as described in Article 14(4). Food can be unfit for human consumption, according to Article 14(5), based on its intended use or when it would be contaminated. As described in Article 14(3), whether a food is determined to be unsafe is based on both the normal conditions of use of the food product and the information that is provided to the consumer about the food and its potential negative effects (European Parliament and Council of the European Union, 2002).

Specific legislative acts regarding foods have been developed subsequent to the entry into force of the GFL in 2002, ranging from rules on the hygiene of foodstuffs (European Parliament and Council of the European Union, 2004), communicating health effects of products (European Parliament and Council of the European Union, 2006), and labelling information for consumers (European Parliament and Council of the European Union, 2011). Various of these regulations have not been developed to deal with a specific adverse situation or crisis, but to proactively protect consumers from safety hazards or from misleading. The precautionary principle is therein key: when scientific uncertainty upon the safety of a product persists, Article 7 of the GFL specifies that the Commission can decide not to allow a product on the market based on this principle (European Parliament and Council of the European Union, 2002). The NFR is one example of such a proactive regulation: when safety of the food or food ingredient cannot be established within the dossier, the product will not be allowed on the European market. Proving that a food is safe is however only possible by analysing in which situations it will *not* be harmful for consumers. Science can never provide 100% certainty that consuming the food is completely without risk.

1.2. Regulation 2283/2015 – the new novel food regulation

In 1997, the Novel Food Regulation (Regulation (EC) 258/97) entered into force. This regulation was developed to ensure that food products, which are new to the market - either because they originate from countries outside the EU or because they are produced using new scientific findings or technologies - are safe for human consumption (European Parliament and Council of the European Union, 1997). With this regulation, differences between national laws in dealing with new products would be discarded with a clear regulatory framework, which should stimulate trade within the internal European market and thereby stimulate innovation (Blind, 2012; European Parliament and Council of the European Union, 1997).

Although the main aim of the 1997 NFR was to ensure the safety of all new food products, it did not intend to develop a premarket authorisation procedure for all food products newly placed on the market but only for significantly changed or completely new products (Coppens, 2013). For all these so-called novel foods (NFs), the risks of consuming these products would be assessed by a national competent authority of the Member State in which the company applied for a NF authorisation (European Parliament and Council of the European Union, 1997; Health Council of the Netherlands, 2007). When requesting this market authorisation, a dossier should be submitted with scientific evidence detailing *i.a.* compositional details, expected consumption patterns, toxicological safety, nutritional safety and allergenicity, to be critically reviewed within the scientific risk assessment procedure (Coppens, Da Silva, & Pettman, 2006; Health Council of the Netherlands, 2002, 2007). Specific requirements for these dossiers were further specified in a Commission Recommendation produced by the Scientific Committee on Food (European Commission, 1997). As described in Article 6 of the NFR, when other Member States or the EC would not agree upon the conclusions of this safety assessment, EFSA (and before the GFL entered into force, the EC's Scientific Committee on Food) would be requested to conduct this risk assessment (Health Council of the Netherlands, 2002, 2007). The positive or negative opinion of this expert panel upon the safety of the product was sent to the EC and the Standing Committee on the Food Chain and Animal Health Foodstuffs (previously known as the Standing Committee for Foodstuffs), who decided upon authorising the NF (Coppens et al., 2006; European Parliament and Council of the European Union, 1997).

Following Article 14 of the NFR, the regulation had to be evaluated

in a report of the EC within five years (European Parliament and Council of the European Union, 1997). Due to this evaluation, the revision of the NFR started in 2002 (Coppens, 2013). With this revision, issues that had been arising due to the practical application of the regulation could be discussed. These issues included differences between Member States' interpretation of the definition of NFs, the ongoing discussion about the safety of genetically modified foods and the time-consuming procedure for authorising a NF request (Coppens, 2013; Coppens et al., 2006). The first attempt to revise the NFR stranded in 2011 due to disagreements on nanotechnology and animal cloning (Ballke, 2014), but a second endeavour resulted in the development of Regulation 2015/2283 which will enter into force on January 1st, 2018 (Commission of the European Communities, 2008; European Parliament and Council of the European Union, 2015; Finardi & Derrien, 2016). Genetically modified foods were already exempted from the regulation due to new legislation developed in 2003 (Coppens et al., 2006; European Parliament and Council of the European; Union, 2003a, 2003b), and the issues on animal cloning and nanotechnology are addressed by drawing new specific legislation addressing animal cloning and requiring additional (delegated) acts concerning nanotechnology in the new NFR (European Parliament and Council of the European Union, 2015; Finardi & Derrien, 2016). All dossiers requesting authorisation under Regulation 258/97 which are not finished at January 1st, 2018 will be reviewed under Regulation 2015/2283. The Commissioner for Health and Food Safety Vytenis Andriukaitis described the revised Regulation to create ‘a more effective regulatory environment’ which will stimulate innovation and ensure food safety for consumers (European Commission, 2015).

1.3. Main adjustments

The main changes from the 1997 NFR to Regulation 2283/2015 concern the (a) definition of NFs; (b) creation of a centralised authorisation procedure; (c) establishment of a Union list of authorised NFs with a generic authorisation decision; and (d) immediate involvement of EFSA in the risk assessment process.

1.3.1. Definition of a novel food

Article 3 of Regulation 2283/2015 defines a NF based on two elements: whether (i) it has *not* been consumed to a significant degree within the EU before 15 May 1997 and (ii) it falls within one of the defined categories of NFs (European Parliament and Council of the European Union, 2015). The first element ensures that food products are not only novel because of technical and scientific innovations, but also products that have not been consumed within the EU are considered as new ingredients or foods. As displayed in Table 1, Article 3(2(a) lists ten specific categories for the second part of the definition (including food with a new or intentionally modified molecular structure), whereas the 1997 NFR only specified six categories for NFs, of which two categories relating to foods containing or produced from genetically modified organisms were already removed from the NFR in 2004 (European Parliament and Council of the European Union, 2003a). As it did not contain categories for NFs, the 2013 proposal for a new NFR led to disagreements about the widened scope of the regulation and potential legal uncertainty that could arise from this broad definition (ENVI (European Parliament's Committee on Environment Public Health and Food Safety), 2014). The final 2015 regulation therefore contains ten categories to specify which type of products would fall into the definition of a NF. The adjusted categories ensure *i.a.* that not only *parts* of foods can be considered as NFs, but also a *complete* plant or animal can be treated as novel and can require the full authorisation procedure with prove of its safety for human consumption (European Parliament and Council of the European Union, 2015). The categories were considered necessary to clarify and update the categories of food that should be seen as NFs (still including food from cloned animals as long as no specific legislation is developed concerning these products), and to ensure no differences can arise between Member States in interpreting the scope of the Regulation (European Parliament and Council of the European Union, 2015; Finardi & Derrien, 2016). The categorisation and its suitability with future developments is however already discussed (Finardi & Derrien, 2016).

1.3.2. Centralised authorisation procedure

Under the 1997 NFR, applicants for the authorisation of a NF submitted their dossier to the competent authority of a Member State. This competent authority conducted the risk assessment regarding the safety of the NF and decided whether additional assessment would be required before the NF could be authorised (Health Council of the Netherlands, 2002, 2007; B. M. J. van der Meulen & van der Velde, 2011). The decision of this competent authority was however often challenged by other Member States or the EC, and EFSA would be requested to conduct an additional risk assessment to inform the final authorisation decision of the EC and the Standing Committee on the Food Chain and Animal Health (Coppens, 2013; European Parliament and Council of the European Union, 1997; B. M. J. van der Meulen & van der Velde, 2011). Under the new NFR, the application for a NF and its dossier for risk assessment is sent directly to the EC, who will publish the summary and immediately make the application available for all Member States. As displayed in Fig. 1, EFSA is requested to conduct the risk assessment to assess the safety of the NF within nine months. These results will be weighed in the authorisation decision, made by the EC and subsequently the Standing Committee on Plants, Animals, Food and Feed (European Parliament and Council of the European Union, 2015). This is followed by an update of the Union list with authorised novel foods (as described in the next section). The EC has a time limit of seven months from receiving EFSA's opinion to decide upon the authorisation request, when EFSA is not consulted (in case an update of the Union list is not expected to have an effect on human health), these seven months start from the date of receiving the valid application. The new and centralised authorisation procedure consists of fewer steps, which should speed up the decision-making process upon the authorisation of a NF and make it less time- and resource consuming for both industrials and decision makers. Although the new process contains fewer steps, the authorisation procedure is still expected to take at least two years without any clock-stops by EFSA or the EC.

The novel food regulation also defines traditional foods from third countries in Article 3(2). A food product is a traditional food only when it is derived from *primary production* and when a *history of safe use* for at least 25 years can be established for a significant number of people in a third country (European Parliament and Council of the European Union, 2015). For these products, a faster and simplified procedure is established. Within this notification process, data upon the product's composition and its country of origin must be provided, accompanied with data to demonstrate the history of safe use and proposals for specific conditions of use and labelling requirements (Turck et al., 2016b). When no objections are raised by Member States or EFSA within four months, the EC will update the Union list with the new novel food. In case of safety objections, the applicant can provide additional information regarding these safety objections as described in Article 16 of the NFR (European Parliament and Council of the European Union, 2015). EFSA will be requested by the EC to review this information and within six months, the EC will receive EFSA's opinion and will decide upon the authorisation (within three months) together with the Standing Committee. When the authorisation is granted, again the Union list will be updated (European Parliament and Council of the European Union, 2015). When these safety objections do not concern the question of history of safe use but address other issues, EFSA's NDA Panel already describes in its guidance documents that applicants are referred to the guidance documents for regular authorisation requests (as described in Article 10 of the NFR) (European Parliament and Council of the European Union, 2015; Turck et al., 2016a, 2016b). In

Table 1
Novel food categories.

Regulation 258/97*	Regulation 2015/2283**
(a) foods and food ingredients containing or consisting of genetically modified organisms within the meaning of Directive 90/220/EEC***	(i) food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997
(b) foods and food ingredients produced from, but not containing, genetically modified organisms***	(ii) food consisting of, isolated from or produced from microorganisms, fungi or algae
(c) foods and food ingredients with a new or intentionally modified primary molecular structure	(iii) food consisting of, isolated from or produced from material of mineral origin
(d) foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae	(iv) food consisting of, isolated from or produced from plants or their parts, except when the food has a history of safe food use within the Union and is consisting of, isolated from or produced from a plant or a variety of the same species obtained by: - traditional propagating practices which have been used for food production within the Union before 15 May 1997; or - non-traditional propagating practices which have not been used for food production within the Union before 15 May 1997, where those practices do not give rise to significant changes in the composition or structure of the food affecting its nutritional value, metabolism or level of undesirable substances
(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 traditional propagating or breeding practices and having a history of safe food use	(v) food consisting of, isolated from or produced from animals or their parts, except for animals obtained by traditional breeding practices which have been used for food production within the Union before 15 May 1997 and the food from those animals has a history of safe food use within the Union
(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	(vi) food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae
	(vii) food resulting from a production process not used for food production within the Union before 15 May 1997, which gives rise to significant changes in the composition or structure of a food, affecting its nutritional value, metabolism or level of undesirable substances
	(viii) food consisting of engineered nanomaterials as defined in point (f) of this paragraph
	(ix) vitamins, minerals and other substances used in accordance with Directive 2002/46/EC, Regulation (EC) No 1925/2006 or Regulation (EU) No 609/2013, where: - a production process not used for food production within the Union before 15 May 1997 has been applied as referred to in point (a) (vii) of this paragraph; or - they contain or consist of engineered nanomaterials as defined in point (f) of this paragraph
	(x) food used exclusively in food supplements within the Union before 15 May 1997, where it is intended to be used in foods other than food supplements as defined in point (a) of Article 2 of Directive 2002/46/EC

* = defined in Regulation 258/97, Article 1(2).
** = defined in Regulation 2015/2283, Article 3(2)(a).
*** = categories removed from Regulation 258/97 by the entry into force of Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed.

that case, the time frames for decisions of EFSA and the EC are a bit shorter than during the regular authorisation process, but the preparation of the scientific dossier will still be equally resource- and time consuming for the applicant.

1.3.3. Union list

Article 6 of the new NFR defines the Union list of authorised NFs, which will be established by the Commission. NFs on this list can be sold in the EU's internal market (European Parliament and Council of the European Union, 2015). The Union list contains generic products, where under the old NFR the product-specific authorisation applied only to the applicant of the dossier (European Parliament and Council of the European Union, 1997). Therefore, the substantial equivalence procedure, which was created in Regulation 258/97 to give companies the opportunity to apply for an authorisation based on the successful authorisation of a similar product, will not exist anymore under Regulation 2015/2283. This generic authorisation could encourage the use of novel ingredients on the European market and thereby stimulate innovation in the food industry. With all product-specific authorisations under the 1997 NFR turning into generic authorisations from January 1st, 2018, the number of products on the European market containing such previously approved ingredients could rise.

The competitive advantage that was gained by the product-specific authorisation of a NF is thereby removed. A first-mover advantage could still be gained by the possibility given to applicants to protect scientific data provided in the dossier for five years (European Parliament and Council of the European Union, 2015; Turck et al., 2016a). Whether this five year data protection will stimulate companies to innovate and increase the number of NFs on the market can however be questioned, as its effect in other European food laws is highly questioned (Alie de Boer & Bast, 2015).

1.3.4. Risk assessment

The general conditions for a NF to be included in the list are described in Article 7 of the new NFR: the food must not pose a risk to human health, its intended use should not mislead the consumer and – when replacing a regular food product – it cannot be nutritionally disadvantageous (European Parliament and Council of the European Union, 2015). As depicted in Fig. 1, the risk assessment to review a NF's safety for human consumption is immediately assigned to EFSA through which the procedure should be simplified and accelerated, to encourage innovations. The guidance documents published by EFSA in November 2016 seem to imply that dossier requirements have not been amended much from the procedure under the 1997 NFR (Turck et al., 2016a, 2016b). Within these guidance documents, the dossier requirements are specified and some suggestions are made for the tests that can be conducted to ensure safety within the different domains (including kinetics [the absorption, distribution, metabolism and excretion of the novel food ingredients], toxicology, nutritional information and allergenicity). Novel methods to assess safety, including *in silico* modelling

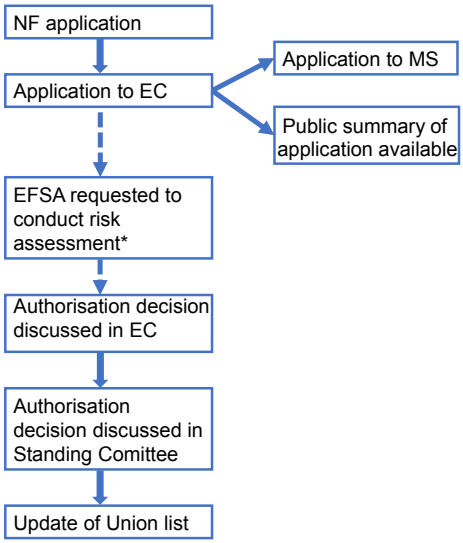

Fig. 1. Flowchart of centralised authorisation procedure under Regulation 2015/2283.
* = It is not required to consult EFSA. Only when a novel food is expected to affect human health, EFSA will be requested to conduct a risk assessment upon the safety of the novel food. Next to the EC, also the applicant and MS will receive the results of EFSA's risk assessment.
NF = Novel food; EC = European Commission; MS = Member States; EFSA = European Food Safety Authority.

and –omics technologies, seem to be disregarded in these guidelines however, whereas such models are promoted in other policy documents such as the EU animal welfare Directive (Directive 2010/63/EU) (European Parliament and Council of the European Union, 2010). Within the next section ('Assessing food safety under the NFR') different methodologies to study the dossier requirements will be discussed.

A Commission Recommendation (a non-binding legal act) was published under the 1997 NFR on how to construct the dossier (European Commission, 1997; European Union, 2012; B. van der Meulen & van der Velde, 2008). Under the current NFR however, two guidance documents on the substantiation of an authorisation request are published by EFSA. Although these guidance document describe to update the Commission Recommendation following Article 29 of the 2015 NFR, it only says to *'present a common format for the organisation of the information to be presented'* and that adherence to the format will *'help EFSA carry out its evaluation and deliver its scientific opinion in an effective and consistent way'* (Turck et al., 2016a, 2016b). As it is the task of EFSA to assist the EC in scientific and technical questions under food law, their role in the development of the guidance documents is not surprising. However, the involvement of the Commission itself in developing the recommendation in 1997 might, even though it is a non-binding legal act, imply a different legal status of the document. Still, this difference is not expected to influence the authorisation requirements for NFs and novel ingredients.

1.4. Assessing food safety under the NFR

In all applications under the NFR, scientific data must be included to substantiate the safety for human consumption of the NF. Only for traditional novel foods, as previously described under 'Centralised authorisation procedure', a notification dossier is sufficient (Turck et al., 2016b).

The scientific dossier must include information upon safety aspects of the NF and its production process, and should include information on the composition of the product, its proposed use and its anticipated intake (Turck et al., 2016a). Additionally, kinetic, toxicological, nutritional and allergenic properties need to be evaluated. When hazards are identified, these hazards need to be placed into perspective of the expected intake and the proposed target population of the NF in order to evaluate the actual risk (Turck et al, 2016a). The methods to analyse these safety aspects are highly debated (Blaauboer et al., 2016; Edwards, 2005; Howlett, 2008). The data requirements as described in EFSA's guidance documents and their implications are analysed in this section.

1.4.1. Kinetics and toxicity

The first aspect to be established for the NF is its fate in the body, by analysing the absorption, distribution, metabolism and excretion (ADME) of the product. Without specifying any methodologies, EFSA describes that kinetic data from both humans and animals are of importance to assess the nutritional and toxicological consequences of consuming this NF (Turck et al., 2016a). Kinetic data should not only identify the potential toxicity of a novel ingredient, it should also establish whether nutritive ingredients such as vitamins and minerals are absorbed and distributed throughout the body. Toxicity testing of a NF, which should be based on kinetic and nutritional data, includes the assessment of genotoxicity, subchronic toxicity, chronic toxicity and carcinogenicity, and reproductive and developmental toxicity. If available, human data from intervention studies or observational studies are requested, to analyse potential adverse effects and containing relevant safety assessment information such as physical examination data, blood or urine analyses, and organ function tests (Turck et al., 2016a). The full risk assessment procedure under the new NFR is expected to be relatively similar to the requirements used to assess safety under the 1997 NFR. Yet, the guidance documents seem to imply that if there are indications for toxic effects, a 90 day-animal study will be required for toxicity testing, where under the 1997 NFR a 28 day-animal toxicity test was considered to be sufficient (Commission of the European Communities, 2008; Turck et al., 2016a).

Within its guidance documents, EFSA's NDA Panel suggests studying single novel ingredients in a similar way to assessing safety of food additives (Turck et al., 2016a). EFSA's food additive guidance document from 2012 recommends to balance data requirements against the risk caused by the ingredient when assessing food additive risks (EFSA ANS Panel, 2012). A method to achieve this balance in generating scientific data is the tiered approach, in which the decision to continue testing specific compounds in a subsequent tier is based on findings from preceding tier tests (Becker, Plunkett, Borzelleca, & Kaplan, 2007). The tiered approach increases the flexibility to adapt analyses to evaluate specific endpoints, reduces required resources and time, and minimises the use and suffering of live animals (Becker et al., 2007; EFSA ANS Panel, 2012). The approach is generally comprised of three tiers, with Tier 1 aiming to develop a minimal dataset applicable to all compounds. To this end, various *in vitro* analyses are conducted in the first tier. In Tier 2, more data is generated by conducting *in vivo* animal experiments on compounds which were in Tier 1 shown to be absorbed or which demonstrated (geno)toxicity. Tier 3 testing is conducted on a case-by-case basis, when specific endpoints from Tier 2 need additional clarification. These tests, including *i.a.* studies with repeated doses in experimental animals and data to predict or show kinetics in humans, can for example be triggered by findings in Tier 2 that indicate possible bioaccumulation, such as limited or slow excretion (Becker et al., 2007; EFSA ANS Panel, 2012). Although avoiding the unnecessary use of animal studies is explicitly mentioned in the guidance, animal *in vivo* data is still required to assess potential human risks. The Panel will only assess the use of alternative testing on a case-by-case basis. The acceptance of such alternative tests to establish kinetics and toxicity of NF ingredients can therefore be questioned. Whereas other EU regulations requiring scientific data on safety aspects (e.g. REACH) are more progressive in recommending reducing animal testing, the NFR seems to overlook this aspect of establishing food safety (Wagner, Fach, & Kolar, 2012).

While single novel ingredients can be studied in a way similar to food additives, whole foods must be 'tested like complex mixtures' since

NFs need to be tested as they are intended to be marketed (Turck et al., 2016a). Kinetic and toxicological analyses are therefore more complex than the assessment of single substances, as the use of setting a single acceptable daily intake (ADI) based on the lowest level of consumption in which no adverse effects are observed, are often not feasible and conducting animal experiments with little amounts of whole foods are less relevant to establish anti-nutritional factors (Blaauboer et al., 2016; Edwards, 2005).

The use of *in vitro* and *in silico* methods to assess food safety is suggested throughout literature, both to improve risk estimates of NF consumption and to reduce the number of animal experiments (Blaauboer et al., 2016; Edwards, 2005; Howlett et al., 2003; Schilter et al., 2014; Wagner et al., 2012). Examples of new concepts and methods that are applied and developed to analyse food safety include quantitative structure-activity relationship (QSAR) analysis, physiologically based toxicokinetic modelling (PBTK) and the Threshold of Toxicological Concern (TTC). Different software programmes can be used to statistically analyse the structure of an ingredient and its biological activity. Subsequent tests of a compound can be based on this predictive *in silico* QSAR analysis (Coecke et al., 2013; Peyret & Krishnan, 2011; Schilter et al., 2014). PBTK is another example of a mathematical method to analyse kinetics of an ingredient, in which anatomical, physiological, physical and chemical data is combined. Findings from QSAR analyses can be used as input parameters in a PBTK model (Coecke et al., 2013; Schilter et al., 2014). Extending and modification of such computational models can allow to combine results from *in vitro* toxicity experiments, ADME data, *in silico* experiments and *in vivo* dose-response curves, which may lead to the development of new methods to reduce or replace tests with experimental animals (Blaauboer et al., 2016). The TTC is another screening prioritisation tool which is used when insufficient data is available, and describes the threshold of exposure to a substance becoming a risk (Bast & Hanekamp, 2017a; EFSA & WHO, 2016; Kroes & Kozianowski, 2002). The TTC is calculated based on exposure data, chemical structure, metabolism and findings on toxicity (EFSA & WHO, 2016). Exposure below the TTC level is considered to not present any safety concern (Bast & Hanekamp, 2017a; EFSA & WHO, 2016). Although exceeding this TTC level does not indicate immediate safety issues, it signals the need to further investigate the specific compound (EFSA & WHO, 2016). Although its use is not considered reliable by EFSA in assessing complex mixtures such as foods (EFSA., 2012), the TTC could be helpful in analysing the safety of novel ingredients.

The use of concepts from systems biology and toxicogenomic approaches (combining genetics, transcriptomics, proteomics, metabolomics and bioinformatics with toxicological data) has also gained increasing interest to analyse food safety risks (Blaauboer et al., 2016; Bucher, 2013; Chen et al., 2012; Hartung et al., 2012; Herrero, Simó, García-Cañas, Ibáñez, & Cifuentes, 2012; Shao et al., 2014). To ensure that these models are used effectively, it is essential to select the correct model for answering specific questions regarding food safety (Blaauboer et al., 2016). As applicants currently rely on the use of the established and accepted methods such as animal experiments, the integration of these new methods in food safety assessment dossiers will only be stimulated by explicitly recommending these methods within regulatory guidance documents. These methods illustrate the paradigm shift in food safety literature: models consisting of intact animals are deemed less necessary to identify adverse endpoints, the current focus is more on using molecular mechanisms of action to characterise all details of the adversity process (Blaauboer et al., 2016; NRC, 2007). But before this paradigm shift can be translated into accepted methodologies in risk assessment regarding food safety, it is necessary to further optimise these methods and their predictive value. Optimisation should focus on reducing the knowledge gaps previously identified in literature (*i.a.* Blaauboer et al., 2016; Edwards, 2005; Kroes & Kozianowski, 2002). These studies specifically advocate to address: (i) current concerns related to the applicability and suitability of available *in vitro* and *in silico* tests in predicting food safety (by means of generating experimental data); (ii) the testing of complex mixtures of whole foods; and (iii) the application of TTC in food safety. Following optimisation of the different methods and after showing their successful application, the paradigm shift swiftly needs to be translated into acceptance of these new methodologies in risk assessments regarding food safety.

1.4.2. Nutritional effects

The scientific dossier should demonstrate that the NF is not nutritionally disadvantageous and therefore it must be established how the food contributes to or interacts with nutrient intake, to identify what the role of the NF in the diet may be (Turck et al., 2016a). Nutritional information should include details upon the nutrient composition and their bioavailability, considering any effects of producing or preparing the food (Turck et al., 2016a). Antinutritional factors, such as inhibiting absorption of modifying bioavailability of nutrients must be determined, as well as known and suspected interactions with other nutrients. Secondly, expected levels of use and estimated intake of the NF for the target population must be presented. Use and intake can be estimated based on relevant scientific literature, the compositional analysis, by comparing it with consumption data of a similar food product, or if needed, data from animal experiments. Within this step, nutrient intake within the regular (background) diet must be considered (Turck et al., 2016a). These expected consumption levels are subsequently compared with health-based guidance values, such as the ADI (Turck et al., 2016a). The intake of vulnerable subgroups such as children must be analysed on a case-by-case basis. When the NF is expected to replace the intake of another food, it must be demonstrated that consuming the NF instead of that other product will not be nutritionally disadvantageous.

Based on the source of the NF, its composition or production, the experienced use, its preparation or findings from literature regarding *i.a.* kinetics and toxicology, additional *in vitro,* animal, and/or human data upon interactions of the NF with other nutrients and the full diet can be requested, next to an evaluation of the compositional data and a review of relevant literature. Again, as described in the previous section, testing whole foods presents a complex issue in this sense. Especially when studying the expected and/or maximum intake of the NF in experimental animals, consumption may give rise to nutritional imbalances in their diets which evoke (adverse) effects unrelated to consumption of the NF itself (Maurici et al., 2007; Paparella et al., 2013). When no direct adverse effects are expected, the use of post-marketing monitoring presents the best option to keep track of potential adversities following consumption. Such post-marketing monitoring, in which reported adverse effects that are attributable to the consumption of foods are analysed, is already mandatory for pharmaceutical products (European Parliament and Council of the European Union, 2001). Such pharmacovigilance systems or post-marketing systems were developed in response to the thalidomide-affair in the 1960s, where birth defects in children were caused by thalidomide intake during pregnancy (A. de Boer, van Hunsel, & Bast, 2015). In France, a nutrivigilance system is already in place to analyse reports of adverse responses following food supplement or functional food consumption (Rihouey-Robini, 2014). Such a nutrivigilance system encompasses a scheme in which adverse events can be reported, that are attributed to food supplement intake or to the consumption of any type of foodstuff such as functional or novel foods. These reports can be filed by health professionals, producers and distributors (Rihouey-Robini, 2014). This scheme can help to identify relationships between *i.a.* novel food consumption and the occurrence of adverse events. Although post-marketing monitoring is costly and will not replace pre-market assessment (Hepburn et al., 2008), when no immediate adverse effects are expected but additional evidence is required, the development of a nutrivigilance system might enable post-marketing monitoring possibilities.

1.4.3. Allergenicity

Since most food allergens are glycosylated proteins, it is important to analyse the potential allergenicity of a NF when a NF contains protein or protein fractions. When proteins are determined in the compositional analysis, the default assumption of EFSA is that these proteins have allergic potential (Turck et al., 2016a). A novel protein can present a risk because of *de novo* sensitisation or cross reactivity. Sensitisation, the initiation of an allergic immune response following from the intake of an allergen, can be caused in several different ways: orally via the gastrointestinal tract (class 1 food allergens such as peanuts or milk); via the respiratory tract in case of class 2 food allergens (aeroallergens such as birch pollen allergens); or via other routes of exposure such as cutaneous exposure through a disrupted skin barrier (Lack, 2012; Valenta, Hochwallner, Linhart, & Pahr, 2015). Early exposure to potential allergens is however also shown to induce tolerance to food proteins (Du Toit et al., 2017; Lack, 2012). The allergen intake leads to a hypersensitive immune response, which can be IgE mediated, non-IgE mediated or a hybrid response. In classic, IgE-mediated food allergies, IgE antibodies are produced which bind to the surface of mast-cells and basophils (Valenta et al., 2015). These cells are thereby activated and produce inflammatory mediators such as histamine and/or cytokines, which may be released upon subsequent contact with the allergen (Valenta et al., 2015). De novo sensitisation indicates that a new protein causes such an allergic reaction. Cross-reactivity describes that a protein, which is homologous to a known allergen, causes a similar allergic reaction as the known allergen. This is seen in for example birch pollen allergens that can cross-react with apple allergens (Valenta et al., 2015).

As there is no known cure for food allergies, management of food allergy relies mainly on avoiding allergens (Sathe, Liu, & Zaffran, 2016; Sicherer & Sampson, 2014). As required by Regulation (EU) No 1169/2011, the European Regulation on Food Information for Consumers (FIC), allergens must be indicated on the label of food products to provide consumers with information about potential allergens (European Parliament and Council of the European Union, 2011). Also for the risk assessment of novel foods, knowledge upon potential allergens is essential.

EFSA's guidance document on NFs suggests various methods to analyse the potential allergenicity of foods, including characterisation of the protein fraction, and human testing. Such human tests include the detection of specific IgE antibodies, skin prick testing or controlled food challenge studies (Turck et al., 2016a). The 2014 guidance document on the evaluation of allergenic foods for labelling purposes developed by EFSA describes various methods that can be selected to test for various allergens. This guidance document however mainly focusses on known allergens and specifically the 14 allergens that are required to be placed on the label under the FIC (EFSA, 2014). Cross-reactivity can be analysed by homology searches and serological testing, but when novel proteins are introduced in the diet, analysis of a putative new allergen is more difficult (Dearman & Kimber, 2009; Verhoeckx, Broekman, Knulst, & Houben, 2016). Verhoeckx et al. (2016) therefore suggest to detect a potential allergen in four phases: (i) *collect information* about the history of exposure to the protein, while taking into account environmental and geographical factors; (ii) *observe the taxonomy* of the NF proteins and the relationship between these proteins and known allergens to indicate potential allergens; (iii) *identify the NF proteins* and compare them with proteins in specific databases; and (iv) consider the way that consumers will *use the product* because of potential matrix changes due to processing and preparation of the NF and its influence on the putative allergenic potential (Verhoeckx et al., 2016). This information can help in determining which proteins of the novel food musts be tested in *in vitro* studies (including IgE binding studies) and subsequent *in vivo* experiments such as functional IgE tests.

2. Conclusion and future perspectives

Current food safety policies aim to provide a reasonable certainty that a food will not pose a risk to consumers, based on its intended use (OECD, 1993). It is of utmost importance for consumers, food scientists and risk managers to be aware that it can never be guaranteed that no consumer will ever experience adverse events, as zero risk does not exist. In the EU, this reasonable certainty that food is safe for human consumption is for new food products ensured by the novel food regulation. The NFR requires premarket authorisation of all foodstuffs new to the European market, based on EFSA's scientific evaluation of the evidence provided by the food business operator to establish the product to be safe for human consumption. The updated NFR, with a new definition of novel foods, a centralised and generic authorisation system and a renewed risk assessment procedure, should be a better fit with the current and future situation in the food industry. As the time frames within the regular novel food authorisation procedure are shortened and the notification procedure for traditional foods is simplified, costs and resources of the authorisation process should be reduced. As safety is still key within the 2015 NFR, all authorisations are based on EFSA's opinion on a scientific dossier containing evidence upon a product's safe history of use with traditional foods, or data upon kinetics, toxicology, nutritional information and allergenicity in the case of novel foods. The requirements for these dossiers, as laid down in the guidance documents developed by EFSA (Turck et al., 2016a, 2016b), however seem to be barely adapted from the 1997 Commission Recommendations. It is especially remarkable that these food safety dossiers still heavily rely on the use of experimental animals, whereas other legislative documents and guidance documents throughout the EU promote the use of new methods to reduce resources and the need for animal experiments. Promoting the development of new methods such as predictive *in silico* models and requiring post-marketing monitoring, by actively encouraging their use and accepting these methods as evidence in scientific dossiers will be of utmost importance to ensure that the 2015 NFR will not be outdated within five years.

This paper exemplifies that the use of scientific standards in legislation inevitably leads to tensions between law and science: where uncertainties are unacceptable in law, science thrives by ongoing discussions that trigger new (methodological) developments. Thereby, laws become outdated easily and due to not fitting into these regulations, the value and potential of scientific endeavours are not always acknowledged. The fundamental role for scientific evidence in legislative schemes, such as the novel food regulation presented in this paper, can even decrease the likelihood of scientific innovations in assessing safety: since these novel methods give no certainty upon their value for risk assessment, they are omitted and not further improved to becoming valuable and acknowledged tools. Next to the scientific community, the risk assessors (here: EFSA) as well as the risk managers (the EC) must acknowledge the need to keep on improving the methods to assess safety of foods, to continuously improve the risk analysis cycle. To foster mutual understanding and to improve the use of science in regulatory acts, it is of utmost importance to bridge the gap between both fields of expertise. Recognising the scientific uncertainties in legislation while stimulating to study these uncertainties thoroughly is required to improve scientific and regulatory developments. By discussing the boundaries of both fields in scientific literature, the limitations of both food law and nutritional science can be acknowledged and addressed.

Conflicts of interest

The authors declare that they have no conflict of interest.

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