



Review

Novel foods and allergy: Regulations and risk-benefit assessment

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ABSTRACT

Hypoallergenic novel foods may have benefits for food-allergic consumers. However, other novel foods may exacerbate the problems associated with food allergy. This paper reviews the existing legislation associated with the introduction of novel foods and specifically considers its coverage of allergy risks and benefits. Various regulations are in place to protect consumer health. These regulations require novel food safety to be assessed before they can enter the market, but do not specify how this assessment, which includes allergenicity, should be performed. It is concluded that including a benefit assessment in the novel food legislation, may be beneficial.

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1. Introduction

There has been considerable societal discussion regarding the potential advantages associated with the introduction of novel foods and ingredients into the food chain, in response to societal recognition of the potential benefits as associated with these products. Proposed benefits may relate to improvements in public health, diversification of nutritional intake, or improved food security or quality (Putten et al., 2006). The designation “novel foods” as used in the current discussion pertains to foods or food ingredients with no history of widespread and safe consumption. The novelty of a food can be the result of: (1) genetic modification

Abbreviations: ACNFP, Advisory Committee on Novel Foods and Processes; DNA, deoxyribonucleic acid; EC, European Community; EFSA, European Food Safety Authority; EU, European Union; FDA, Food and Drug Administration; FOSDU, Food for Special Dietary Uses; FOSHU, Foods for Specified Health Uses; FSANZ, Food Standards Australia New Zealand; GM, genetically modified; GMO, GM organism; GRAS, generally recognized as safe; IgE, immunoglobulin E; MHC, major histocompatibility complex; NDA Panel, Panel on Dietetic Products, Nutrition, and Allergies; UK, United Kingdom; US, United States; USA, United States of America.

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of the food itself, or its production using genetically modified (GM) organisms, (2) the application of novel processing techniques, such as new types of heat processing, non-thermal preservation methods and the application of new processes catalysed by enzymes, or (3) the food in question having no prior history of consumption in general, or in a specific region or country, such as for “natural” non-GM foods (Putten et al., 2006).

Food allergy is a hypersensitivity reaction initiated by immunologic mechanisms to normally harmless food components, for which the prevalence ranged between 3 and 35% for self-reported allergies, and between 2 and 5% for reports based on objective measures, such as symptoms and sensitisation (Rona et al., 2007). In the discussion that follows, food allergy is understood to refer to immunoglobulin-E-(IgE)-mediated reactions of the human immune system to food. The development of hypoallergenic novel foods and ingredients may be utilised to develop a food allergy management strategy that potentially improves the quality of life of food-allergic consumers by eliminating or substituting proteins which provoke allergic responses. However, it is also important to acknowledge that the introduction of other novel foods and ingredients has the potential to introduce allergenic proteins into the food chain. For example, at the time of writing, concerns exist about the potential of novel foods to introduce new allergens into the foods chain (Putten et al., 2006).

An example of an allergenic novel food introduced onto the market before relevant legislation came into force is that of kiwi fruit, as discussed elsewhere in this article (Section 3.3). An example of another novel food that might have allergenic properties is honey with added bee venom, which has been on the market in New Zealand since 1996 and was recently submitted for approval as a novel food to the United Kingdom’s (UK) Advisory Committee on Novel Foods and Processes (ACNFP). Whereas the applicant stated that its primary purpose was to alleviate arthritis, it also stated that bee venom could be used for immunotherapy against bee venom allergy. The latter argument was not accepted by the ACNFP given the fact that therapy requires careful medical assistance. Based on several case reports of anaphylaxis in New Zealanders consuming the honey containing bee venom, the ACNFP considered that it could not conclude that the products was safe but, if it still were to be approved, should be clearly labelled as an allergen (ACNFP, 2009).

Another novel food for which a petition has been submitted to ACNFP is Touchi soup, *i.e.* an extract of fermented soybeans to be used as a food supplement. The application and the draft opinion mention that no allergic responses were reported in individuals who consumed the soup during six months. As a possible explanation for this observation, it is argued that the fermentation process can degrade the allergenic proteins in soybean to fragments that do not further cause allergies (ACNFP, 2008).

There is little information available regarding consumer attitudes towards novel hypoallergenic foods, independent of whether consumers suffer from a food allergy (Schenk et al., 2008). Both in case of a novel food improving the quality of life of food-allergic consumers and in case of a novel food exacerbating the incidence of food allergy, it is important to examine how existing regulatory frameworks designed to optimise consumer protection deal with the case of novel foods and food allergy. For this purpose, it is interesting to compare these frameworks as being operational in different countries worldwide.

The aim of this paper is to review the existing legislation associated with the introduction of different types of novel foods, to specifically consider its coverage of risks (and benefits) of novel foods associated with food allergy, and to identify where additional information may be required to protect food-allergic consumers. The focus of the review will be the European legislation. This will be compared to a select number of legislations with well-established regulations pertaining to

novel foods, *i.e.* Canada, the United States of America (USA), and Australia–New Zealand. Existing regulatory frameworks have been developed to protect human health in relation to novel food safety. These frameworks do not indicate how novel food allergenicity should be assessed. Therefore, the safety assessment methods currently available for the different types of novel foods are presented. It is also important to note that various emerging food risk governance models posit that an assessment of both the risks as well as the benefits associated with a food issue are required, and furthermore, to broaden risk and benefit assessments towards the impacts on health and other socio-economic issues (*e.g.* Wentholt, Rowe, König, Marvin, & Frewer, 2009; EFSA, 2010b). Therefore an overview of the potential benefits of novel foods for food-allergic consumers will be discussed.

2. Novel food legislation

Various legislations have regulations in place that require novel foods be legally approved before entering the market. Such regulations usually also require that these novel foods be assessed for their safety. In an increasingly globalised and complex food system, it is important to consider how different legislatures consider specific food safety issues, as lack of regulatory harmonisation may be problematic if foods and food ingredients are exported between different regions of the world (Marvin et al., 2009). This applies to novel foods and ingredients entering the food chain, whether as products which have the potential to sensitise new populations hitherto unexposed to the problematic proteins, or who may differentially respond to novel hypoallergenic foods assessed in different regulatory regimes.

2.1. European Union

The European Union (EU) defines novel foods as “foods and food ingredients that have not been used for human consumption to a significant degree within the Community” (European Commission, 2010b). To enable a novel food to be placed on the market in the European Union, Regulation (EC) No. 258/97 of the European Parliament and the Council applies (European Parliament and the Council, 1997). At the time of writing, a new proposal for amendment of Regulation (EC) No. 258/97 is being discussed at the EU political level. As no decision has been taken yet to the adoption of the proposed amendments, it is not possible to discuss these.¹ When Regulation (EC) No. 258/97 went into force, it applied to novel foods and food ingredients that had not been available on the EU market to a significant degree before May 1997. Initially, the scope of Regulation (EC) No. 258/97 also included GM foods and ingredients. However, since 2005, GM foods and ingredients have to be assessed for their safety, and to be approved for their market introduction under Regulation (EC) No. 1829/2003 (European Parliament and the Council, 2003b).

Before being placed on the EU market, the novel foods and food ingredients referred to in Regulation (EC) No. 258/97 must undergo a safety assessment, as a result of which an authorisation decision may be taken by the European Commission.² If neither the Commission, nor a Member State raises an objection, and if no

¹ The proposal for amendment of Regulation 258/97 intends to exclude foods derived from cloned animals and their offspring from the scope of the regulation, as well as to have foods produced by nanotechnology to undergo a specific risk assessment before being approved for use.

² This safety assessment focuses on the systematic and objective evaluation of all available information about the novel food. During the assessment procedure, the competent authority of a Member State that receives an application must make an initial assessment and determine whether or not an additional assessment is required, then forward it to the Commission, which will disseminate the information to all other Member States for their comments or reasoned objections.

additional assessment is required, the applicant will be informed that he may place the product on the market. In other cases, a procedure is followed in which the European Commission seeks scientific advice from the European Food Safety Authority (EFSA), based upon which the European Commission drafts a decision. Whereas EFSA did not exist yet at the time of the adoption of the Regulation, the procedure involving EFSA was implemented after establishment of EFSA, under the General Food Law, *i.e.* Regulation (EC) No. 178/2002 (European Parliament and the Council, 2002). The decision drafted by the European Commission is subsequently submitted to the Standing Committee on the Food Chain and Animal Health, and, depending on the outcomes of that, may be submitted to the Council of Ministers, before an official decision can be taken by the Commission (SCADPlus, 2010).

The information needed when a novel food application is made, depends on the characterizations of the type of novel food, and is described in Commission Recommendation 97/618/EC (European Commission, 1997). Specifically, information is required in thirteen categories, ranging from a specification of the novel foods and the effect of the production process on the novel foods to projections of anticipated intakes, which are needed to evaluate the dietary and nutritional consequences of the novel food. Toxicological information, which includes information about the potential allergenicity, is also required (European Commission, 1997). These recommendations only indicate what type of information should be presented. It does not recommend how this information should be gathered. This may relate to the fact that allergenicity assessments need to be carried out on a case-by-case basis (Codex Alimentarius Commission, 2003; Taylor & Hefle, 2001).

At the time of writing, a total of 115 novel foods have been submitted for authorisation in the EU (European Commission, 2010b). Table 1 gives an overview of novel foods that have received an EU decision about their authorisation under Regulation (EC) No. 258/97 (European Commission, 2010a). GM novel foods that are only novel because of genetic modification are not listed in this table. This is because not all GM novel foods which have been authorised in the EU have been evaluated under Regulation (EC) No. 258/97. Some of the applications have been withdrawn, and for others the assessment procedure is still pending at the time of writing.

Most novel food applications that have been made in the EU are products that can be used as an ingredient for food products. The European Commission has made a decision on the authorisation of 48 novel foods (GM crops not included). Five of these novel foods have been refused because their compliance with the criteria laid down in article 3 (1) of Regulation (EC) No. 258/97 could not be demonstrated. This article states that “novel foods and food ingredients must not present a danger to the consumer; mislead the consumer or differ from foods or food ingredients which they are intended to replace to such an extent that their normal consumption would be nutritionally disadvantageous for the consumer”. In the case of *Stevia rebaudiana*, a novel food to be used as a sweetener (SCF, 1999) and of Nangai nuts from the Ngali tree, a novel introduction to the European market from the Pacific region (SCF, 2000), the scientific opinions were based on the lack of essential data, including, but not confined to, data on allergenicity, pre-empting a conclusion on the safety of these products. For betaine, a food additive claimed to prevent cardiovascular disease, the scientific opinion is explicit about the fact that no clarification has been provided for test-substance related effects in an animal toxicity study, and therefore no safe levels could be established (EFSA, 2008a). For iodine-enriched eggs, which result from the combination of the Columbus egg, rich in polyunsaturated fats, and the Japanese Hikari egg, which is rich in iodine, the authorities of the EU member state (Belgium) where the application had been filed raised objections based on the possibility of the exceedance of

the safe upper level of iodine intake by consumers, about which the other members did not express disagreement (pp. 25–27 of SHC, 2002). With regard to red deer's antler powder to be used as a dietary supplement, the French competent authority that had carried out the initial assessment had stated its concerns about the limited nutritional value, the lacking specifications of the products, and the incomplete data on the potential toxicity and allergenicity of the product, among others. Similar concerns were voiced by other Member States' authorities (ACNFP, 2003a; ACNFP, 2003b).

Forty-three novel foods have been authorised for marketing in the EU because their safety has been sufficiently demonstrated and because they do meet the criteria as laid out in Regulation (EC) No. 258/97. The European Commission's Community Register of GM organisms (GMOs) with authorised uses in food and feed currently contains 33 GMOs, including six GM cotton, 17 GM maize, biomasses from two GM micro-organisms, three GM oilseed rape, one GM potato, three GM soybeans, and one GM sugar beet. These have several authorised uses each, for example the BT11 maize that is authorised to be used for foods and food ingredients, food additives, feed, and for other products (European Commission, 2010c). The dossiers on the novel foods as summarised in the published safety assessments do contain information in the relevant categories from Commission recommendation 97/618/EC. However, little detailed information can be found on the allergenicity assessment of the non-GM novel foods in the published approvals and summaries of the dossier evaluations, given that the original dossiers are usually confidential and not freely accessible. This contrasts with the evaluations of GM foods, for which the allergenicity assessment is a common feature. Whereas attention is paid to the potential allergenicity of non-GM novel foods in the summaries of the evaluations of many dossiers, the assessment is usually more limited than for GM products, referring to, for example, the lack of residual proteins in the final product; the absence of data on allergenicity; the lacking or limited reports of allergic reactions to the novel food based on a history of consumption outside the EU; or the allergenic potential of the novel food as compared to conventional foods (*e.g.* vegetable oils processed in a novel way as compared to conventional oils) (Table 1). For only a limited number of novel foods, such as Ice Structuring Protein, which has benefits both in terms of nutritional and organoleptic profile, and greater temperature stability (Crevel et al., 2007), the scientific opinion's summary of the dossier reflects a more extensive allergenicity assessment, such as amino acid sequence comparison to known allergens, *in-vitro* breakdown by pepsin, IgE binding screening, and skin-prick tests (MEB, 2010) (Table 1). For some novel foods, scientific studies can be found that investigate the (potential) allergenicity. Crevel et al. (2007) report a study with human subjects who consumed ice structuring protein for several weeks and remained in good health, and who developed no IgE antibodies, affirming previous conclusions that these ice structuring proteins are unlikely to have allergenic potential (Crevel et al., 2007). In addition, the EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA Panel) describes a sensitisation study in guinea pigs, which received repeated subcutaneous injections (*i.e.* beneath their skin) of extracts of leaves of the Noni plant (*Morinda citrifolia*), which can be used as an ingredient for fruit juices, but which did not exhibit signs of allergic reactions after oral challenge with the same extracts (EFSA, 2008b). This is similar to a sensitisation test in guinea pigs that has been performed with the juice of Noni fruits (SCF, 2002). Some of the opinions on these applications also mention potential health benefits. An example is provided by phytosterols, which potentially inhibit the absorption of cholesterol (MEB, 2010). On the other hand, the assessment of Chia seeds, rich in omega-3 fatty acids and a potential source of antioxidants, as a novel food by EFSA's NDA Panel revealed cross-reactivity with peanut in serum binding and with sesame in skin-prick testing when Chia was tested (EFSA, 2009).

Table 1

The evaluation of potential allergenicity of novel foods for which the regulatory procedure has been finalized in the EU.

Description of Food or Food Ingredient ^{a,b}	European Commission decision	Additional information	Issues of food allergenicity addressed in scientific opinions? ^{c,d,e}
<i>Stevia rebaudiana</i> (plant and dried leaves)	Refused	Sweetener	Yes, the absence of data on allergenicity in the application dossier was mentioned by SCF in its opinion
Phospholipids from egg yolk	Authorised	Novel processing technique	Yes, the data considered by SCF pertained to possible traces of egg white within the product
Yellow fat spreads with added phytosterol-esters	Authorised	Lower blood cholesterol	No (not specifically addressed in SCF opinion)
Fruit preparations pasteurized using a high-pressure treatment process	Authorised	Novel processing technique	Yes, the impact on intrinsic allergenicity as compared to conventionally treated products was considered (mentioned in Commission Decision 2001/424/EC)
Nangai nut	Refused	Novel food	Yes, the absence of data on allergenicity in the application dossier was mentioned by SCF
Bacterial dextran	Authorised	Polysaccharide for use in bakery products	Yes, data on allergic reactions in humans receiving non-oral clinical dextran were considered by the SCF
Salatrim	Authorised	Fat replacer	No (not specifically addressed in SCF opinion)
Tahitian Noni juice	Authorised	Ingredient in fruit juice mixtures	Yes, the SCF considered data on absence of allergic reactions in experimental animals, while noting the difficulty to predict allergenicity based on animal data. Also reports from post-market surveillance on allergic reactions had been provided by the applicant
Fungal oil SUN-TGA40S	Authorised	Novel baby food ingredient, to enhance brain development	Yes, EFSA's NDA Panel considered the history of allergenicity of the producer organism, the potential presence of traces of soybean allergens in the product, as well as the non-detectability of proteins in the product
Trehalose	Authorised	Sweetener	Yes, the application dossier initially assessed by the UK's ACNFP mentions the issue of allergenicity, referring to data on the allergenicity of carbohydrates in general and the level of protein impurities in the product to be used for food purposes
REDUCOL™	Authorised	Lowers blood cholesterol	No (not specifically addressed in the opinion of EFSA's NDA Panel)
Plant-sterol-enriched rye bread	Authorised	Improves blood cholesterol	No (not specifically addressed in the opinion of the SCF)
Coagulated potato protein and hydrolysates thereof	Authorised	Novel food ingredient	Yes, the initial opinion of the Dutch national authority summarizes the findings on allergenicity of coagulated potato protein and its hydrolysates, based on data on raw and cooked potatoes. It also addresses the issue of sulphite levels in the final product
Docosahexaenoic-acid-(DHA)-rich oil	Authorised	Novel food ingredient with energy reduction effect	The initial assessment by UK's ACNFP addresses the issue of potential allergenicity taking into account the very low level of residual protein and carbohydrate in the final product consisting of refined oil
Phytosterol-enriched fat ingredient – Diminicol	Authorised	Lower blood cholesterol	No (not specifically addressed in the opinion of the SCF)
Multibene® - ingredient (containing phytosterols/phytostanols)	Authorised	Lower blood cholesterol	Yes, the lack of data on allergenicity from post-market monitoring studies is mentioned in the opinion of the SCF
Plant sterols and sterol esters	Authorised	Lower blood cholesterol	No (not specifically addressed in the opinion of the SCF)
Rapeseed oil high in unsaponifiable matter	Authorised	Novel food ingredient	Yes, the opinion of the EFSA's NDA Panel concludes on the allergenic potential compared to conventional, low-erucic-acid rapeseed oil
Maize germ oil high in unsaponifiable matter	Authorised	Novel food ingredient	Yes, the opinion of the EFSA's NDA Panel concludes on the allergenic potential compared to conventional maize germ oil
ENOVA™-oil/diacylglycerol oil (DAG oil)	Authorised	Replace conventional oils	No (not specifically addressed in the opinion of EFSA's NDA Panel)
Phytosterol-esters: Use in a range of products	Authorised	Lower blood cholesterol	No (not specifically addressed in the opinion of the SCF)
Iodine-enriched wild-type eggs	Refused	Novel food (consumption egg)	No (not mentioned by the Belgian authorities' summary of their initial assessment)
Betaine	Refused	Use in drinks, cereal products, confectionary and dairy products	No (not specifically addressed in the opinion of EFSA's NDA Panel)
Deer horn powder	Refused	Dietary supplement	Yes, the initial opinion of the French authorities (quoted by the UK's ACNFP) mentions a lack of data on allergenicity
Whole Chia (<i>Salvia hispanica</i> L.) and ground whole Chia	Refused	Novel food ingredient	Yes, the opinion of EFSA's NDA Panel considered the outcomes of clinical and in-vitro studies on the potential cross-reactivity with other allergens (food challenge, skin-prick testing, sera binding), as well as

Table 1 (continued)

Description of Food or Food Ingredient ^{a,b}	European Commission decision	Additional information	Issues of food allergenicity addressed in scientific opinions? ^{c,d,e}
Isomaltulose	Authorised	Sweetener	bibliographic data on reported allergies against Chia and related plants. Yes, the initial opinions of the UK's ACNFP and the German authorities (as summarized by ACNFP) on two different applications considered the likelihood of allergenicity taking into account the trace levels of protein in the product.
Lycopene from <i>Blakeslea trispora</i>	Authorised	Novel food ingredient	Yes, the EFSA NDA Panel's opinion considers potential allergenicity based on the lack of reported allergies against the producer organism and the low level of protein in the product to be consumed.
Leaf extracts from lucerne	Authorised	Novel food ingredient and dietary supplement	Yes, the EFSA NDA Panel's opinion considers data from various studies, <i>i.e.</i> bioinformatics, in-vitro and in-vivo, on potential cross-reactivity between the lucerne-derived protein concentrate and leguminosae, in particular peanut
Lycopene oleoresin from tomatoes – extension for food use, and also for use in foods for special medical purposes (FSMP) (two separate applications covered by the same opinion of EFSA and decision of the European Commission)	Authorised	Novel food ingredient (besides existing use as colorant)	Yes, the EFSA NDA Panel's opinion concludes on the potential allergenicity of the product as compared to tomatoes based on the fact that the protein fraction is not enriched in the product to be consumed
<i>Allanblackia</i> seed oil for use in yellow fat spread and cream-based spreads	Authorised	Ingredient in yellow fat and cream-based spreads	Yes, the opinion of EFSA's NDA Panel discusses the lack of history of allergic reactions towards the producer and related organisms, as well as the low frequency of allergic reactions towards highly refined seed oils
α -Cyclodextrin	Authorised	Added as dietary fibre	Yes, the opinion of EFSA's NDA Panel considers the potential allergenicity of the final product in the light of the low levels of residual protein
<i>Morinda citrifolia</i> leaf	Authorised	Novel food ingredient (for tea infusions)	Yes, the EFSA NDA Panel's opinion considers the outcomes of an in-vivo animal sensitisation experiment
Additional uses of DHA-(docosahexaenoic acid)-rich oil from micro-algae <i>Ulkenia</i> sp.	Authorised	Novel food ingredient (extending the food categories to which it can be added)	No (not mentioned in the UK ACNFP's summary of initial opinion of the German authority)
Diminicol® rice drink with added phytosterols	Authorised	Extended use of phytosterol ingredient diminicol	No (not mentioned in statement of EFSA's NDA Panel)
Tagatose	Authorised	Sweetener	The initial opinion of the UK's ACNFP discusses the potential allergenicity of the product to be consumed with regard to the possible presence of traces of milk whey proteins derived from milk whey used as a source material for the production process
MultOils (oil containing a diacylglycerol-rich fat component and a free phytosterol-esters component)	Authorised	Lower blood cholesterol	No (not mentioned in the initial opinion of the Dutch authorities)
(Synthetic) lycopene in sunflower oil dispersion	Authorised	Novel food ingredient and dietary supplement	Yes, EFSA's NDA Panel in its opinion considered the possible allergenicity of lycopene itself (based on public literature) and the possible presence of allergenic fish gelatin proteins in the product to be consumed
<i>Morinda citrifolia</i> L. fruit puree and concentrate (extension of use)	Authorised	Novel food ingredient (extending the existing use of juice from fruits of <i>M. citrifolia</i>)	Yes, in the opinion of EFSA's NDA Panel, reference is made to reports on allergic reactions collected through post-market surveillance, and also to data on allergenicity discussed in a previous opinion of the SCF on juice from <i>Morinda citrifolia</i> (noni)
Sucromalt	Authorised	Sweetener	No (not mentioned in the initial opinion of the Dutch authorities)
Ice structuring protein type III HPLC 12 preparation for use in edible ices	Authorised	Novel food ingredient (envisaged use in edible ice products)	Yes, the data considered in the opinion of EFSA's NDA Panel include a range of studies, including bioinformatics, in-vitro and in-vivo studies focusing on potential cross-reactivity of the final product with fish allergens as well as the potential allergenicity of residues of the producer organism (yeast)
Baobab (<i>Adansonia digitata</i>) dried fruit pulp	Authorised	Use in fruit bars and smoothies	Yes; in its initial opinion, the UK's ACNFP considered data on the lack of reported allergenicity of baobab and related species and concluded on the potential cross-reactivity with known allergens as well as <i>de novo</i> allergenicity of baobab itself

(continued on next page)

Table 1 (continued)

Description of Food or Food Ingredient ^{a,b}	European Commission decision	Additional information	Issues of food allergenicity addressed in scientific opinions ^{c,d,e}
Refined Echiium oil (<i>Echium plantagineum</i>)	Authorised	Novel food ingredient	Yes, the UK's ACNFP, in its initial opinion, considers the potential allergenicity in relation to the known occurrence of cytochrome C allergens in Echiium and the small amounts of protein present in the final product.
Lipid extract from <i>Euphausia superba</i>	Authorised	Novel food ingredient, ingredient of dietary foods for special medicinal purposes, and food supplements	Yes, the opinion of EFSA's NDA Panel considers the data on the potential presence of residual proteins in the final product, and their potential cross-reactivity with fish and crustacean allergens
Cold water dispersion (CWD) lycopene (from <i>Blakeslea trispora</i>)	Authorised	Novel food ingredient (besides the existing use as food colorant)	Yes, in the opinion of EFSA's NDA Panel, the allergenic potential of the final product is considered in relation to the non-detectability of proteins in the product to be consumed
Docosahexaenoic-acid-(DHA)-rich algal oil from <i>Schizochytrium</i> sp. for additional food uses	Authorised	Novel food ingredient (extending the existing list of applications in foods)	Yes, the UK ACNFP's initial opinion considers the potential allergenicity in relation to the low level of protein being present in the product to be consumed
Synthetic lycopene	Authorised	Novel food ingredient (besides the existing use as food colorant)	(no details of initial assessment by Irish authorities available)

^a Reference European Commission (2010a), list as of 25 June 2010.

^b The list contains those non-GM novel foods for which the full regulatory procedure has been completed (i.e. withdrawn and ongoing applications, as well as notifications for products being equivalent to other novel foods that have already been authorised, are not mentioned here).

^c This list does not include data on dermal sensitisation considered during the safety assessment, while such data are described in the scientific opinions on α -cyclodextrin, baobab, betaine, lycopene (synthetic, in sunflower oil), lycopene oleoresin, phospholipids from egg yolk, and various plant-sterol-enriched foods.

^d The scientific opinions considered for this list includes opinions of the European Commission's Scientific Committee on Food (SCF) and, since 2003, the European Food Safety Authority's (EFSA) Panel on Dietetic Products, Nutrition, and Allergens (NDA Panel), if these have been solicited by the European Commission. In other cases in which only initial assessments have been carried out by the respective authority of the member state where the application was filed, reference is made to that particular assessment.

^e The quoted scientific opinions can be retrieved from the websites of SCF (European Commission, 2010d), EFSA (EFSA, 2010a), the United Kingdom's (UK) Advisory Committee on Novel Foods and Processes (ACNFP) (ACNFP, 2010), the Dutch Committee on Safety Assessment of Novel Foods (MEB, 2010), and the Belgian Superior Health Council (pp. 25–27 of SHC, 2002).

In addition to legislation regarding the marketing of novel foods, the EU also has legislation regarding the labelling of allergens. Novel foods are subjected to the general labelling requirements (Directive 2000/13/EC) (European Parliament and the Council, 2000), but they may require specific additional information. Directive 2003/89/EC amends the general labelling directive and states that in order to protect food-allergic consumers, the use of certain ingredients should be specified on the product label. These ingredients are cereals containing gluten, crustaceans, nuts, eggs, fish, peanuts, soybeans, milk and dairy products, nuts, sesame seeds, and sulphite at concentrations of at least 10 mg/kg or 10 mg/l (European Parliament and the Council, 2003a). It should be noted that this labelling directive applies to foods that are available in the EU. This directive will only apply to novel foods, once they have been approved in the EU under Regulation (EC) No. 258/97.

2.2. Australia–New Zealand, Canada, and USA: differences and similarities with EU legislation

Table 2 gives an overview of the novel foods safety assessment procedures in the EU, in comparison to procedures in Canada, Australia–New Zealand, and the USA.

The Canadian legislation describes novel foods as foods that result from a process not previously used for food, as products that do not have a history of safe use as a food, or as foods that have been modified by genetic modification also known as genetically modified foods, GM foods, genetically engineered foods, or biotechnology-derived foods (Health Canada, 2010a). In practice, this means that most of the novel foods assessed are GM or derived from certain mutation-bred crops. The Canadian approvals also pertain to a number of novel processes, e.g. UV-disinfection of apple juice and high-pressure pasteurisation of meat (Health Canada, 2010b). Allergenicity assessment is included as part of the approval process. How the potential allergenicity should be assessed is specified in neither Canadian legislation nor European legislation.

The Food Standards Australia New Zealand (FSANZ) agency describes novel foods as non-traditional foods with characteristics that require an assessment of public health and safety considerations (Food Standards Australia New Zealand, 2010b). A non-traditional food is a food that has no history of human consumption in Australia or New Zealand. This also includes substances derived from a food, that have not been consumed other than as a component of the food, and substances that come from a source without history of consumption in Australia or New Zealand. Key areas influencing the interpretation of the term “history of human consumption” are the length of use; the extent of use; the quantity (level of intake) of use; and the purpose or context of use (Food Standards Australia New Zealand, 2010a). As is the case in Canada and the EU, allergenicity assessment is included as part of the approval process, but regulations do not specify how this allergenicity assessment should be performed.

The USA does not specifically distinguish novel foods as a class of products. Instead, a substance that will be added to food is subject to pre-market approval by the US Food and Drug Administration (FDA) unless its use is generally recognized as safe (GRAS) by qualified experts, or if it is a prior sanctioned substance that the FDA or the US Department of Agriculture (USDA) determined safe for use in food before 1958 (Food and Drug Administration, 2010a). The GRAS procedure is a notification procedure. A product is GRAS through (1) scientific procedures, which may be corroborated by (un)published studies and other data and information, or (2) experience based on common use in foods requires a substantial history of consumption for food use by a significant number of consumers (Food and Drug Administration, 2010a). With regard to the scientific procedures, applicants should provide a comprehensive set of scientific data, information, methods, or principles, including data on the probable consumption and any cumulative effects if substances with similar chemical or pharmacological activities are present in food. Any unfavourable information that would appear to be inconsistent with a GRAS determination should

Table 2

Legal categories of novel foods and processes in Australia–New Zealand, Canada, the EU, and the USA.

Nation(s)	Specific novel food regulations (yes/no)	Legal category	Definition of novelty	Guidance for safety testing (yes/no)	Examples of favourably assessed products	Law/decreed No.
Australia–New Zealand	Yes	Novel food	<ul style="list-style-type: none"> Novel food: Non-traditional food requiring an assessment of public health and safety considerations with regard to: potential adverse effects; the composition/structure of the food; the process used to obtain the food; the source of the food; exposure to the food; or other relevant matters Non-traditional food: a food without history of human consumption in Australia or New Zealand; a food substance that does not have a history of consumption in Australia or New Zealand other than as a component of the particular food; or any other substance, where the substance itself or its source do not have a history of consumption as a food in Australia or New Zealand 	Yes (Food Standards Australia New Zealand, 2010a; Food Standards Australia New Zealand, 2010c)	<ul style="list-style-type: none"> Dried marine micro-algae that are rich in the omega-3 fatty acid docosahexaenoic acid Certain foods with added phytosterols, phytosterols, and their esters Certain carbohydrates (e.g. α- and γ-cyclodextrin, isomaltulose, D-tagatose, trehalose) 	Australia New Zealand Food Standards Code, Standard 1.5.1, “Novel Foods” (Food Standards Australia New Zealand, 2010d)
Canada	Yes	Novel food	<ul style="list-style-type: none"> Without a history of safe use as a food Obtained through a process that has not previously been applied to the food or that causes it to undergo a major change Genetically modified if the genetic modification causes the food to exhibit previously unobserved characteristics or to lose previously observed ones, or if one or more of its characteristic no longer fall within anticipated ranges 	Yes (Health Canada, 2006)	<ul style="list-style-type: none"> Foods with added phytosterols Foods containing high levels of added lutein (carotenoid, antioxidant) Foods pasteurized through application of high hydrostatic pressure Animal-derived foods that are enriched in their content of omega-3 fatty acids Genetically modified crops Conventionally bred herbicide-resistant crops Fruit preparations pasteurized through high-pressure treatment Various foods containing phytosterols and phytosterols Certain carbohydrates (isomaltulose, tagatose, trehalose, α-cyclodextrin) Oil rich in the omega-3 fatty acid docosahexaenoic acid Certain steviol glycosides isolated from the plant <i>Stevia rebaudiana</i> Baobab dried fruit pulp Flaxseed Phytosterols and phytosterols from pine trees Krill oil 	Consolidated Regulations of Canada, chapter 870, Food and Drugs Act, Food and Drug Regulations, Part B, “Foods,” Division 28, “Novel Foods” (Department of Justice Canada, 2010)
EU	Yes	Novel food	<ul style="list-style-type: none"> Foods that have not been used for human consumption to a significant degree within the European Union before 15 May 1997 	Yes. Commission Recommendation 97/618/EC (European Commission, 1997)	<ul style="list-style-type: none"> Fruit preparations pasteurized through high-pressure treatment Various foods containing phytosterols and phytosterols Certain carbohydrates (isomaltulose, tagatose, trehalose, α-cyclodextrin) Oil rich in the omega-3 fatty acid docosahexaenoic acid Certain steviol glycosides isolated from the plant <i>Stevia rebaudiana</i> Baobab dried fruit pulp Flaxseed Phytosterols and phytosterols from pine trees Krill oil 	Regulation (EC) No 258/97 (European Parliament and the Council, 1997)
USA	No	Non-GRAS (generally recognized as safe), food additive	<ul style="list-style-type: none"> Not generally recognized as safe, including food substances that were not used as food in the USA before January 1, 1958; and/or foods for which no recognition of safety based on scientific procedures exists yet. This also includes processes and breeding/selection applied to GRAS substances so that the characteristics (e.g. composition, 	Yes. General guidance: “Redbook 2000” (Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients) (Food and Drug Administration, 2007)	<ul style="list-style-type: none"> Certain steviol glycosides isolated from the plant <i>Stevia rebaudiana</i> Baobab dried fruit pulp Flaxseed Phytosterols and phytosterols from pine trees Krill oil 	Federal Food Drug and Cosmetic Act, Chapter II (Definitions), Section 201(s), and Chapter IV (Food), Section 409 (Unsafe Food Additives) (Food and Drug Administration, 2004); Implementing regulations: Code of Federal Regulations, Title 21 (Food and Drugs), Subchapter B (Food for Human Consumption),

(continued on next page)

Table 2 (continued)

Nation(s)	Specific novel food regulations (yes/no)	Legal category	Definition of novelty	Guidance for safety testing (yes/no)	Examples of favourably assessed products	Law/decreed No.
			levels of toxicants) are changed, such as extracts, isolates, distillates, and reaction products of GRAS substances, as well as synthetic analogues of GRAS substances of biological origin			Part 170 (Food Additives), Sections 170.3 (Definitions) and 170.30 ["Eligibility for classification as generally recognized as safe (GRAS)."] (Food and Drug Administration, 2009)

be thoroughly discussed as well. Moreover, applicants should be able to corroborate the conclusion that there is consensus among qualified experts that the substance is not harmful (Food and Drug Administration, 2010b). If a substance is not generally recognized as safe or a prior sanctioned substance, it is considered a food additive and must be subject to a mandatory safety assessment by FDA, which includes comprehensive toxicological testing, genetic toxicity, acute oral toxicity, short term toxicity, (sub)chronic toxicity, and reproduction and developmental toxicity (Food and Drug Administration, 2007). Potential allergenicity is not specifically mentioned in the FDA Redbook, which applies to all food additives. The potential allergenicity of transgenic proteins is considered in their safety assessment (Food and Drug Administration, 1992). It should be noted that the definition of a food additive may diverge between the American and other legislations. In the EU, for example, food additives are defined by Directive 89/107/EEC as food substances that are added to foods in limited quantities and that serve a technological purpose, examples being colorants and sweeteners (Council of the European Union, 1989). As for the other legislative frameworks considered, allergenicity assessment is included as part of the approval process, but how this should be done is not specified.

When comparing the various novel food regulations, it is relevant to note that Canada regulates GM foods as novel foods, where in the EU this has not been the case since 2005 with the implementation of a specific regulation pertaining to GM food and feed, *i.e.* Regulation (EC) No. 1829/2003, amending the Novel Food Regulation, *i.e.* Regulation (EC) No. 258/97 (European Parliament and the Council, 2003b). The Food Standards Australia New Zealand (FSANZ), as is the case in the EU, does not classify GM foods as novel foods. Canadian legislation refers to a lack of a history of safe use of the food for the food to be novel, whereas EU legislation only refers to a history of use. The FSANZ does not use "history of safe use" as a criterion to define a non-traditional food. Instead, the Advisory Committee on Novel Foods, which advises FSANZ applies a two-step procedure in which it considers the "history of use" in Australia or New Zealand when describing non-traditional foods, while, in a second step, it considers if there is a necessity to consider it a novel food based on the safety data available. For a number of non-traditional foods, the committee has previously concluded that these need not being considered novel foods because there were no safety concerns, for example based on a history of safe consumption in other countries (Food Standards Australia New Zealand, 2010e). Appropriate regulatory agencies in each country assess the safety of all novel foods proposed for sale in the particular countries. When comparing the safety assessment procedures, caution must be taken because definitions of novel foods in these countries differ and, as a consequence, the assessment procedures also differ, in such a way that they cannot be compared directly. All countries do include allergenicity in the safety assessment. However, no comparisons are possible since the allergenicity assessment procedures are not described for non-GM novel foods, while the potential allergenicity of GM foods is assessed according to the principles outlined in the guidance of Codex alimentarius (Codex Alimentarius Commission, 2003). It is important to note that although the various novel food legislations have some similarities, authorisation of a novel food in one country does not imply that the novel food can be imported to another country without further safety assessment.

3. Risk management of potential allergenicity of novel foods

Risk management decisions, such as the approval of novel foods and specific requirements for product labelling, are based on the outcomes of safety assessment and also on other considerations,

such as public health protection and the costs and benefits of the measures to be implemented. While the safety assessment of the potential allergenicity focuses on risks, the risk managers' need for information on benefits constitutes an argument for the assessment of benefits as well. This section and its subsections discuss the safety of novel foods with regard to their potential allergenicity while their potential benefits are considered in Section 4.

Before the safety of novel foods can be discussed, two points need to be clarified. The first point is that sensitisation to potential allergens is required before allergic reactions will take place upon re-exposure to these same allergens. Food products that contain potentially sensitising novel proteins could change the exposure of the population to these proteins, thereby potentially giving rise to the development of new allergies. For the allergenicity assessment two aspects are important: (1) *de novo* sensitisation by completely new allergens and (2) cross-reactivity with allergens that are similar to the ones to which the food-allergic consumer is already sensitised. *De novo* sensitisation by completely new allergens is more difficult to predict than cross-reactivity. Therefore, this paper focuses on potential cross-reactions of novel foods rather than on sensitisation. Given that, by definition, novel foods have no history of safe use in the EU, safety assessment is necessary to assure human health. The second point is that where possible, safety assessment of foods uses traditional foods and ingredients as reference points and the assessment process focuses on the differences between these and the novel foods and ingredients under assessment (Howlett et al., 2003). An example of this is the evaluation of substantial equivalence of oil derived from two distinct GM cotton lines, Insect Protected line 531 and Roundup Ready line 1445. It was agreed that processed oils derived from these lines were equivalent, in composition, to oils from conventional cottonseed varieties (ACNFP, 2010).

The methods available to test novel foods allergenicity vary for and depend on the type of novel food under assessment. This part provides an overview of the various (complementary) assessment methods that are available to assess the safety of the different types of novel foods. Section 3.1 discusses the methods to assess the potential allergenicity of GM foods according to the internationally harmonized approach (Codex Alimentarius Commission, 2003; FAO/WHO, 2001). This is followed by Sections 3.2 and 3.3, which discuss possible methods to determine allergenicity of non-GM technological novel foods, for which, at the moment, fewer methods are available, as well as testing methods for other novel foods. Section 3.4 discusses the outcomes of the novel food safety assessment and how they should be handled.

3.1. Safety of GM novel foods

As explained above, there are two possible ways in which a novel food (including GM foods) can act as an allergen, *i.e.* by cross-reactivity with another allergen to which patients have already been sensitised, and by *de novo* sensitisation by the novel food itself, which would then be a new allergen in its own right. In order to test for cross-reactivity, for example, antisera from patients that are allergic to the known allergen can be used to test for their binding to extracts or purified components (such as proteins) from the novel food. A positive binding test would provide an indication of possible clinical cross-reactivity, which may then be explored further using other tests if possible. Besides identifying a potential risk of cross-reactivity or *de novo* sensitisation, the safety assessment of a novel food should also take into account the likelihood of exposure of consumers to the allergen and identify vulnerable subpopulations. For example, if a certain allergen exhibits cross-reactivity with the novel food, patients who are allergic to this allergen will constitute a subpopulation at risk and therefore the

prevalence of allergies towards the cross-reactive allergen will have to be taken into consideration.

The allergenicity assessment of GM products (usually common food crops into which a foreign gene coding for a novel protein has been introduced) considers both the novel protein and the product that receives the novel protein. A specific concern for food safety in the case of GM novel foods is the expression of novel allergenic proteins in transgenic crops. No single test exists that is fully predictive of the potential allergenicity of any specific novel protein (Taylor, 2006) and therefore the assessment of potential allergenicity should combine various criteria, according to the "weight of evidence approach" recommended by Codex alimentarius, including the source of the protein, amino acid sequence homology to known allergens, pepsin resistance and specific serum screening (Codex Alimentarius Commission, 2003).

One of the criteria considered in the assessment of potential allergenicity of GM novel foods is the gene source. If, for example, the gene has been obtained from an allergenic source, *i.e.* an organism known to cause allergic reactions in allergic consumers, then the potential allergenicity of the gene product in these consumers has to be considered. Moreover, if the protein encoded by the specific gene, *i.e.* the gene product has already been established as an allergen, then it has to be verified whether it has maintained its allergenic properties in the transgenic plant (Stewart, Richards, & Halfhill, 2000). An example of the product of a gene derived from an allergenic source is the Brazil nut's 2S albumin, an allergenic protein that showed reactivity in Brazil nut allergic consumers, including positive outcomes in serum screening and skin-prick testing, after its transfer to an experimental GM soybean (Nordlee, 1996). If the gene source has an unknown history of allergenicity this still requires further investigation on whether it may be allergenic in a transgenic plant according to various criteria described below. In addition, also the history of allergenicity of the recipient organism of genetic modification is considered with regard to potential changes in intrinsic allergens caused by the genetic modification.

Amino acid sequence comparison may be a tool to estimate whether a novel protein has allergenic potential. IgE cross-reactivity between the novel protein and a known allergen should be considered a possibility if there is more than 35% identity in a segment of 80 or more amino acids, or if both proteins share a segment of identical contiguous amino acids (Codex Alimentarius Commission, 2003; FAO/WHO, 2001). If there is no sequence homology, this indicates that the linear sequence of the novel protein is not similar to that of known allergens and less likely to be cross-reactive to known allergens. A positive sequence homology result indicates that the protein is potentially cross-reactive with the known allergens. If the novel protein's similarity to allergens is considered further, it should be assessed using serum from individuals sensitised to the identified allergenic source (Codex Alimentarius Commission, 2003). Orruño and Morgan (2006) note that sequence homology and structural similarity to known allergens are not sufficient to predict cross-reactivity involving conformational epitopes consisting of a discontinuous amino acid sequence along a folded protein (Orruño & Morgan, 2006). According to these authors, more information is needed to exactly pinpoint epitopes. They do not explain their assumption as to why it is not possible to predict potential cross-reactivity of conformational epitopes. Obviously, the availability of tools to predict and compare three-dimensional protein structures, including their antibody-binding sites, will facilitate the identification and assessment of conformational epitopes. Aalberse and Stadler (2006) claim that allergenic potential can be easily assessed by a combination of *in silico* homology searches with a 50% cut-off in overall sequence alignment, and *in-vitro* IgE antibody assays

(Aalberse & Stadler, 2006). They claim that the major limitation of bioinformatics, *i.e.* the use of computer algorithms to investigate data on and predict the properties of biological molecules, is the number of allergens missing from the database, particularly minor allergens from airborne sources, such as pollen, insects and moulds. Aalberse and Stadler (2006) do acknowledge that by focussing on the primary sequence, post-translational modification, which is a possible source of cross-reactivity, is overlooked since these processes are not fully determined by only the DNA sequence. Moreover, in a more general sense, algorithms that are used for sequence homology searches aim at elucidating the evolutionary relationship between proteins rather than their relationship as cross-reactive allergens.

Since a number of food allergens are stable to digestion, the latter represents an important criterion to predict allergenicity. While not all stable proteins are allergens, for the purpose of allergenicity evaluation, digestible proteins are believed to have lower potential for systemic exposure of the intact protein (Taylor, 2006). This means that such proteins are less likely both to sensitise and cross-react through the oral route, and to trigger allergic reactions upon subsequent oral exposure. Resistance to degradation by the stomach enzyme pepsin in *in-vitro* model tests indicates that further analysis should be conducted. A lack of resistance to pepsin *per se* does not exclude that the novel protein can be an allergen (Codex Alimentarius Commission, 2003).

For proteins that originate from a known allergenic source or that have sequence homology with a known allergen, testing in immunological assays should be performed where sera are available. If a novel protein from a known allergenic source has negative results in *in-vitro* immunoassays, this protein should undergo additional testing such as skin-prick tests. A positive result would indicate a potential allergen. For proteins from sources not known to be allergenic and which do not exhibit sequence homology to known allergens, targeted serum screening with sera from patients allergic to allergens that are broadly related to the source of the transgene has been previously proposed but is considered by Codex alimentarius as something that could become useful in future, as scientific knowledge and technology evolves (Codex Alimentarius Commission, 2003).

Very little information exists regarding threshold doses for sensitisation and cross-reactions. According to Taylor (2006), however, the level of expression of the novel protein is another factor that should be considered in the safety assessment of GM novel foods. Foods produced through GM are less likely to become allergenic if the novel proteins are present in low concentrations, especially with regard to the expression in the edible portion of the modified plant.

It should be noted that the allergenicity assessment strategy for transgenic proteins cannot be applied to novel foods in which a gene has been down-regulated, thereby preventing the presence of a potential allergen in the product. When such a hypoallergenic novel food is developed, the safety assessment should involve the same testing procedures, and in addition the reduced allergy impact of this allergen should be assessed. The American Academy of Pediatrics (2000) has formulated requirements for hypoallergenic infant formulae to be labelled “hypoallergenic” with respect to their elicitation of allergic reactions in cow’s milk allergy patients. For this purpose, the formulae should undergo pre-clinical testing followed, if appropriate, by clinical tests. If the formula does not provoke allergic reactions in at least 90% of the patients following double-blind placebo-controlled challenges, it will meet the criterion for being labelled “hypoallergenic.” In addition, for allergy prevention claims, it is recommended performing longitudinal studies over a number of years (American Academy of Pediatrics, 2000). The proposed tests apply to a known allergenic

food whose allergenicity has been reduced by a certain process, such as hydrolysis of the allergenic proteins (either by physical–chemical treatment or with enzymes). As noted above, the legislations in various countries include novel food processing methods into the scope of novel foods regulations, and therefore a scenario similar to the infant formula may also apply to these processes besides methods of genetic modification. Contrary to foods that are completely novel in their own right, the food may already be known to be allergenic, such as in the case of milk-based infant formulae, so that patients can be recruited for testing. It should be cautioned, though, that certain boundaries with regard to the ethics of performing the proposed tests can exist. Another example of a new but not a novel food that has been assessed for potential changes in allergenicity is a microparticulated fat replacer. The microparticles in this product are formed by egg and/or cow’s milk proteins in solution to heat and high shear forces. Immunoblots showed that the proteins in the new food displayed comparable binding by antibodies as those in egg and cow’s milk (Sampson & Cooke, 1992).

3.2. Safety of non-GM technological novel foods

During food processing, allergenicity can be altered by various procedures such as storage time, preparation techniques, heating, prolonged washing and interactions with other food components. As a result, the allergenic potential may be unaffected, decreased or even increased. Alterations in stability caused by processing may alter the resistance to digestion and the nature of the interaction with the immune system. Allergenicity can also be increased when new epitopes are exposed at the surface of the protein or formed by chemical reactions such as the Maillard reaction between carbohydrates and proteins while it can be reduced when former conformational epitopes are lost. An example of the exposure of a new epitope is the protein Beta-lactoglobulin from cow milk, which has a linear epitope buried within its structure. This linear epitope becomes exposed when the proteins structure changes through denaturation (Liu, Chen, & Mao, 2007). Alterations in allergenicity due to the exposure of new epitopes cannot be detected using amino acid sequence comparisons, which is an important assessment step for GM novel foods. For GM novel foods, the novel protein is the most important subject of assessment. The proteins in the product are not known for all non-GM technological novel foods, which makes this strategy less useful.

Validated animal models may offer the most direct approach for the determination of the intrinsic sensitising potential of novel proteins in the future. Currently, however, no validated and widely accepted animal model is available (Orruño & Morgan, 2006). Food allergy follows exposure to food as it is normally eaten, and not following exposure to isolated proteins. It is important to note that the normal allergenicity of the protein may be influenced by the interaction with other components present in the food matrix, such as lipids and sugars and of wider aspects of structure and localisation (Orruño & Morgan, 2006).

For GM novel foods, the result of the safety assessment procedure is a conclusion as to the likelihood of the novel protein being an allergen. Since for the assessment of non-GM technological novel foods, less well described assessment methods are available, the outcome of this safety assessment contains more uncertainties.

3.3. Safety of natural novel foods

Kiwi is an example of a food that had an unknown history of allergenicity, but nonetheless manifested itself as allergenic (Lucas et al., 2005). In the case of kiwi, two issues are at stake, including cross-reactivity between the kiwi and known allergens, such as

bananas and latex, and *de novo* sensitisation for the kiwi itself. Whilst the cross-reactivity of new proteins is assessed for GM foods following a weight of evidence approach, this approach will not always be feasible for each new protein within a novel food, such as kiwi. If a food is completely new and it is not feasible to follow a weight of evidence approach for all new proteins within a novel food, the currently available allergenicity tests will not be sufficient to identify a truly novel allergen (Dearman & Kimber, 2009). Animal models could provide insight in the potential allergenicity of the food. Although currently no validated and widely accepted animal model is available, this is the most direct approach for determining the intrinsic sensitising potential of novel foods (Orruño & Morgan, 2006). A possible limitation for animal models is that certain allergies are associated with specific major histocompatibility complex (MHC) haplotypes, for which further refinement of animal models may be useful, such as the use of human-MHC-transgenic mice (Chapoval & David, 2003).

Gubesch et al. (2007) designed an approach to screen novel foods for the presence of pan-allergens, IgE binding of food allergens and clinical relevance of IgE binding. Their conclusion is that this three-step approach seems to be applicable for allergenicity testing of natural novel foods (Gubesch et al., 2007). However, they do recognise that, as long as no validated methods for assessing *de novo* sensitisation capacity are available, the overall allergenic potential of novel foods is impossible to predict. If indications for cross-reactivity exist based on the allergenic history of the food or its phylogenetic relationship with other allergenic foods, it is recommended that the allergenicity assessment of foods and food proteins should include IgE from the sera of allergic patients using tests such as solid phase immunoassays [radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA), enzyme allergosorbent test (EAST)]. When the identification of the allergenic components of a food material is required, sodium dodecyl sulphate – polyacrylamide gel electrophoresis (SDS-PAGE) followed by immunoblotting is generally applied.

3.4. Risk management of potential allergenicity of novel foods

As explained above, the assessment of a novel food's potential allergenicity considers two possible ways in which the food may become an allergen, namely by *de novo* sensitisation as a new allergen, and by cross-reactivity with existing allergens. For the first, less extensive guidance has been developed than for the latter. The end result of the assessment procedures is a conclusion as to the likelihood of the novel foods being an allergen. Depending on the type of novel food, and the available information about that novel food, the likelihood contains varying uncertainty. Risk managers will base their risk management decisions on these assessments and on other considerations, such as public health protection and the costs and benefits of the measures to be implemented, of which the latter is discussed in more detail in section 5.

No safety or risk assessment procedure can lead to the guaranteed safety of novel foods for food-allergic consumers, as the allergenicity of any given food or protein cannot be precluded completely, although the list of major food allergens is relatively limited (Breiteneder & Mills, 2005). For food-allergic consumers who need to avoid all foods that contain the protein(s) to which they are allergic, this likelihood information is not sufficient (Putten et al., in press). Research about the labelling needs of food-allergic consumers (Cornelisse-Vermaat, Pfaff, et al., 2008) shows that one of the problems faced by food-allergic consumers is the uncertainty about whether a product contains allergens or not, especially when "may contain" labelling is used. Some food-allergic consumers may even ignore the warnings on the label and try the food product to

test whether an allergic reaction will occur and, if it does, never buy the product again (unpublished data). This phenomenon may not always be noticed by post-market monitoring. Consumers may respond similarly when informed about the remaining uncertainties of the current allergenicity assessment procedures. This calls for complete, clear and publicly available allergenicity risk assessment information that allows consumers to interpret the risk assessment results and make the risk management decisions that meet their individual needs best. Health professionals and patient organisations may play an important role in interpreting the allergenicity risk assessment information and helping food-allergic consumers to decide whether a novel food is safe for them. Another factor adding to the uncertainty associated with the results of the safety assessment procedures are individual (genetic) differences in allergic responses. It has been frequently observed that different individuals react differently to different proteins within the same allergenic food (Orruño & Morgan, 2006). So-called major allergenic proteins are bound by the IgE antibodies in 50% or more of individual sera from people with an allergy against the organism from which the protein is derived. In addition, minor allergens exist to which less of the IgE in sera from the allergic population is bound. When a major allergen is removed or mutated, some patients still may react to the minor allergens in a product, which makes it not safe for them to consume at all.

The questions that remain relate to the level of risk which is acceptable, *i.e.* which level of safety is safe enough for food-allergic consumers. The safety of a specific novel food depends on the allergy of an individual. Deciding when a food is safe for enough people, so it can be allowed on the market is a task for risk managers. The information that a safety assessment procedure provides is a first requirement to make further evaluations about whether novel foods may improve quality of life of food-allergic consumers.

4. Potential benefits of novel foods for food-allergic consumers

Various novel food regulations aim to ensure consumer protection and require therefore risk assessment before novel foods can be marketed. At the present time, food risk management decisions are primarily based on risk assessment information, and allergy assessment does not differ in this regard (FAO/WHO, 1997). Emerging food risk governance models are based on an assessment of both risks and benefits associated with a food issue, and, furthermore, that these risks and benefit assessment should be broadened to embrace not only health impact, but also other socio-economic and ethical impacts (Wentholt et al., 2009). In the case of novel foods there are arguments to support the idea that this broader definition of impact assessment should be formally included in management decisions. Formal inclusion at the assessment stage would imply the introduction of novel methodological approaches to quantification of risk and benefit, as well as their distribution across different population groups, so that both risks and benefits can formally be considered at the management stage.

Food-allergic consumers may profit from benefits of hypoallergenic novel foods through increased dietary variation and reduced restrictions on product selection and thereby reduction in the social limitations that food-allergic consumers experience. Food allergy can have a profound impact on quality of life, not only because of the immediate clinical effects related to individual's allergic condition, but also because of the alterations in daily life that have to be made to prevent the occurrence of symptoms and the influence on psychosocial functioning of the individual (Blok et al., 2007; Oude Elberink et al., 2002; Sicherer, Noone, & Muñoz-

Furlong, 2001). Exposure to a food allergen can result in anaphylaxis, which may be severe enough to be life-threatening (Jackson, 2003; Sampson, 1999). Other factors potentially influencing the quality of life of food-allergic consumers include increased time spent shopping (Cornelisse-Vermaat, Voordouw, Theodoridis, Yiakoumaki, & Frewer, 2008; Voordouw et al., 2009) and increased costs to both the household and to the health services (Fox et al., 2009).

Thus novel hypoallergenic novel foods have the potential to improve the quality of life of food-allergic consumers, although one might assume the impact on quality of life experienced by the allergic consumer is contingent on the degree of severity of the reaction experienced and the level of certainty that it will be avoided by consuming the hypoallergenic novel food. Against this, there is also potential for novel foods to increase the prevalence of allergic responses, through the introduction of problematic proteins into the food chain. When novel foods are considered to be safe for food-allergic consumers, this can become a benefit. However, the results of the safety assessment procedures regarding allergenicity are conclusions as to the likelihood of the novel foods being an allergen. This means that the conclusions regarding benefits are somewhat uncertain. Another issue is that allergenicity is not a simple matter of deciding whether a novel food is allergenic. Depending on the allergenic content and the individual response of the food-allergic consumer, one novel food may be more allergenic than another. The same principle applies to benefits. When a novel food is considered to be hypoallergenic, it means that it contains less allergen than the traditional variant of the food. A question arises as to what level of certainty regarding the hypoallergenicity of novel foods is required for novel foods to be used as allergy management strategy. No legal definition of the term “hypoallergenic” exists, although it is commonly understood to mean “containing fewer allergens” (Wiktionary, 2010). In clinical terms, hypoallergenic formulae (infant milk) are defined as those that are tolerated by $\geq 90\%$ of infants with documented cow's milk allergy (Herz, 2008). In an ideal situation, absolute certainty regarding the absence of potential for allergic reactions would be available. For most novel foods, this absolute certainty cannot be provided. Absolute certainty about the hypoallergenicity of the novel food or ingredient may not be required by all consumers. However, it is important to make information about the risk and benefit assessment available to food-allergic consumers, allowing them to make their own risk management decision. How this information should be made available to consumers needs to be addressed in future research. Formal risk assessment procedures should also consider potential benefits. Regulations should take this into account as well and make the results of the risk (and benefit) assessments of novel foods publicly available.

Currently, the risk assessment procedures do not include the potential severity of the allergic responses. This information is relevant for risk managers, especially when considering the potential benefits of novel foods. Foods that are not allergenic may have more benefits for people with a severe and life-threatening allergy than for people with a mild allergy, since the former are likely to experience more problems with the strict and necessary food avoidance. However, the increased severity of an allergic response may also be associated with an increased level of uncertainty regarding the hypoallergenic properties of the food or food ingredient (Voordouw et al., 2009). Including the potential severity of an allergic reaction to a novel food will probably entail clinical testing which may have its ethical and practical limitations.

No summary of novel food applications in the European Union mentions benefits of the novel food regarding hypoallergenicity. It can be envisaged though that some of the experiments that may be carried out *in-vitro* or *in-vivo* with human or animal subjects to

support health claims can also provide additional, useful indications of any safety issues linked to the consumption of the novel food. It should be noted that such health claims are not assessed under Regulation (EC) No. 258/97, but have to be assessed through a separate procedure, which falls outside the scope of this review. At the time of writing, no novel foods that have been legally authorised by the European Union could be identified as hypoallergenic, while examples of novel foods for which applications have been filed with potential hypoallergenicity or allergy-curing properties include bee-venom-containing honey and fermented soybeans, as discussed in the introduction (Section 1). Further examples among the novel foods that have been assessed in Canada are “delicious soybean” and “TUSC-1 wheat” in which the levels of major allergenic proteins have been reduced (Health Canada, 2010b). The reported purpose of these modifications relate to organoleptic or technical properties and therefore not to allergy. It is possible that new food products access the EU and other markets without evaluation under the regulations pertinent to novel foods because these new products are not considered novel according to the definitions in the regulations. An example is the Santana apple, an apple cultivar that is the result from the crossing of the cultivars Elstar and Priscilla. The aim of this crossing was to combine the fruit quality of Elstar apples with the disease resistance of Priscilla (Mitham, 2007). There is evidence that Santana apples are hypoallergenic, at least for some consumers (Kootstra, Vlieg-Boerstra, & Dubois, 2007). Other examples can be found in literature such as rice (Nakamura & Matsuda, 1996), soybean (Herman, Helm, Jung, & Kinney, 2003), apple (Gilissen et al., 2005), and peanuts (Dodo, Lonan, & Viquez, 2005). However, this review was limited to novel foods and a review of other new foods is recommended for the future. It may be worthwhile to investigate how many other unusual but not novel foods exist that may be associated with hypoallergenic properties.

5. Conclusions

This paper reviewed allergenicity legislation, assessment procedures, and potential benefits of novel foods to improve quality of life of food-allergic consumers. Various regulations are in place to protect consumer health. These regulations require novel foods' safety to be assessed before they can enter the market. However, the current regulatory frameworks do not specify how these assessments should be performed. The EU recommends which information is needed for a novel food application, but besides from mentioning that allergenicity information is required, it is not specified how this allergenicity assessment should be performed. In Canada, the USA and Australia–New Zealand, allergenicity assessment is also part of the approval procedure, but, like in the EU, how this assessment should be performed is not specified in the legislations. This may relate to the fact that the safety assessment methods available and best suited depend on the type of novel food under assessment. None of the safety assessments include benefits assessment. However, when a hypoallergenic novel food with benefits for food-allergic consumers is being evaluated, it can be argued that information about the potential benefits should be formally included in management decisions and therefore the assessment of benefits would be helpful.

Currently, benefit assessment is not part of the pre-market safety assessment of novel foods as carried out in the various legislations considered in this article (Table 2). Benefits may have to be assessed under parallel legislation in particular circumstances, such as for various categories of health claims made for the food (e.g. in advertisements and on labels) or if the food is to be used for specific dietary purposes, such as for medical patients or individuals with certain physiological conditions. Various countries have

national regulations in place for these benefit-related issues, which, to a certain extent, have been harmonized at the international level through Codex alimentarius standards on health claims on foods and foods for specific dietary purposes (Codex Alimentarius Commission, 1991a, 1991b, 2009). In this regard, novel foods with health claims could also be regarded “functional foods,” although the latter does not exist as a separately regulated category of foods within the national legislations considered by the authors. Interestingly, Japanese regulations, which have not been considered in detail here because of the limited official data in English, are considered to be well-developed in this area. Japanese legislation regulates several categories of foods that are particularly relevant for the topic of this article, including foods for specified health uses (FOSHU) which are claimed to exert physiological effects, and foods for special dietary uses (FOSDU) (MHLW, 2010a, 2010b). The regulations on FOSDU explicitly mention hypoallergenic foods, i.e. “allergen-removed” foods, as part of the specific subcategory of medical foods for the ill, whereas allergy is not explicitly mentioned as a specified health use of FOSHU (MHLW, 2010a, 2010b).

Given that information on both risks and benefits is of importance to the risk-benefit manager in order to reach a decision on appropriate risk-mitigating measures, an integrated risk-benefit assessment to be provided by the risk-benefit assessor would be particularly valuable. Interestingly, EFSA’s Scientific Committee recently published guidance on how to perform an integrated risk-benefit assessment. In this guidance, a stepwise approach is recommended in which risk-benefit-assessors and risk-benefit-managers communicate with each other at each step of the procedure (EFSA, 2010b). At the basis of each assessment lies a problem formulation, which may pertain to the potential adverse and beneficial health effects of either a specific food substance (e.g. a vitamin or mineral) or whole food (with different substances that may exert positive and negative effects). Benefits are considered to be either positive health effects or reduced adverse health effects. The process of benefit assessment is supposed to follow a similar approach as for risk assessment, including subsequent stages of effect identification, effect characterization, exposure assessment, and benefit characterization, followed by a comparison of characterized risks and benefits. At the first step in the assessment, an estimate is made of the risks and benefits at high and low exposure. Unless it is clear that either the risks outweigh the benefits or, *vice versa*, the benefits outweigh the risks, the assessment will proceed to the second step, in which a more quantitative estimate is made based on more refined data on exposure, including that of subpopulations, and on incidences of morbidity and mortality. If the data are not sufficient to support policy measures, it may be decided to proceed to the third and last step in which a composite metric for both risks and benefits will be used, such as “disability-adjusted life years (DALYs)” or “quality-adjusted life years (QALYs)”. EFSA’s Scientific Committee also highlights the importance of addressing the uncertainties in the outcomes of the assessments, for example based on variability within the human population, on the extrapolation of animal data to human scenarios, or on the assumptions underlying the use of quantitative metrics (EFSA, 2010b).

The end result of the current risk assessment procedures is a conclusion as to the likelihood of the novel food having allergenic potential. This implies that for approved novel foods, some uncertainty remains regarding the allergenicity. In order to deal with this uncertainty and to be able to evaluate the efficacy of risk management measures, risk managers may need monitoring and reviewing the outcomes of their decisions. This could entail, if applicable, post-market surveillance (non-specific) or post-market monitoring (specific) for allergic reactions to the novel food in order to verify if the assumptions regarding the exposure to the

novel food and its potential allergenicity made during the pre-market risk assessment are correct or need being adjusted. How consumers respond to this uncertainty needs to be addressed in future research.

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