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A spotlight on analytical prospects in food allergens: from emerging allergens and novel foods to bioplastics and plant-based sustainable food contact materials

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Abstract

The present review throws a spotlight on new and emerging food safety concerns in view of a well-established food allergen risk arising from global socio-economic changes, international trade, circular economy, environmental sustainability, and upcycling. Food culture globalization needs harmonization of regulations, technical specifications, and reference materials towards mutually recognised results. In parallel, routine laboratories require high-throughput reliable analytical strategies, even in-situ testing devices, to test both food products and food contact surfaces for residual allergens. Finally, the currently neglected safety issues associated to possible allergen exposure due to the newly proposed bio- and plant-based sustainable food contact materials requires an in-depth investigation.

Keywords: food allergens, novel foods, emerging allergens, bio-based materials, sustainable food contact materials; migration

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1. Introduction

Concerns over public health related to food allergies continue to grow, requiring a proper management that is a shared responsibility between food manufacturers, government agencies and consumers. Much is known about incidence of food allergy and priority allergens in developed countries; however, emerging economies and dietary habits merit proper consideration, especially in the modern era of globalization, with increasing interest towards new food ingredients and tastes (Boye, 2012). Currently, an adequate level of food safety should involve not only analytical assessment for trace content of major food allergens, on which regulatory bodies have enforced mandatory labelling, but also the identification of other possible sources of food allergen exposition, such as (i) emerging allergens, (ii) novel foods as well as (iii) food contact materials (FCMs). In particular, in the last case, bioplastics and plant-based materials are driving the evolution towards sustainable alternative to petroleum-based counterparts; however, their safety as FCMs has still to be thoroughly demonstrated since the presence of harmful substances migrating from bio-based items has been recently evidenced (Zimmermann et al., 2020). These materials could pose a risk not only related to the migration of toxic chemicals, but also associated to the possible release of food allergenic proteins. It is worth to mention that the last topic is still completely unexplored, and scientific evidence is strictly required to support safety assessment and conformity of those materials. In fact, more studies are needed to determine if sustainable and green alternatives to common food ingredients, food processing and materials actually carry more benefits than risks (Fasolin et al., 2019).

In the last years, the scientific community has boosted its efforts to cope with this ongoing and evolving issue through research studies in different fields such as analytical chemistry, epidemiology, immunology, sociology, and food technology (Haeusermann, 2015; de la Cruz et al., 2017; Ekezie et al., 2018; Sampath et al., 2021). As for the reviews covering analytical aspects, they deal with methodological approaches involving mass spectrometry-based proteomics and/or emerging biosensing platforms (Gómez-Arribas et al., 2018; Monaci et al., 2018; Marzano et al., 2020; Mattarozzi et al., 2021) as well as reference materials for method validation (Bianchi et al., 2018; Mattarozzi & Careri, 2019). In addition, a very recent review on novel foods focused the attention on the need for characterization of protein derived from alternative sources like insects and related allergenicity risk assessment (Pali-Schöll et al., 2019a). The originality of the present review relies on put a spotlight on new trends that the scientific community could be called to address in the near future, in parallel to the most recent research interests, topics and tendencies, such as bioplastics and plant-based materials for food contact. After an initial focus on current allergen legislation and global initiatives aimed at safeguarding consumers' health, the review addresses the new and emerging

69 safety concerns for people with food allergy and gathers new scientific perspectives, paying particular
70 attention to analytical trends.

71

72 **2. Current legislation**

73 Due to the number of allergenic foods that can elicit immune-mediated adverse reactions, and due to
74 the different ranges of sensitivities in the population, the development of labelling regulation for food
75 allergens has been complicated and long, in particular for the multiple ways in which allergenic foods
76 and derivatives are used as ingredients (Gendel, 2012).

77 According to Food and Drug Administration (FDA), more than 160 foods have been identified to
78 cause food allergies in sensitised individuals; however, regulatory agencies have figured out the
79 necessity to focus allergen labelling regulations on the most recurring allergens, accounting for 90 %
80 of food allergies. Food Allergy Research and Resource Program (FARRP) consortium provides
81 through an International Regulatory Chart, updated on February 2022, a complete and accurate
82 information on international food allergen labeling regulations
83 (<https://farrp.unl.edu/documents/Regulatory/International-Allergens-2-3-22.pdf>, accessed March 3,
84 2022); this document reports 25 allergenic foods for 37 countries, including European Union,
85 CARICOM organization, Central America and GSO organization, showing that despite the
86 globalisation and the spread of international food trade there are significant differences among the
87 regulatory frameworks all over the world.

88 In response to the request from Codex Alimentarius for scientific advice on food allergens and their
89 management, in 2020 FAO and WHO established an ad hoc Joint FAO/WHO Expert Consultation
90 on Risk Assessment of Food Allergens. In the first of a series of three meetings (FAO/WHO, 2021),
91 the expert Committee reviewed and validated the list of foods and ingredients listed in section 4.2.1.4
92 of the General Standard for the Labelling of Packaged Foods (GSLPF) through a risk assessment
93 based on key criteria of prevalence, severity and potency of immune-mediated hypersensitivity. The
94 expert Committee updated the “The Big 8” allergenic foods, recommending that the following should
95 be listed as priority allergens: cereals containing gluten (i.e., wheat and other Triticum species, rye
96 and other Secale species, barley and other Hordeum species and their hybridized strains), crustacea,
97 eggs, fish, milk, peanuts, sesame, specific tree nuts (almond, cashew, hazelnut, pecan, pistachio and
98 walnut). In addition, due to the lack of data on prevalence, severity and/or potency, or due to regional
99 consumption of some foods, the Committee recommended that some of the allergenic foods, such as
100 buckwheat, celery, lupin, mustard, oats, soybean and tree nuts (Brazil nut, macadamia, pine nuts),
101 should not be listed as global priority allergens but may be considered for inclusion on priority
102 allergen lists in individual countries.

103 As Europe concerns, according to European Regulation No. 1169/2011 (2011) of the European
104 Parliament and of the Council of 25 October 2011 on the provision of food information to consumers,
105 only 14 food ingredients are notifiable allergens. Allergy to buckwheat is one of the most common
106 food allergies in Asia, and its labelling is mandatory in Japan and Korea; however, in other continents,
107 buckwheat does not represent a notifiable allergen, even if buckwheat allergy is becoming a serious
108 problem, also due to its widespread use as substitute of celiotoxic cereals. In this context, the
109 development of harmonious food allergen labelling regulation is essential, starting from a unique
110 terminology and a plain use of the language in the ingredients list, since using scientific or technical
111 terms could create confusion in the consumer (Gendel, 2012). For example, a consumer may not be
112 able to recognize that “casein” is a protein of milk, or that “ovalbumin” is contained in egg (Yeung
113 & Robert, 2018). In addition, a common language for scientists is required: in this regard, the
114 WHO/IUIS (World Health Organization and International Union of Immunological Societies)
115 Allergen Nomenclature Sub-Committee is responsible for maintaining and developing a unique,
116 unambiguous and systematic nomenclature for allergenic proteins (<http://allergen.org/>, accessed July
117 1, 2021).

118 Precautionary allergen labelling (PAL) was introduced as one of the measures to mitigate and manage
119 hidden allergen risk; according to European Regulation No. 1169/2011 (2011), PAL that is provided
120 on a voluntary basis, shall not mislead the consumer, not be ambiguous or confusing and, where
121 appropriate, be based on relevant scientific and quantitative data. Actually, consumers are not aware
122 of PAL policies, taking decisions based on self-determined risk assessment (Gupta et al., 2021).
123 Despite the relevant activities within the Integrated Approaches to Food Allergen and Allergy Risk
124 Management (iFAAM) project for the transparency of PAL, there is still need of a global initiative to
125 ensure that every food industry is able to provide consistent information to the allergic consumers
126 (DunnGalvin et al., 2019).

127 Setting a reference value on the basis of a threshold amount for the protection of at least 95% (eliciting
128 dose ED₀₅) or 99% (eliciting dose ED₀₁) of allergic people would allow a more controlled use of PAL
129 avoiding its inconsistent application for food products in which the thresholds for the content of
130 accidental allergens were not exceeded (Houben et al., 2020; Madsen et al., 2020). This represents
131 the idea behind the Allergen Bureau’s VITAL (Voluntary Incidental Trace Allergen Labelling)
132 Program, which has been developed to make available a single simple standardized precautionary
133 statement to help food producers submit consistently allergen advice for sensitive consumers. The
134 Reference Doses (mg of total protein from an allergenic food) are recommended by VITAL Scientific
135 Expert Panel (VESP) based on clinical reactivity in food challenge studies and the values are
136 constantly updated and implemented over the years in new versions of the VITAL program. The lastly

137 proposed reference doses were published in 2019 under the heading ‘VITAL 3.0’ (Allergen Bureau,
138 2019). As pointed out by Holzhauser et al. (2020), the possibility of implementing food allergen risk
139 management based on VITAL reference doses requires at the same time the availability of proper
140 analytical methods sufficiently accurate, precise and reliable for allergen determination at
141 recommended VITAL doses.

142

143 **3. Novel foods and emerging allergens**

144 Nowadays globalization, travelling worldwide, increasing curiosity towards new tastes, innovative
145 and sustainable food processing strategies, as well as alternative sources of protein and nutrients, are
146 leading to a progressive increase in food trade, and a rapid diffusion of ingredients with a spread of
147 food products all over the world. Some examples include lipid extract from Antarctic Krill (*Euphausia*
148 *superba*) as novel food ingredient (European Commission, 2019), mealworm larvae as alternative
149 protein source (EFSA NDA Panel, 2020), microalgae to produce meat analogues (Fu et al., 2021),
150 irradiation or nanotechnology as new ways of producing food (EFSA Scientific Committee, 2018).
151 European Regulation 2015/2283 (2015), in force since January 2018, defines as “novel foods” any
152 food that was not used for human consumption to a significant degree within the Union before 15
153 May 1997, including foodstuffs produced with new technologies, derived from new sources, or
154 containing engineered nanomaterials. The Novel Food Catalogue of Europe Commission lists foods
155 of animal and plant origin, and other substances that are subjected or not to the Novel Food
156 Regulation, based on information provided by the European Union (EU) Member States; it is a non-
157 exhaustive list, and serves as a guideline for determining whether a product will need an authorisation
158 under the Novel Food Regulation. European Food Safety Agency (EFSA) represents the only entity
159 in the EU responsible for novel food risk assessment and market authorization grant. In this context,
160 Ververis et al. (2020) recently published a thorough analysis of EFSA reports and databases
161 concerning novel food risk assessment, evidencing how the most represented categories in the last
162 years include products from animals, plants, microorganisms, fungi and algae. Reliable scientific data
163 and literature dealing with different safety issues regarding novel foods, such as (i) compositional,
164 nutritional and toxicological information, (ii) production process effects, (iii) allergenicity, are
165 fundamental to support both applicant dossiers for producer authorization request and subsequent
166 EFSA risk evaluations (Ververis et al., 2020). Most food allergens are proteins; exposure to new
167 proteins may trigger immune-mediated reactions due to *de-novo* sensitization (new food allergens)
168 or through cross-reactivity in sensitive consumers due to sequence homology with known allergens
169 (Verhoeckx et al., 2016; Remington et al., 2018, Pali-Schöll et al., 2019b). As for “novel food”
170 derived proteins, technological processes involved in protein extraction or novel preparation, such as

171 yeast expression system, require an in-depth investigation since they can influence the allergenicity
172 potential of the obtained extracts or proteins (Polikovsky et al., 2019; Reyes et al., 2021).
173 Allergenicity assessment becomes even more complicated for complex mixtures and whole foods that
174 may contain many different proteins.

175 Very recently, Costa and co-workers provided a holistic picture of the impact of various
176 physicochemical properties on the allergenicity of plant and animal food proteins across protein
177 families and within family members (Costa et al. 2022a, 2022b). The authors reported evidence that
178 several physicochemical properties may shape the allergenicity of proteins, paving the way to data
179 integration into multivariate models for a more comprehensive approach. In particular, since most
180 foods require some degree of processing, it is crucial to explore the effect of food processing on IgE-
181 binding capacity of the allergenic protein, related to its stability to heat, pressure, light/radiation as
182 well as to mechanical and chemical/enzymatic activities. Each food processing technology has a
183 distinct effect on the allergenicity of each protein family, even with different extent between plant
184 and animal proteins. Among all, heat stability is a parameter of primary importance for allergenic
185 proteins and all conventional thermal treatments (autoclaving, frying, boiling, dry or wet roasting,
186 blanching, baking, canning, broiling, pasteurization) have distinct effects on the allergenicity
187 depending on each protein family. Structure unfolding after heat treatment can increase the allergenic
188 potential of the allergens due to exposure of hidden linear epitopes, can maintain the allergenicity, or
189 can reduce or eliminate IgE-binding capacity by destructing the conformational epitopes and
190 formation of aggregates. Furthermore, allergenicity can also be affected by the combination of
191 different process conditions, as thermal exposure with certain conditions of pressure and pH as well
192 as food matrix components. For in-depth details of the effect of various physicochemical properties
193 and food processing on allergenicity for each protein family the reader can refer to the works of Costa
194 et al. (2022a, 2022b). In addition to the fourteen allergenic foods subjected to mandatory labelling
195 EU requirements, beyond allergens from novel foods, also emerging allergens related to EU
196 traditional foods are proving important for the next future. At the end of 2018, the French Agency for
197 Food, Environmental and Occupational Health & Safety (ANSES, Agence nationale de sécurité
198 sanitaire de l'alimentation, de l'environnement et du travail) published a report titled "Allergies
199 alimentaires: état des lieux et propositions d'orientations" (n° 2015-SA-0257), referring to data
200 collected in France from 2002 to 2017. In this period, 164 different allergenic foods were identified
201 for 1951 cases of anaphylaxis in children and adults (ANSES, 2018). The most cases concerned the
202 fourteen allergenic foods regulated within the EU. However, among the others, it is necessary to point
203 out those allergens exceptionally involved in severe forms of food allergy despite a current
204 consumption, the so-called emerging allergenic foods. They were associated with at least 1% of cases

205 of severe anaphylaxis: buckwheat (3.0 %), goat or sheep milk (3.1 %), kiwi (1.7 %), pine nut (1.4%)
206 and galactose- α -1,3-galactose (α -gal) (1.2 %). Furthermore, lentils, peas, banana, avocado, peach, fig,
207 mango, carrot, apple and Anisakis fell in the 0.6-1% incidence range.
208 Due to current dietary trends including an increased consumption of plant-based foods and alternative
209 protein sources, the Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens has
210 recommended that pulses, insects and other foods such as kiwi fruits be included in a “watch list” and
211 evaluated for the priority allergen list when data on the three key criteria established (prevalence,
212 severity and potency) become available (FAO/WHO, 2021). Concerning novel foods and emerging
213 allergenic foods, the FARRP website (<https://farrp.unl.edu/resources/gi-fas/informall>, accessed 18
214 February 2022), in addition to the priority allergens, reports information on allergies to cereals that
215 do not contain gluten, legumes, fruits, vegetables, seeds, spices and herbs, and “others” (i.e. meat
216 from beef, chicken and frog, honey mushrooms, textured mycoproteins). Attention towards non-
217 priority allergens is increasing, especially for legumes (Hildebrand et al., 2021; Romano et al., 2021),
218 such as chickpeas, peas, lentils as well as lupins. Romano et al. (2021) highlighted critical aspects
219 due to allergenic proteins contained in lentils, which are often heat-stable and protease resistant. This
220 has to be taken into account in light of the fact that legume flour is increasingly exploited in bakery
221 and extruded products thanks to its interesting nutritional, functional properties, and technological
222 potential. Another example is the α -gal syndrome whose onset is associated to tick bites (Kiewiet et
223 al., 2020): it is a new form of food allergy to mammalian meat (e.g. beef, pork, lamb, horse, rabbit),
224 involving IgE antibodies specific to α -gal, a highly expressed carbohydrate in non-primate mammals.

225

226 **4. Food Contact Materials**

227 The common controls relating to the safety assessment of materials entering in contact with food
228 regard the search for possible contaminants that might migrate onto products. The control of the
229 possible presence of contaminants should be of great concern along the entire food production chain,
230 taking into account that, during the different production stages, a food product comes into contact
231 with many materials that can potentially compromise its safety. The scheme reported in Fig. 1 shows
232 two main sources of potential contamination, such as surfaces that can come in contact with multiple
233 raw materials and ingredients, and might be responsible for cross-contamination, and innovative bio-
234 based materials for single use items and packaging. The latter, proposed as plastic substitutes, include
235 bio-based materials, and may contain proteins useful for realisation of active packaging, whose
236 migration on food may have harmful effects.

237 A first phase of contact regards raw material supply and transport involving contact with tanks and
238 containers; then, several consequent steps take place, which are related to the processing in industrial

239 equipment (use of choppers, mixers, kneaders, baking trays, molds, conveyer belts, etc..). Those steps
240 can even occur at high temperature, thus allowing easier migration of potential migrating substances.
241 Allergen evaluation should be taken into account along these steps, considering that often the same
242 parts of an industrial equipment are used for different types of food at different times. Therefore, if
243 they are not properly cleaned, traces of allergens may be retained and could become a source of cross-
244 contamination.

245 A final step is the packaging procedure, followed by a variable period of storage that can be quite
246 long. The treatments for meal preparation, involving contact with cutlery and crockery should be also
247 accounted for, especially in restaurants and refectories that provide meals to a wide population.

248 A timely and standardized cleaning procedure is obviously mandatory for all the components
249 involved in food preparation, every time a different product is processed. However, it is not so
250 obvious that the procedure used is effective in eliminating all traces of possible harmful components.
251 Besides, it is not assured that the usual systems of control of the cleaning process effectiveness are
252 reliable in detecting any traces of allergens.

253 European Regulation No 1935/2004 (2004) sets out the general principles of safety and inertness for
254 all Food Contact Materials (FCMs), intended as objects that can “reasonably be brought into contact
255 with food or transfer their constituents to the food under normal or foreseeable use”. It has to be taken
256 into account that migration can also occur via indirect contact, when food is contaminated by a
257 material or surface not being in direct contact with it. An example could be the phenomenon occurring
258 due to a contact between the outside and inside layers of materials during storage or transport.

259 The managing of the risk of food allergens, as far as restaurants and caterings concerns, is set by the
260 European Regulation No. 1169/2011 (2011). In general, control of allergens in restoration or school
261 canteen has focused on the ingredients used for preparing meals, but little or no attention is paid to
262 cross-contact through working surfaces and utensils. It has been observed that the use of exclusive
263 food-contact surfaces to avoid allergen cross-contact is not sufficient, and for this reason it is
264 necessary to establish particularly effective cleaning procedures. Ortiz et al. (2018) carried out an
265 analysis of the allergenic residues in fifty school canteen kitchens with qualitative lateral flow tests
266 (LFIA) for on-site rapid verification and quantitative ELISA tests for validation of the traditional
267 cleaning process. The occurrence of three allergens (milk, egg and gluten proteins) was evaluated one
268 at a time. The results showed that milk is easily removed, whereas egg and gluten proteins are more
269 difficult to remove. It is clear that traditional cleaning procedures in the main school canteens are not
270 efficient enough, and need to be implemented. Using a detergent with protease can significantly
271 reduce residues of milk, egg and gluten on surfaces. Furthermore, it has been reported that rising the

272 utensils with water before their use and washing them by hands instead of using a dishwasher is more
273 effective in reducing allergen contamination (Galan-Malo et al., 2019).
274 In this context, a key challenge could be to incentivize food producers to improve food allergen
275 management towards good practices, as pointed out in a recent article by Jia and Evans (2021).
276 In addition, an important point that has rarely been considered when dealing with food contact
277 materials is material ageing, which affects the quality and the properties of many surfaces, such as
278 part of industrial plants and cutlery. Material degradation occurs naturally over time and is accelerated
279 by repeated contact with aggressive components, or heat treatments, or mechanical damage, and can
280 even depend on the action of light and humidity. Degradation may increase the adsorption of
281 molecules occurring in food and the migration of undesired compounds, especially if repeated use
282 has caused scratches in the item (Bignardi et al., 2017). It is remarkable to underline that cleaning
283 protocols are set up when materials are new; the controls of possible adsorption of molecules by
284 surfaces, or release of possible contaminant agents (additives, oligomers) are not repeated during
285 ageing, even though the same equipment or cutlery are commonly used for several years.

286

287 *4.1. Biobased materials for single use items and packaging*

288 An important recent field of research on food contact materials regards the necessity to replace single-
289 use plastic items according to the new European regulation on waste management of plastics
290 (European Directive No. 2019/904, 2019). This Directive focuses on the need to reduce the impact
291 of plastic products on the environment, and it is focused on the development of new solutions. The
292 choice of natural substances as a starting material for making innovative packaging is described as a
293 promising tool, and has given rise to the so-called bio-based materials for food contact materials
294 (BBFCMs). Nowadays, the attention on biodegradable biomaterials is raising rapidly, aiming to
295 reduce the impact of plastic products on the environment (Schmid & Müller, 2019; Assad et al.,
296 2020).

297 Bio-based materials could be divided into three categories: the first includes polymers extracted
298 directly from natural marine and agricultural sources (polysaccharides, proteins or lipids). The second
299 category consists of polymers produced by chemical synthesis using renewable bio-based monomers
300 (polylactic acid, PLA). Lastly, the third category includes polymers produced by microorganisms or
301 genetically modified bacteria (poly-hydroxyalkanoates, PHAs and poly-hydroxybutyrate, PHB, and
302 bacterial cellulose, BC). Many researchers and industries are looking at solutions involving BBFCMs
303 derived from renewable biological resources, also in the context of the circular economy and
304 promoting the concept of zero-waste (Ramos et al., 2018; Nešić et al., 2020).

305 Regardless of whether the biomaterials come from food processing waste or not, it is necessary to
306 evaluate the associated allergenicity. Table 1 lists potential allergenic proteins occurring in protein-
307 based biomaterials, and their common applications are underlined.

308 Nowadays, all materials obtained by plant sources proposed as alternative to plastics are widely
309 accepted, and their use is encouraged by consumers who are becoming very sensitive to environment-
310 friendly solutions. However, it should be noted that some researchers have lately focused their
311 attention on the possible release of contaminants from plant-based materials, and have discovered the
312 migration of many chemicals of toxic concern from single-use items (Zimmermann et al., 2020).

313 Other research groups have focused their attention on the evaluation of migration of oligomers from
314 bio-based materials such PLA (Úbeda et al., 2019a, 2019b) and odorant compounds from starch-
315 based (Osorio et al., 2019a, 2019b), and bamboo-based biopolymers (Osorio et al., 2020). The effect
316 of the action of microwaves on polylactide-based materials was also evaluated (Bor et al., 2012).

317 Studies on the potential allergenicity of materials are limited to items used for medical applications
318 (Bedian et al., 2017). Since potential allergenic molecules such as polymers and proteins including
319 proteins from milk, egg, soy, corn and gluten are used to produce packaging materials (Álvarez-
320 Castillo et al., 2021; Mihalca et al., 2021), it is essential to evaluate the allergenic potential in the
321 final product. Similar components are added to films or cellulose to provide the desired structural or
322 functional properties, such as surface waterproofing to fat or water (Bonwick et al., 2019), and studies
323 on the stability of the items in contact with food and beverages would be required. In particular, milk
324 proteins are described as useful ingredients in the preparation of packaging to improve the
325 technological properties of materials and to increase food shelf-life (Daniloski et al., 2021).

326 Among BBFCMs, chitosan plays a central role, because has antimicrobial properties, it is not harmful
327 when digested, it can be produced from waste substances, and it does not produce emission associated
328 with waste (de la Caba et al., 2019). Chitins and chitosan are commonly extracted from shellfish, and
329 when effectively purified, they do not show any allergenicity (Muzzarelli, 2010). However, if the
330 purification procedure is not complete, there is the possibility of presence of tropomyosin, the main
331 allergenic protein in seafood (Bonwick, 2019).

332

333 4.2. Active packaging

334 Among the novel bio-based materials, significant attention should be paid to active bio-packaging,
335 designed with the aim of releasing active components into food. Among the bio-based active
336 packaging, many solutions containing natural antioxidants are nowadays a subject of study and
337 attention (Riaz et al., 2020). Essential oils such as rosemary, oregano, tea tree, are often incorporated
338 into films, although some of their components can produce allergic reaction after skin contact (Avonto

et al., 2016; Mortimer & Reeder, 2016). Gavril et al.(2019) evaluated the effect of the addition of aromatic plants extracts to bio-based packaging, and found that sage and lemon balm leaf extract reduced the migration of both linear and cyclic polylactic acid oligomers.

Edible coatings and edible films are commercially available, and show some advantages for improving shelf life of seafood, inhibiting the microbial growth, and preserving the sensorial and nutritional properties (Dehghani et al., 2018). The theme of antimicrobial activity has also recently gained a central role, and some studies even show the integration of antimicrobial agents in bio-nanocomposite materials for food packaging (Kumar et al., 2017; Al-Tayyar et al., 2020). Lysozyme is a widely used antimicrobial agent, and is incorporated in active packaging solutions with the aim of acting only for contact (Corradini et al., 2013; Syngai & Ahmed, 2019). Those materials should be tested for allergenic purposes, as an eventual migration of even small traces of this protein can be a source of a dangerous immune reaction. Therefore, in all similar cases, a strict analytical evaluation of the packaging behaviour, also during storage and ageing of the material, should be encouraged.

352

353 **5. Analytical issues**

The evolution of analytical techniques and bioinformatics tools is supporting the development of strategies to address the various issues related to food allergens, ranging from target analysis of novel/emerging allergens to untarget protein identification and sequencing, useful also for the assessment of allergenic potential of novel foods (Sena-Torralba et al., 2020).

A recent review by Benedé et al. (2021) deals with current and new prospects in the use of novel instrumental techniques applied to study structural and functional properties of proteins in food allergen research. The mechanisms of action and interaction between biomolecules have also been considered, covering new possible applications in several areas of the food allergy field.

In particular, the technique of choice in proteomic studies is mass spectrometry coupled to liquid chromatography (LC-MS), which offers high versatility in terms of mass analyzer resolution, and acquisition modes for identification, characterization and quantification of proteins (Monaci et al., 2018). Mass spectrometry can be exploited for the investigation of allergenic potential, mainly through epitope mapping technologies and cross-reactivity prediction based on protein sequencing; however, as discussed by Pali-Schöll et al. (2019a), in this case harmonization and validation of strategies are strictly required in the next future. In particular, to address the new issues regarding food allergens, many efforts have been made and will be still required in terms of:

370

(i) assessment and prediction of allergenic potential in novel foods through proteomics and genomics supported by bioinformatics analysis and comparison against allergen databases (Pali-Schöll et al.,

2019a; Reyes et al., 2021; Abdelmoteleb et al., 2021). Potential proteins from novel foods can be predicted from genomic sequences. Codex Alimentarius through the publication titled “Foods derived from modern biotechnology” (Codex Alimentarius Commission, 2009) suggests a weight-of-evidence approach for evaluating the possible allergenicity of newly expressed proteins in foods derived from recombinant-DNA plants (Annex 1), stating that IgE cross-reactivity between a protein and a known allergen should be considered a possibility when there is more than 35 % identity in a segment of 80 or more amino acids. The application of these guidelines and criteria can also be extended to other kinds of novel foods and preparations.

The prediction of food allergy risks of novel foods requires the establishment of structured, timely update, and freely accessible allergen databases, versus comparing sequence homology (Radauer, 2017; Radauer & Breiteneder, 2019). For a detailed and critical discussion of the available allergen databases and the WHO/IUIS systematic allergen nomenclature, the reader can refer to the works of Radauer (2017). An updated list of the allergen sequence is available in the peer-reviewed AllergenOnline database (<http://www.allergenonline.org/>, accessed July 1, 2021) set up in 2005 by FARRP; it is updated annually and the current Version 21 dated February 2021 (<http://www.allergenonline.org/AllergenOnlineV21.pdf>, accessed March 3, 2022) contains a comprehensive list of 2233 protein sequence entries that are classified into 913 taxonomic-protein groups of proven or putative allergens (food, airway, venom/salivary and contact) from 430 species. Prediction of protein allergenicity is achieved through sequence comparison.

For example, Reyes et al. (2021) reported a summary of bioinformatics results for seven proteins of *Pichia pastoris*, used as expression system, in a new preparation of the soy leghemoglobin C2: for the protein glyceraldehyde-3-phosphate dehydrogenase, isozyme 3, a minimal risk of allergy could be hypothesized based on the alignment with GAPDH from *T. aestivum* according to Codex recommendations. However, very recently Abdelmoteleb et al. (2021) have exploited the green alga *Chlorella variabilis*, the red alga *Galdiera sulphuraria*, and the fungus *Fusarium* strain flavolapis, as novel test foods to estimate the commonality of false positive matches when the homology criteria of the CODEX guidelines are used for the assessment of IgE cross-reactivity. An over-prediction of the potential risks of allergy, especially if applied to the whole genome, was observed; consequently, the authors recommended a redefinition of the methods for risk assessment. The investigation of biochemical and biophysical properties of proteins should be explored to improve the potential allergenicity predictions.

(ii) identification of unknown allergenic proteins and epitopes both in notifiable allergenic food (Lee et al., 2018; Yang et al., 2020; Han et al., 2020; Crespo et al., 2021) and in emerging/novel sources

407 of food allergens (Righetti et al., 2015; Srinroch et al., 2015; Nikolić et al., 2018; Cardona et al.,
408 2018; Pali-Schöll et al., 2019a). Protein extraction and proteome analysis from plant tissue is not
409 straightforward due to poor protein yield and the presence of many interfering compounds and
410 intrinsic differences in concentration range of proteins. This could hide the low- and very low-
411 abundance proteins (Boschetti et al., 2009). Regarding this aspect, in the work of Nikolić et al. (2018)
412 the difference in the expression levels of proteins in the banana protein extract was mitigated by the
413 use of a combinatorial library methodology of peptide ligands (CPLL, Combinatorial Peptide Ligand
414 Library), which allows to improve the detection and analysis of low abundance proteins in the
415 development of representative protein fingerprint. This approach allowed to identify catalase as a
416 novel allergen from banana through 2-D PAGE analysis, mass spectrometry and 2-D immunoblot
417 (Fig. 2).

418 The identification and characterization of allergen epitopes is important not only for allergy
419 diagnosis/prognosis, immunotherapy, but also for cross-reactivity studies, as well as the development
420 of innovative food processing strategies capable of reducing immunogenicity/immunoreactivity of the
421 allergen (Ekezie et al., 2018; Zhu et al., 2018; Pali-Schöll et al., 2019b; Costa et al., 2022a, 2022b)

422

423 (iii) development and validation of reliable analytical methods for accurate and sensitive
424 determination of target allergens in raw materials and in processed foods. As for target analysis, LC-
425 MS-based methods offer the possibility to perform multiplexed analysis allowing the determination
426 of different allergenic proteins in a single run (Monaci et al., 2020; Seki et al., 2021). Very recently,
427 Seki et al. (2021) developed a LC-MS/MS method to monitor not only the target peptides of celiotoxic
428 cereals, but also those of buckwheat; since most countries include only wheat among allergenic
429 grains, gluten-free grains (i.e., buckwheat) are often excluded in method development (Manfredi et
430 al., 2015).

431 It should be noted that the methods developed for the determination of allergens and risk management
432 for food allergy should be able to reach an adequate sensitivity for compliance with the action levels
433 prescribed by the latest version of the VITAL program (currently the VITAL 3.0). In 2020,
434 Holzhauser et al. (2020) investigated whether current analytical methodologies could verify the
435 published VITAL 2.0 and VITAL 3.0 eliciting doses in portions ranging from 5 to 500 g, evaluating
436 limit of detection, quantitative capability, matrix compatibility, and specificity of commercial ELISA,
437 PCR and mass spectrometry methods. The authors concluded that the available analytical methods
438 are capable of assessing the compliance of peanut, soy, hazelnut and wheat allergens; however, cow's
439 milk and hen's egg are more problematic, largely due to matrix incompatibility. In this regard,
440 recently Monaci et al. (2020) developed a target LC-(MRM)MS/MS method for the simultaneous

detection of milk and egg allergen contamination in model cookies, considering that the VITAL threshold levels for egg and milk are set at 0.2 mg total protein of the allergenic ingredient as a reference dose for action level 1 (below this threshold no precautionary labelling statement is required). The cookie reference material developed by MoniQA Association was used for the estimation of method recovery. The calculation of the flowchart for the conversion of target synthetic peptide concentration into total protein concentration (basis of clinical thresholds) is not trivial (Monaci et al., 2020) (Fig. 3): harmonization of conversion strategies and reporting units is therefore recommended not only for compliance assessment but also for the comparability of results (Holzhauser et al., 2020).

It should also be highlighted the current trend to move analysis from the laboratory to real-time in situ monitoring through the development of biosensors and microfluidic strategies (Neethirajan et al., 2018; Zhou et al., 2019; Mattarozzi et al., 2021; Su et al., 2021). A typical biosensors device involves a biorecognition element (antibody, aptamer, enzyme, molecularly imprinted polymer) is-integrated or associated with an optical, electrochemical or piezoelectric transducer to ~~give~~ convert the recognition event into a measurable signal (Manfredi et al., 2016; Chinnappan et al., 2020; Costa et al., 2021; Costa et al., 2022c). The choice of the proper bioreceptor is essential not only for high affinity and selectivity/specificity towards the target analyte, but also to ensure adequate analytical performance when applied to real matrix extracts; in this case, a great deal still needs to be done especially for aptasensor and apta-assays (Mattarozzi et al., 2021).

The combination of advances in analytic devices and in IoT (Internet-of-Things) wireless technology is part of the technological evolution Analytics 4.0, as defined by Mayer & Baeumner (2018), making portable devices completely autonomous by performing data processing and calibration on-board, beyond IoT information sharing (Lu et al., 2019; Bianchi et al., 2020).

iv) assessment of the possible migration of allergenic proteins from BBFCM into food simulants and food products, and investigation of cross-contamination of food from preparation surfaces. Taking into account the heterogeneity of the composition of the raw materials used for bio-based material production (e.g. plant-based materials), an initial untarget LC-MS-based investigation of the protein content of the material should be carried out. Then, target migration studies can be performed by simulating different usage conditions.

As previously discussed, food preparation surfaces can also pose the risk of allergen cross-contamination due to non-exhaustive cleaning procedures. For this issue, the availability of high throughput analytical strategies could be desirable and can be developed thanks to recent evolutions in ambient ionization mass spectrometry (AIMS) techniques. In addition, AIMS techniques

475 associated with the upcoming miniaturization of mass analyzers gives rise to portable instruments for
476 on-site analysis, coupling point-of-care testing to mass spectrometry performances (Blokland et al.,
477 2020). According to the philosophy of ambient MS methods, sample handling should be minimal,
478 simple, and fast. Unlikely, for the analysis of small molecules it has to be considered that bottom up
479 proteomics requires proteolytic digestion before mass spectrometry analysis. However, strategies for
480 in situ extraction and enzyme digestion could also be devised, such as those recently developed for
481 non-invasive MS-based analysis of artworks (Calvano et al., 2020). Swab touch spray mass
482 spectrometry could also be an innovative strategy for investigation of allergen residuals on a surface
483 (Fedick & Bain, 2017).

484

485 An overview of the methodological approaches developed to address the current and future safety
486 issues related to food allergens is shown in Figure 4. This figure reports not only the methods already
487 exploited, but also possible innovative analytical strategies, such as ambient-MS.

488

489 **6. Conclusion and future prospects**

490 Nowadays there are still serious incidents, which pose great concern in the management of the allergy
491 risk. As the legislation in the field of allergens is not homogeneous, a proper food safety assessment
492 should be required. Furthermore, since sometimes the consumption of certain products is only
493 allowed in a specific country, in a world characterized by increasing globalization, this issue should
494 be faced and resolved.

495 Novel foods are a source of great concern in terms of potential allergenicity related to both new
496 sources of ingredients and innovative technological processes. Innovative and environmentally
497 sustainable food-contact materials, including biopolymers proposed as packaging and single-use
498 items, represent a still unexplored safety problem for sensitive people. In fact, these materials are
499 often widely used without sufficient and proper preliminary tests on the presence of allergens and on
500 the risk of exposure. Lately, the diffusion of new food products and bio-based materials has been
501 encouraged, and many items are imported from countries where strict mandatory controls are not
502 imposed.

503 As far as future analytical perspectives are concerned, the safety issues previously discussed can be
504 addressed through reliable analytical approaches, ranging from sophisticated omics investigations to
505 reveal protein homology and predict cross-reactivity, to high-throughput target analysis. In the last
506 case, mass spectrometry-based methods and biosensing platforms can be developed, which require
507 adequate validation and performance assessment not only in raw materials but also in processed
508 foods. The sensitivity of the method should comply with continuously updated reference doses. In

509 this regard, the sample treatment procedure also represents a crucial step that cannot be overlooked,
510 with the need to go beyond the proof of concept, especially in the development of biosensing
511 strategies for in situ screening analysis.

512 Although much work has been done on food allergens in the last decades, the interest in research on
513 this topic is constantly evolving, moving in parallel with new social, economic, environmental needs
514 and trends.

515

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 1054

1055 **Figure captions**

1056 **Fig. 1.** Overview of potential allergenic sources from food contact materials.

1057

1058 **Fig. 2.** Schematic representation of the strategy based on proteomic and immunological methods used
 1059 for identification of catalase as novel allergen from banana. Combinatorial peptide ligand library
 1060 methodology with 2-D PAGE, mass spectrometric and 2-D immunoblot analysis were employed.
 1061 Reprinted with permission from Nikolić et al. (2018).

1062

1063 **Fig. 3.** Flowchart to convert synthetic peptides concentration ($\mu\text{g}_{\text{peptide}}/\text{mL}_{\text{extract}}$) into total protein
 1064 concentration of allergenic ingredient ($\mu\text{g}_{\text{tot prot}}/\text{g}_{\text{matrix}}$), which is the reporting units of the
 1065 recommended VITAL 3.0 reference doses. Reprinted with permission from Monaci et al. (2020).

1066

1067 **Fig. 4.** Overview of the main methodological approaches in food allergy research and food allergen
 1068 detection to address current and emerging safety concerns for sensitised individuals.

1069

1070 **Table 1**

1071 List of proteins occurring in common materials used for bio-based packaging production.

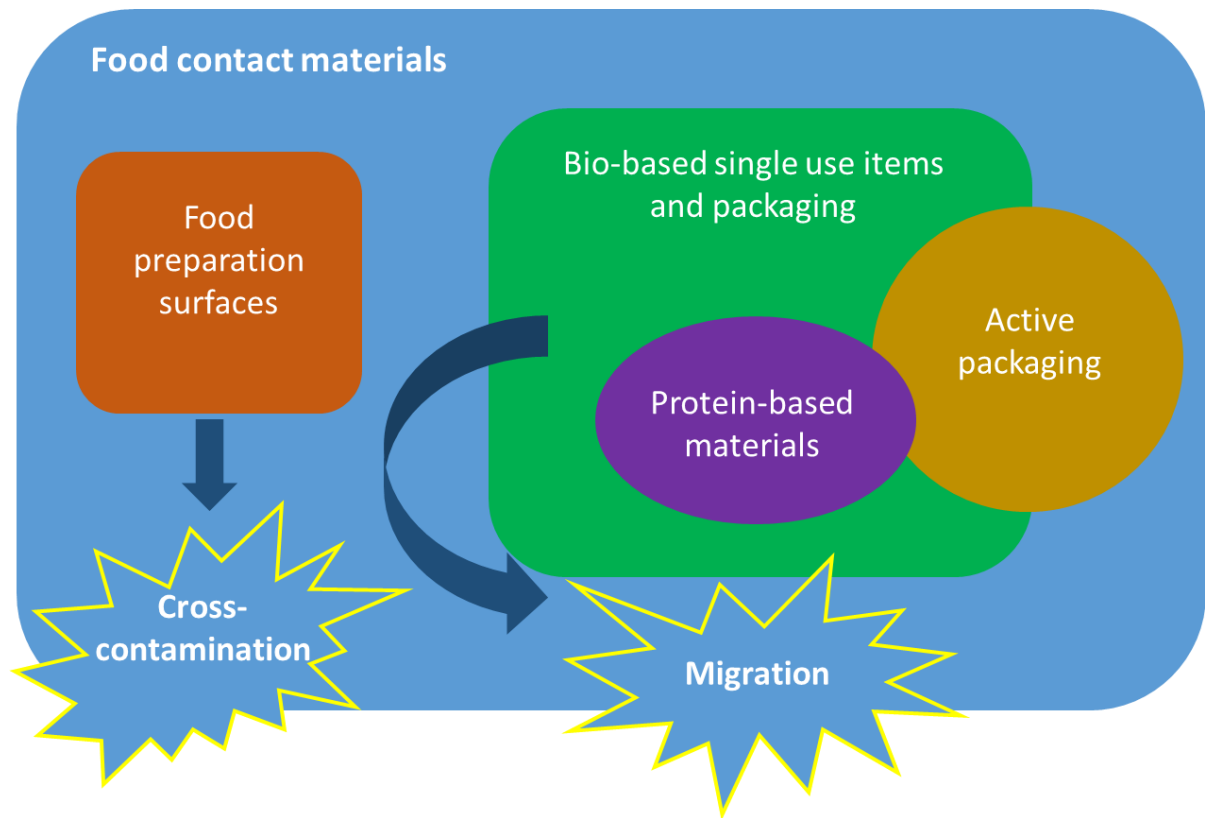
1072

Source	Protein	Origin	Use	References
Animal	Lysozyme	Egg	Active packaging	Syngai & Ahmed, 2019; Pranata et al., 2019

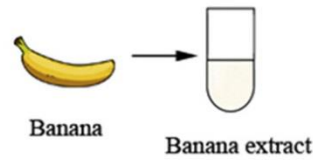
Plant	Tropomyosin; arginine kinase	Chitins and Chitosan from shellfish	Film	de la Caba et al., 2019; Hajji et al., 2021
	Casein	Milk	Film/coating	Mohamed et al., 2020
	Whey proteins	Milk	Film	Whag et al., 2014; Oses et al., 2009
	Collagen	Connective tissues	Film/coating	Wang et al., 2015; Ahmad et al., 2016
	Gelatin	Bovine hide, pig skin	Film/coating	Ramos et al., 2016;
	Keratin	Feather	Film	Pardo-Ibáñez et al., 2014
	Quinoa proteins	Quinoa	Film	Caro et al., 2016
	Sunflower proteins	Sunflower	Film	Salgado et al., 2013
	Soy proteins	Soybeans	Film/coating	Swain et al., 2004; Han et al., 2018
	Pea proteins	Pea	Film/coating	Acquah et al., 2020
	Zein	Corn	Film/coating	Cho et al., 2010
	Gluten	Wheat	Coating	Mihalca et al., 2021

1073

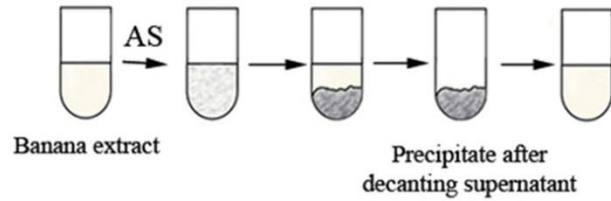
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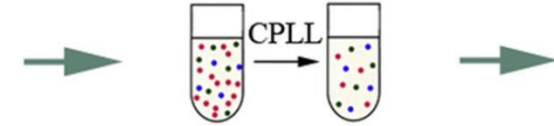
1. Banana extract preparation



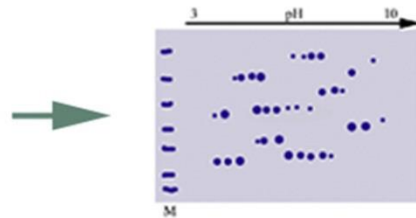
2. Removal of interfering substances.



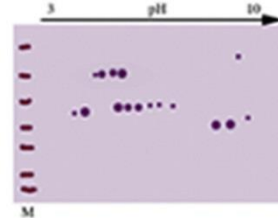
3. CPLL treatment



4. 2-D PAGE of banana proteins



5. 2-D IgE immunoblot

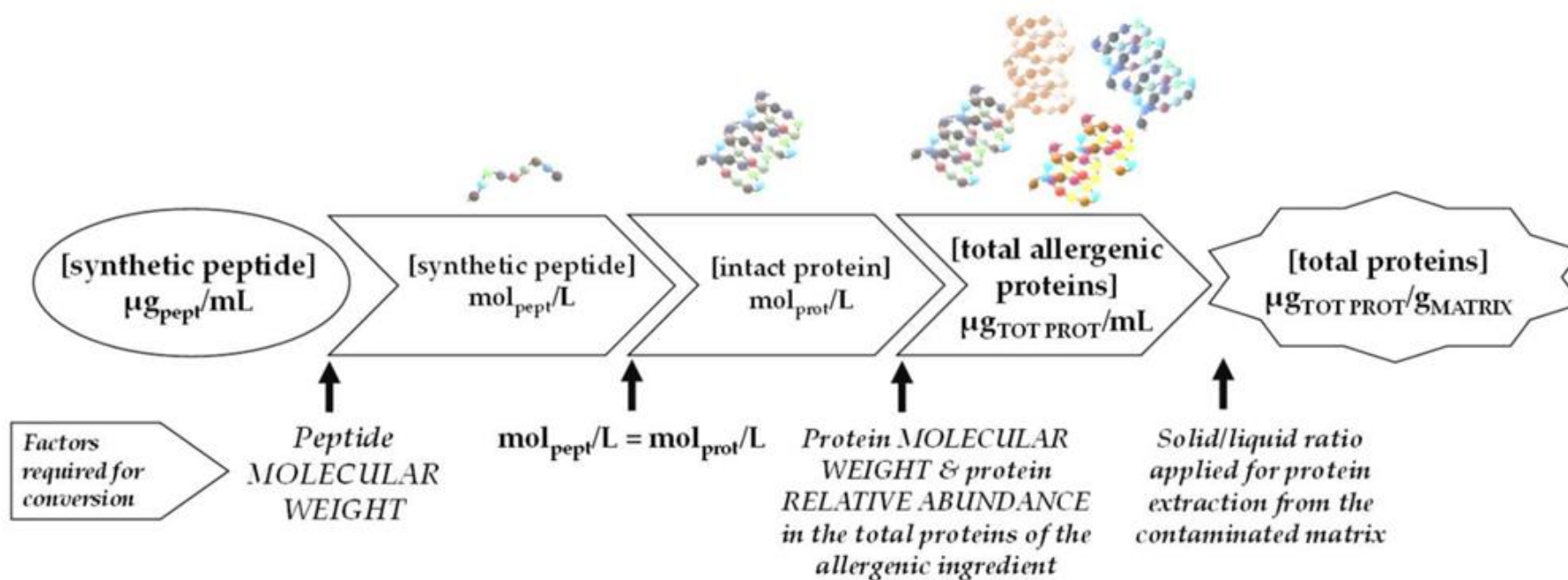


6. MS analysis of IgE reactive protein

catalase2 [Musa acuminata AAA Group];
 Protein View: ABV55108.1
 Protein sequence coverage: 48%
 Matched peptides shown in **bold red**

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1  HPTVTPSS  SPTNFTTN  AGAPVNDQ  ALTVCSQPI  LLEPMVEK
51  IAPFADEEP  EDVNRAGS  AGFECTHO  VYLTCAQPL  RAPVQVPII
101  LPTSTYCHP  GPTSTQDR  GRAPPTTC  GKKLLQNP  PPTVQDCA
151  PPTVQDPEP  NQCSQGVN  RUPDLSNP  ETLQFFLF  DQVQSDNR
201  HNEGFQNTY  TPVSDQGN  YAPNRPIC  QVCLLEDA  EVGGQNSR
251  ATQALYSCA  ADHFFNELF  VQNPQSDI  PDSPLDET  KYNQLPLI
301  QPVGLVLM  KDNFFSNE  QLAFGLVY  PCVYSDDM  LQEVVATGR
351  TQVTELGNY  LFLPVNAC  AHRNRPGL  RQNRNREK  DTPPSKSLI
401  KQVETSTYV  RVTGSRNK  VYRQDQIQ  INQVNDAP  NQVSPVNR
451  AEQLAPVVS  YELSEKTSF  LSKDTSLSQ  KYNQLNMA  NI
  
```



Prediction of the allergenic potential of novel foods focused on possible IgE cross-reactivity due to sequence homology with known allergens

- Liquid chromatography-high resolution mass spectrometry-based shotgun proteomics, top-down proteomics and intact protein analysis; Bioinformatics analysis of sequence homology, using for example Allergen Online and NCBI databases
- Prediction of proteins from genomic sequences; Bioinformatics analysis of sequence homology, using for example Allergen Online and NCBI databases

Identification of unknown allergenic proteins and epitopes in notifiable allergenic foods, emerging allergenic foods and novel foods

- Combinatorial peptide ligand library enrichment of low-abundance proteins (for fruit and vegetable extracts); 1D and 2D gel electrophoresis analysis on total protein extract; IgE-immunoblotting using sera or pool sera of sensitive/allergic individuals; Mass spectrometry-based bottom-up proteomic on IgE-reactive spots
- Peptide library in glass microarrays slides and fluorescence immunoassay using sera or pool sera of sensitive individuals; Similarities study of IgE-binding epitopes, using for example the Structural Database of Allergenic Proteins
- Biopanning of a phage display random peptide library for selection of mimotopes; Structure modeling and epitope mapping of protein allergen

Determination of target allergens in raw materials and in processed foods

- Target liquid chromatography-mass spectrometry-based analysis of proteolytic peptides
- Enzyme-linked immunosorbent assay
- Polymerase chain reaction
- Electrochemical or optical biosensors
- Swabbing tests (Enzyme-linked immunosorbent assay, Lateral flow immunoassay, Ambient-mass spectrometry)

Determination of target allergens in food simulants or food product due to migration of allergenic proteins from BBFCM and investigation of cross-contamination of food from preparation surfaces