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Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens

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Abstract

In older children, adolescents, and adults, a substantial part of all IgE-mediated food allergies is caused by cross-reacting allergenic structures shared by inhalants and foods. IgE stimulated by a cross-reactive inhalant allergen can result in diverse patterns of allergic reactions to various foods. Local, mild, or severe systemic reactions may occur already after the first consumption of a food containing a cross-reactive allergen. In clinical practice, clinically relevant sensitizations are elucidated by skin prick testing or by the determination of specific IgE *in vitro*. Component-resolved diagnosis may help to reach a diagnosis and may predict the risk of a systemic reaction. Allergy needs to be confirmed in cases of unclear history by oral challenge tests. The therapeutic potential of allergen immunotherapy with inhalant allergens in pollen-related food allergy is not clear, and more placebo-controlled studies are needed. As we are facing an increasing incidence of pollen allergies, a shift in sensitization patterns and changes in nutritional habits, and the occurrence of new, so far unknown allergies due to cross-reactions are expected.

Food as a trigger for allergic reactions is gaining more importance, and up to 60% of food allergies in older children, adolescents, and adults are linked with an inhalant allergy. In contrast to classical food allergies where primary sensitization is thought to occur in the gastrointestinal tract and is directed mostly against stable food allergens, primary sensitization in pollen-related and some other cross-reactive food allergies is considered to be against aeroallergens.

Although epidemiologic data are scarce, there is no doubt that the increase in pollen allergies is going to be followed by an increase in the so-called pollen-related food allergies (1–4).

Cross-reaction is based on the binding of an IgE antibody to homologous allergen structures—shared linear or—in most cases—conformational epitopes (i.e., structural similarities). Such structures may be conserved among proteins with

similar functions (5, 6). While for some cross-reactivities the primary sensitizer is known (e.g., Bet v 1 homologues), much less information is available for other cross-reactivities such as those caused by thaumatin-like proteins (7).

Examples of allergens which share allergenic epitopes are members of the pan-allergen families PR10, profilins, glucanases, and tropomyosins (8). IgE cross-reactivities to carbohydrates in plants may also occur, yet in most cases, they are not linked with a clinical reaction. They can be identified by testing specific IgE to bromelain or its glycan structure, MUXF, coupled to a protein backbone, for example BSA (9).

Reports on specific food allergies linked with specific aeroallergens are inconsistent. This apparent inconsistency is not surprising, as today the majority of allergic patients are sensitized toward pollen or other inhalant allergens from more than one plant species, and therefore, there is a plethora of possible cross-reactions. Moreover, geographic differences and different nutritional habits may also play an important role in this context.

Recently EAACI published evidence-based guidelines for Food Allergy and Anaphylaxis (10, 11). The aim of this position paper is to extend the knowledge on cross-reactivities between inhalant and food allergies. In addition to the condensed information from the guidelines, this document aims to provide expert-based advice and recommendations for diagnosis and therapy accordingly.

Cross-reactions are also frequent in primary food allergy caused by stable food proteins (e.g., in hazelnut and other nuts, in peanut and other legumes, in cow's and goat's milk, in codfish and other fish species). However, these are not within the focus of this position paper.

Table 1 Common and uncommon food allergies due to cross-reactions

Inhalant allergen	Food allergen
Common cross-reactions to foods	
Tree pollen	Apple, cherry, nectarine, peach, hazelnut, carrot, celeriac, soybean, peanut, potato, kiwifruit, sharon fruit, jackfruit
Less Common cross-reactions to foods	
Mugwort pollen	Spices, carrot, celeriac, lychee, mango, sunflower seeds, grapes, peach
Natural latex	Pineapple, avocado, banana, potato, tomato, kiwifruit, chestnut
Uncommon cross-reactions to foods	
Ficus benjamina	Fig
Bird allergens	Poultry, egg, innards
House dust mites	Shellfish and molluscs
Sycamore/peach*	Apricot, plum, apple, lettuce
Animal epidermis	Cow's milk, meat, innards
Unproven cross-reactions to foods	
Artemisia and Ambrosia pollen	Melon, zucchini, cucumber, banana
Grass and grain pollen†	Flour, bran, tomato, legumes

*Primary sensitization to non-specific lipid transfer proteins (nsLTPs) not yet fully understood, possibly gastrointestinal to peach as the 'main allergen.' nsLTP-related allergies are clinically 'aggressive' and common in Spain and other Mediterranean countries.
†Considering the frequency of grass and grain allergy, cross-reactions with food are extremely rare.

Clinical background

Table 1 summarizes common and less frequent food allergies due to cross-reactions with inhalant allergies in Europe. While many of the cross-reacting allergens have already been determined (12), others still have to be identified.

Symptoms of food allergy generally appear within minutes to two hours following the ingestion of food and may involve one or more target organs, including the oral mucosa, the skin, the gastrointestinal and respiratory tracts, and the cardiovascular system.

Contact urticaria of the oropharyngeal sites (previously designated as oral allergy syndrome; OAS) is by far the most frequent clinical presentation of food allergy seen in adolescent and adult patients (13). Symptoms generally appear within 5 to 15 min following the food ingestion and consist of pruritus of the lips, tongue, palate, ears, and throat, and mild angioedema at the same sites may be associated. In a subset of patients, red patches or short living blisters of the oral mucosa might be observed. Spontaneous resolution is seen in most cases within 10–30 min, although some patients may subsequently develop systemic reactions. These mucosal symptoms can be elicited by any food and are in particular frequently observed as an isolated symptom in pollen-allergic patients with an associated allergy to fruits and nuts. In contrast, sensitization to fresh fruits and nuts without concomitant pollen allergy usually lead to more pronounced symptoms (14, 15).

After the oral mucosa, the *skin* is the target organ most often involved in allergic reactions to food and also in cross-reactive food allergy. Acute generalized *urticaria*, with or without angioedema, is the most common cutaneous presentation of food allergy. Sometimes only a generalized *flush,* that is, a pruritic erythema, is observed (16). Furthermore, *contact urticaria* (a local wheal and flare reaction at the contact site with the food) is rather commonly observed. Of note, *atopic dermatitis* can exacerbate in patients who are sensitized to pollen upon oral provocation with cross-reactive foods (17).

Gastrointestinal symptoms (nausea, cramps, vomiting, diarrhea) are rarely the sole manifestation of cross-reacting food allergy. Similarly, food allergy-induced *respiratory symptoms* such as rhinoconjunctivitis, bronchospasm, or laryngeal edema are exceptionally seen as the sole manifestation of food allergy but more frequently in association with allergic reactions at other target organs. Although relatively rare, also severe anaphylactic reactions are observed in pollen-associated food allergies (18, 19). In this context, the role of

food matrix effects, the abundance of the causative allergen, and potential augmentation factors remain to be investigated (20).

Due to the existence of cross-reacting pan-allergens in plant foods, it is of clinical relevance to notice that already the first ingestion of a food containing such pollen-related allergens may lead to allergic reactions. This has been shown for three novel vegetables, that is, water spinach, hyacinth bean, and Ethiopian eggplant for a subset of so far not exposed pollen-allergic individuals (21). Other examples have been reported for allergy to jackfruit due to the presence of Bet v 1 homologues in the exotic fruit (22) and Bet v 1 homologues in kiwifruits (23).

Diagnostic approach

Diagnosing food allergy is quite similar to diagnosing other allergic diseases although some particular aspects have to be considered (Table 2). If food allergy is suspected, knowledge about sensitizations against inhalant allergens potentially leading to cross-reactivity to foods is very helpful. The pattern of sensitizations to common pollens can easily and reliably be determined with standardized extracts in skin prick tests or measurement of specific IgE. Additional information will be obtained by testing food-specific IgE. In some situations, IgE testing with single molecules *in vitro* using conventional or microarray format may be useful. If the patient's medical history is not clear, a mucosal and/or oral challenge test is currently the only means available to determine whether a food allergy is present. Oral provocation testing is the only way to confirm food allergy and is therefore of significant relevance in clinical practice especially for patients at risk to develop severe systemic reactions.

The individualized diagnostic procedure may vary due to the patients' histories and their presentations of symptoms, respectively (Table 2).

Specific aspects of skin testing in clinical practice

In suspected food allergy due to cross-reactions, prick testing with the inhalant allergen and the related food allergens is usually indicated and provides information on sensitization which is not always followed by clinical significance. Moreover, c*ommercially available food extracts* are not biologically standardized. Particularly, for plant-derived food allergens, commercial extracts for SPT show a low sensitivity resulting in a high rate of false-negative results (24). This phenomenon is related to the low abundance and/or the lack of stability of several allergens to endogenous enzymatic processes taking place in plant food extracts. Here, skin testing with native foods by the prick–prick technique is superior. Native foods can be tested in different forms (e.g., raw or heated). The *prick–prick test* with native material from fresh fruits and vegetables places limits on the comparability of the tests due to differences in the allergenic raw material depending on the variety used, and the degree of ripeness and storage (25, 26). Other limitations of native prick–prick tests are the low specificity reflected by a high rate of false-positive results without clinical relevance and its dependence on the availability of the fresh food in question.

Specific aspects of *in vitro* testing in clinical practice

Allergen-specific IgE detection is generally indicated in case of suspected food allergic reactions associated with uncertain history or negative skin tests, with suspected foods not applicable for skin testing, with severe reactions to foods, and with conditions hampering skin testing or its interpretation (e.g., active skin disease or application of antihistamines) or in case of young children (10, 27, 28). Moreover, *in vitro* testing offers the possibility to determine specific IgE directed to single proteins (molecular or component-resolved diagnosis). However, the interpretation of the test implies that the clinician is familiar with the most important allergen protein

Table 2 Clinical settings in food allergy due to cross-reactions to inhalant allergies

Setting	History	Recommended diagnostic procedure	Management
1	*Convincing* history of an allergy against pollen and *local* reactions after ingestion of corresponding cross-reacting foods	Validation of the sensitization to the pollen / food by skin prick tests and/or *in vitro* IgE testing	Advice to stop eating the food once local reactions developed*
2	*Convincing* history of an allergy against inhalant and a *systemic* allergic reaction after ingestion of corresponding cross-reacting foods*	Validation of the sensitization to the pollen and to food by skin prick or *in vitro* IgE testing	Advice to stop eating the food having caused the systemic reaction
3	*Unclear* history of allergy against inhalant and a *systemic* allergic reaction after ingestion of corresponding cross-reacting foods†	Skin testing and specific IgE-testing with inhalant allergens and foods followed by oral provocation tests under clinical supervision	Advice to stop eating the food causing a positive challenge reaction

*In many cases, cooked or processed food does not lead to clinical symptoms in these patients (individual testing required).
†For example, birch–carrot, mugwort–celeriac, house dust mite–shrimps, latex–banana.

families. Several databases provide useful information (see: www.allergen.org; www.allergome.org).

IgE antibodies directed against the carbohydrate epitopes of vegetable glycoproteins, the so-called N-glycans, are present in 10–20% of patients with an allergy to pollen (29). These IgE antibodies are highly cross-reactive against almost all vegetable foods. In most cases, these antibodies are biologically inactive and therefore not of clinical relevance (30).

The measurement of food-specific IgG or IgG_4 does not provide clinically relevant additional information in suspected food allergy (31).

Discrepancy between the immunological and clinical findings

For the interpretation of sensitization against cross-reacting allergens, the differentiation between a clinically relevant and irrelevant cross-reaction is necessary. More cross-reacting allergens are detected with skin tests and/or *in vitro* tests than using the history of clinical symptoms to corresponding foods. Up to date, the underlying mechanisms leading from sensitization toward clinically significant cross-reactions after food ingestion are not completely understood (32). Serum levels of IgE antibodies are only of limited predictive value for the outcome of oral challenge tests or the severity of clinical reactions. The assumption that only patients with severe seasonal pollen-related symptoms develop pollen-related food allergy could not be confirmed. There is a group of patients developing food allergy symptoms long after their first symptoms of pollen allergy. In rare cases, it is possible that the pollen allergy remains 'silent,' whereas the sensitization to cross-reacting foods becomes clinically apparent (33).

Oral provocation tests

When the patient's history remains inconclusive, an oral provocation test is the only diagnostic tool instrument to differentiate between clinically relevant food allergy and silent sensitization (11). In particular for fruits and vegetables, challenge meals have to be freshly prepared. The same problems in raw material selection as reported for prick–prick tests affect oral challenges. Open challenges are valid if they lead to negative or clearly positive results with objective symptoms. Recently efforts were undertaken in an EU funded project (Europrevall) to work toward standardized protocols for DBPCFCs (34).

Double blinded, placebo-controlled challenge with native allergenic food is the best available test procedure for the confirmation of aeroallergen-related food allergy (35–38). It is based on two meals [e.g., drinks, pudding etc. (11)] with identical color and consistence as well as identical taste: one contains the chopped native food in a defined amount and the other does not. Initially, a mucosal provocation can be performed. The amount of allergen in the provocation meal varies depending on the allergen and the patient's history. For example, 1 ml of drinking solution should contain 0.14 g of celeriac. For 'classical foods,' the dosage can be much lower. The interval between verum and placebo should be at least 24 h and longer in case of reactions that needed treatment. Subjective symptoms (e.g., OAS, itching, etc.) as well as objective symptoms of the allergic reactions like rhinoconjunctivitis, allergic asthma, urticaria, angioedema, diarrhea, vomiting, dyspnoea, or loss of blood pressure, which should appear only after verum and not placebo administration, have to be registered. A cumulative dose of the native food on the following day may be required due to possible matrix effects (39).

In case of suspected worsening of atopic dermatitis or of delayed onset of gastrointestinal symptoms, the diagnostic procedure and the significance of oral provocation differ from the described approach; repetitive provocations may be necessary (39, 40).

Therapeutic consequences after detection of cross-reactions

An elimination diet should be recommended only if food allergy due to cross-reactions is based on a clear history or on a clinical observation after oral provocation tests. More detailed information/recommendation is presented in the Food Allergy Guidelines (11). Of note, atopic individuals must not be put on diet according to their sensitization pattern alone.

Symptomatic therapy is orientated on general guidelines for the treatment of allergies with antihistamines, corticosteroids, and epinephrine (11).

Allergen immunotherapy has been described to be beneficial in some pollen-associated food allergies in some studies. Some studies suggest that allergen immunotherapy with pollen ameliorates mucosal symptoms resulting from the associated food (41, 42). Unfortunately, these results are not consistent in different studies (43–45).

One year of SLIT with birch pollen extract did not improve oral symptoms to apple despite measurable decreases in birch-related symptoms with therapy (46). In contrast, subcutaneous immunotherapy using modified birch pollen allergens for the treatment of oral symptoms showed efficacy in celery allergic individuals with birch pollen allergy (47).

A definitive evaluation of the allergen immunotherapy with pollen extracts in pollen-associated food allergies can only be given from larger prospective, placebo-controlled studies. For patients with a severe food allergy but without clinical symptoms of a tree pollen allergy, immunotherapy cannot generally be recommended today.

Specific aspects of relevant inhalant allergens leading to food allergy

Birch

Birch pollen- or tree pollen-associated food allergies are most important because of their high prevalence in northern and central Europe. Usually birch pollen-related food allergies are accompanied by mild symptoms. However, in some studies on birch pollen-mediated soy allergy (18, 19, 48), a considerable percentage of patients responded with systemic symptoms including anaphylaxis. Also consumption of

sharon fruit and jackfruit induced anaphylactic episodes in birch pollen-allergic patients (22, 49). Moreover, studies on celeriac and carrot allergy in pollen-allergic subjects reported systemic reactions in approximately 50% of the patients according to case histories, and up to 50% of the patients experienced systemic reactions under challenge (35, 36).

After cooking, characteristically most of the tree pollen-associated foods containing heat-labile allergens are well tolerated by the majority of the patients. However, studies have provided evidence that small quantities of pollen-related allergens from roasted hazelnuts (50) and cooked celeriac (37) are still able to provoke symptoms in highly sensitized patients (51).

In central Europe, all well-characterized cross-reacting allergen families of pollen and vegetable foods can be found in birch pollen. In contrast, species-specific cross-reacting allergens in mugwort and grass pollen could not be identified so far. The major allergen of birch pollen, Bet v 1, is recognized by more than 95% of birch pollen-allergic patients. Related allergens in plant-derived foods have been identified as the predominant major allergens in pollen-related food allergy [Table 3, (12)].

Minor allergens are recognized by 10–32% of birch pollen-allergic patients. Besides Bet v 1, four birch pollen allergens (Bet v 2, Bet v 6, Bet v 7, and Bet v 8) are known to be responsible for cross-reactions with vegetable foods. Cross-reactivity between Bet v 1, Bet v 2, or Bet v 6 and exotic fruits have led to relatively severe reactions even when eaten for the first time.

Bet v 1-related allergens are often underrepresented in extracts. Therefore, the diagnosis of birch pollen-related legume allergy should not be excluded on a negative skin prick test or negative IgE testing to legume extracts. Gly m 4 from soy and Ara h 8 from peanut are commercially available and are recommended in birch pollen-allergic patients with suspicion of soy or peanut allergy, but negative extract-based diagnostic tests (Table 3, (19, 52). So far, only hazelnut extracts are 'spiked' with recombinant major allergen Cor a 1 to increase the sensitivity in one commercial *in vitro* test system.

Table 3 Birch pollen (Bet v 1*)-associated food allergies

Family	Food	Related food allergen	For *in vitro* testing available
Rosaceae	Apple	Mal d 1	✓
	Cherry	Pru av 1	
	Pear	Pyr c 1	
	Peach	Pru p 1	✓
Apiaceae	Celeriac	Api g 1	✓
	Carrot	Dau c 1	
Other	Hazelnut	Cor a 1.04†	✓
	Soybean	Gly m 4	✓
	Mungbean	Vig r 1	
	Kiwifruit	Act d 8	✓
	Peanut	Ara h 8	✓

*Bet v 1 is a member of pathogenesis-related (PR) protein family and the major source of pollen-related food allergy in central Europe.

†Hazelnut test is spiked with rCor a 1.04 in a commercial IgE test system.

Mugwort

Artemisia vulgaris pollen is a major cause of late summer pollinosis in Europe. Cross-reactive food allergies seem to be by far less frequent than in patients with tree pollen allergies, but in part, these food allergies can be more severe (Table 4, (53). Several cases of anaphylactic reactions to celeriac have been reported in patients with mono-sensitization to mugwort pollen (35, 37).

The dominant allergen for sensitization is the glycoallergen Art v 1 to which >95% of the patients are sensitized (54, 55). Unfortunately, there is no reliable data regarding the prevalence of food allergy in patients sensitized to mugwort pollen only. Using two allergens (Art v 1 and Art v 4), 91% of the patients could be identified as mugwort pollen-sensitized patients by IgE *in vitro* tests (56). However to date, there are no data available demonstrating cross-reactivity of well-defined single Artemisia allergens with plant food allergens.

A number of associations have been described on the basis of clinical case studies (Table 4) and *in vitro* cross-reactivity studies. In a few mugwort-/celery-allergic patients, the presence of celery allergy was confirmed by DBPCFC (35, 37).

Recently Art v 3, the nsLTP from mugwort, was identified as the sensitizing pollen allergen in a Chinese peach allergic patients' collective (57).

Grass

Grass pollen is one of the most important airborne allergen sources worldwide. Carbohydrate-reactive IgE antibodies have been attributed to grass pollen sensitization and found to cross-react with the glycan structures from other allergen sources, particularly vegetable foods. Cross-reactive IgE directed to carbohydrate determinates of glycoproteins as

Table 4 Mugwort-associated syndromes

Syndrome	Food allergic reactions to:
Celeriac–birch–mugwort–spice–syndrome	Celeriac and other vegetables as well as spices of the Apiaceae or Umbelliferae family (e.g., carrot, caraway seeds, parsley, fennel seeds, coriander seeds, aniseed)
Celeriac–mugwort–spice syndrome	Apiaceae, Solanaceae (paprika), Piperaceae (pepper), Anacardiaceae (mango), and Liliaceae (garlic, onion)
Mugwort–mustard allergy syndrome	Mustard, Brassicaceae vegetables other than mustard (e.g., broccoli, cabbage, and cauliflower), nuts, legumes, Rosaceae fruits, corn
Mugwort–peach association	Peach (allergy caused by nsLTP: Art v 3 and Pru p 3)

found in grass pollen-sensitized patients has poor biologic activity (30, 58).

Another cause of extensive cross-reactivity is the group 12 allergens (profilins) that belong to a family of proteins highly conserved throughout the plants (59). The majority of profilin-sensitized individuals do not react to corresponding foods in challenge tests (60). Recent data confirmed that IgE to grass pollen profilin was detectable in bakers with asthma, food, and pollen allergy (61). Of note, patients with wheat allergy alone show extensive *in vitro* cross-reactivity to other grains but little to taxonomically related grass pollen. By contrast, patients with grass pollen allergy alone showed extensive *in vitro* cross-reactivity to both, cereal grains and grasses.

Taken together, the role of grass pollen-associated food allergy is doubtful.

Ragweed

The concept that ragweed pollen may share allergens with plant-derived foods appeared 40 years ago when Anderson and co-workers noted an association between allergy to melon and banana and ragweed pollinosis (62). At the beginning of the new century, other studies showed that many melon-allergic subjects clinically react to a number of botanically unrelated plant-derived foods, including peach, fig, and kiwifruit, and can show latex sensitization as well (63). The major melon allergen was identified as the pollen pan-allergen profilin (64). Confirmation of profilin sensitization in ragweed allergic individuals (which is detectable in the minority of those allergic persons only) may be due to Bet v 2 reactivity.

Whether ragweed-specific allergens are able to induce clinically relevant sensitization to cross-reactive foods still remains unclear. This seems rather unlikely as no patient out of a series of 140 consecutive subjects mono-sensitized to ragweed pollen reported any adverse reaction induced by vegetable foods (65).

Plane

An association between plane tree pollinosis and plant food allergy has been described (66), but the detailed characterization of the cross-reacting allergens still remains to be completed.

Until now, four allergens of plane pollen have been identified: Pla a 1 and Pla a 2 seem to be the best indicators for specific plane tree pollinosis because they are responsible for 79% of the IgE-binding capacity against plane tree pollen extract. Both allergens together are sufficient for a reliable diagnosis of plane tree pollinosis (67). The presence of profilin-specific IgE antibodies has been described as a cause of cross-reactivity among botanically unrelated allergen sources. Profilin sensitization has been shown in about 47% of patients with plane tree pollinosis. Nevertheless, it seems that neither the two major allergens nor profilin can explain the cross-reactivity detected between plane tree pollen and plant foods (68).

Finally, Pla a 3 (plane lipid transfer protein nsLTP) was characterized as a minor allergen (27%) in plane pollinosis without associated food allergy. This is considered as a major allergen (64%) in plane pollen-allergic patients with peach allergy recruited in the Mediterranean area (69). Likewise, no general conclusions on the primary sensitizer could be made as Pla a 3 and peach nsLTP showed different biological activities in histamine release assay depending on individual patients' sera tested (70).

Latex

Since 1980s, natural latex gained importance as allergen following more frequent occupational use and private exposition. High-risk groups for the development of a latex allergy are medical staff, workers in latex industry, and patients with multiple surgeries. Latex (*Hevea brasiliensis*) allergy presents as contact urticaria or respiratory symptoms after inhalation of latex particles or anaphylaxis during surgery. For healthcare workers, the prevalence of latex allergy seems to be declining in some countries due to successful prevention measures (71).

A number of latex allergens have been identified (Table 5). Patients with sensitization or allergy against latex may develop allergies against avocado, banana, kiwifruit, chestnut, and other foods. Recently, case reports on cross-reactivity between latex and cassava (72) and latex and curry-spice have been reported (73). Probably depending on nutritional habits, different patterns of food allergies have been reported to be associated with latex allergy (74). In a study with 137 patients having a well-documented latex allergy, sera were screened for fruit-specific IgE antibodies. Fruit-specific IgE antibodies were found in 69% of the sera; 42% of the patients reported allergic symptoms after ingestion of specific foods (75). By contrast, 86% of patients with a positive history of fruit allergy but without risk factors for a latex sensitization had latex-specific IgE antibodies and 11% showed significant clinical symptoms after latex challenge (76). Again, local reactions such as mild to moderate OAS are most common. In approximately 10% of the cases, latex-associated

Table 5 Latex allergens

Clinical aspects	Allergen	CRD reagents
Major allergens (e.g., health care workers)	Hev b 5, Hev b 6.01 and Hev b 6.02	rHev b 5, rHev b 6.1, rHev b 6.02
Patients with frequent surgeries (Spina bifida)	Hev b 1 and Hev b 3	rHev b 1, rHev b 3
Cross-reactive allergens in the latex–fruit syndrome	Hev b 2, Hev b 6.01, Hev b 6.02, Hev b 6.03, Hev b 7, Hev b 8, and Hev b 11	rHev b 6.1, rHev b 6.02, rHev b 8, rHev b 11,
No or low clinical relevance	CCD	MUXF3, CCD, Bromelain

food allergy presented with severe anaphylactic symptoms. Recently the cross-reactivity between hevein from latex and the hevein-like domain from fruit class I chitinases was investigated, and despite high cross-reactivity between these molecules, no correlation to the incidence of latex-associated plant food allergies could be detected (77).

Ficus benjamina, which is a popular indoor plant in private homes and offices, releases allergens into the air. The development of an allergy via inhalation followed by allergic symptoms after consumption of figs is possible (78, 79). The presence of cross-reacting structures has been demonstrated (80).

Olive

Pollen from olive tree (*Olea europaea*) is a relevant sensitizer in southern Europe and the coastal Mediterranean area, where the plants are cultivated for olive fruit and olive oil production. Oleaceae pollen allergy has been seldom reported as linked to food allergy. No reports exist on olive pollen mono-sensitized patients being affected by food allergy comparing to what we know about the birch pollen mono-sensitization (81). Contribution to the food-pollen cross-reactivity comes from homologous components shared by the olive pollen, namely the profilin, the nsLTP, and a glucanase (81–84). Peach, apple, pear, kiwifruit, melon, and nuts have been reported as causes of oral allergy syndrome in olive pollen-allergic patients (81). Severity of the food-associated symptoms seems to be related to the involved allergen, being nsLTP the one mostly detected positive in severe reaction, and profilin when oral allergy syndrome is recorded. Data on the relevance of olive pollen glucanase sensitization and food allergy are currently scarce.

House dust mite

Crustaceans and molluscs can be a cause of severe food allergic reactions. The major allergen has been identified as the muscle protein tropomyosin. Allergenic tropomyosins are not only found in crustaceans (e.g., shrimp, lobster, crab, crawfish) and molluscs (e.g., squid, snail and mussels) but also in arachnids (e.g., house dust mites) and insects (e.g., cockroaches). In contrast to these invertebrate tropomyosins, vertebrate tropomyosins seem nonallergenic (85). The mite tropomyosins Der p 10 and Der f 10 show a high degree of similarity to tropomyosins from crustaceans and molluscs (86). The amino acid sequence similarity and epitope reactivity are the basis of the *in vitro* cross-reactivity among invertebrate species (87).

Table 6 Available allergens for component-resolved diagnosis in food allergy possibly related to cross-reactions to inhalant allergens

Food	Allergens	Symptoms	Allergens available for CRD
PEACH	Pru p 1 (PR-10)	Oral	rPru p 1, rBet v 1
	Pru p 4 (Profilin)	Generally oral	rPru p 4, rBet v 2
	Pru p 3 (nsLTP)	Oral and/or systemic	rPru p 3
MELON	Cuc m 1 (Cucumisin)	Oral and/or systemic	N/A
	Cuc m 2 (Profilin)	Oral	N/A, rBet v 2 (as a substitute)
	Cuc m 3 (PR-1)	Oral and/or systemic	N/A
PEANUT	Ara h 1 (Vicilin)	Systemic	rAra h 1
	Ara h 2 (2S Albumin)	Systemic	rAra h 2
	Ara h 3 (Legumin)	Systemic	rAra h 3
	Ara h 5 (Profilin)	Generally oral	N/A (rBet v 2 as a substitute)
	Ara h 8 (PR-10)	Oral	rAra h 8, rBet v 1
	Ara h 9 (nsLTP)	Oral and/or systemic	rAra h 9, rPru p 3
	Ara h 10 (Oleosin)	Systemic	N/A
HAZELNUT	Cor a 1 (PR-10)	Oral and/or systemic	rCor a 1, rBet v 1
	Cor a 8 (nsLTP)	Systemic	rCor a 8
	Cor a 9 (Legumin)	Systemic	
	Cor a 14 (2S Albumin)	Systemic	
KIWIFRUIT	Act d 1 (Cysteine Protease)	Systemic	nAct d 1
	Act d 2 (Thaumatin-like protein)	Oral and or systemic	nAct d 2
	Act d 5 (Kiwellin)	Oral and/or systemic	nAct d 5
	Act d 8 (PR10)	Oral and/or systemic (rather mild reactions)	Act d 8, rBet v 1
CELERY	Api g 1 (PR-10)	Oral and/or systemic (rather mild reactions)	rApi g 1.01, rBet v 1
SOY	Gly m 4 (PR-10)	Oral or systemic (sometimes severe)	rGly m 4, rBet v 1
SHRIMP	Pen a 1 (Tropomyosin)	Systemic	rPen a 1, nPen m 1, rDer p 10

CRD, Component-resolved diagnosis; LTP, nonspecific lipid transfer protein.

For house dust mite allergic individuals, there are reports of reactions against shrimp (86). Usually, tropomyosin seems to be the protein involved in this cross-reactivity. Interestingly, inhibition tests have shown that sometimes mites seem to be the sensitizing agent and sometimes shrimps (86, 88). Snails seem to be the main mollusc involved in clinical relevant cross-reactions with dust mites. Inhibition experiments have shown that house dust mites usually are the sensitizing agents (86, 88). Interestingly, in this cross-reactivity other non-tropomyosin allergens seem to be involved too, including Der p 4, Der p 5, Der p 7, and hemocyanin (88).

Animal epithelia

Respiratory allergy to allergens released by animal epithelia is commonly recorded in the allergic population. Most of the subjects react on exposure to a given animal, as pets at home, as poultry or birds for breeders, or at countryside. Reports on associated food allergy are not so frequently published. The two most frequently described syndromes are the pork–cat syndrome (89) and the bird–egg syndrome (90).

The cat–pork syndrome includes patients having a clinical picture of inhalant allergy to cat epithelium and reacting at ingestion of pork meat. These cases are regularly reported in the literature (89, 91), and some authors suggest that this syndrome could be somewhat underestimated in terms of either prevalence or severity (89). The allergenic molecule involved in this cross-reactivity seems to be the mammal albumin (92) although other still unknown proteins could be involved. Based on albumin IgE recognition, a broader clinical reactivity to both other epithelia and meats would be expected. Some reports point toward this direction (93–96). Recently several studies provided evidence of delayed allergic reactions to alpha-gal present on mammalian meat proteins. Primary sensitization is thought to occur via tick bites. A recent study by Gonzalez-Quintela reported a significant correlation between alpha-gal-specific IgE and cat ownership (97). However, it remains to be verified which cat proteins are airborne and trigger the sensitization pathway.

The bird–egg syndrome describes patients reacting to the inhalation of bird skin/feather-derived dropping products and shed in indoor environments and allergy to chicken egg yolk ingestion (90). The bird serum albumin is involved in this cross-reactivity, being its inhalation the cause of sensitization (98). Several reports are in the literature and, as for the mammal albumin, a broader clinical reactivity caused by eggs and feathers from other bird species can be expected (90, 99, 100).

Cross-reactivity: from allergen sources to single allergens

As Charles Blackley in 1873–1880 demonstrated grass pollen as the causative agent of hay fever, many allergenic sources eliciting both inhalant and food allergies have been described, and while new sources are still being reported, it seems likely that identification of yet unknown sources will only contribute marginally to the overall picture. It is possible, however, that the continuously increasing globalization of the food market may lead to populations being exposed to new foods (21, 101). Global warming may also impinge on hitherto unexposed regions inducing inhalant allergies in new populations. As for the individual allergenic molecules, the last twenty years have brought an explosion in characterized molecules, many of which are already available in recombinant forms. This wealth of knowledge of allergenic sources and molecules is now real time documented on web platforms [Table 1, 6 (101)].

After identification of allergen sources and molecules responsible for the individual inhalant and food reactions, there is now a third wave where our understanding of the cross-reactive patterns may allow us to describe the whole risk profile of a patient with a certain IgE response. Technical platforms are now becoming available for the analysis of a large number of individual allergens (21, 102, 103), but these should be carefully validated and used for research, driven by clinical rather than technological needs (104). For example, by comparing related sequences and structures,

Table 7 Food allergy due to cross-reactions to inhalant allergens: Major messages for clinical practice)

	Clinical practice
Recommendation 1	Sensitizations to different inhalant allergens are responsible for a broad spectrum of sensitizations against foods.
Recommendation 2	The detection of a sensitization with skin or *in vitro* testing is not sufficient to proof clinical relevance. Taking a good clinical history is more important than screening specific IgE against possible cross-reactive allergens.
Recommendation 3	No general dietary advises should be given due to lists of known cross-reactivities between inhalant and food allergies. Diets should only be based on a proper diagnosis of food allergy.
Recommendation 4	For some foods, the prick–prick test with fresh materials is better than a prick test with commercially available food extracts to detect sensitizations.
Recommendation 5	The testing of individual allergens ('component-resolved diagnosis') *in vitro* may be individually helpful for the detection of a sensitization to a food. Testing of individual allergens may also be helpful in predicting the risk profile for systemic reactions in individual patients.
Recommendation 6	In cases of an unclear history, oral provocation tests with suspected foods are necessary before advising a therapeutical elimination diet.
Recommendation 7	Allergen immunotherapy to cross-reactive inhalants is not recommended based on the food allergy alone but should be given on the basis of respiratory symptoms.

potential cross-reactive determinants with clinical significance *vs* the ones without clinical relevance will be determined.

Setting standards for future research

From the current knowledge on immunological and clinical cross-reactivity, it is now evident that the latter is based on the presence of IgE recognizing shared epitopes among allergenic molecules. This immunological condition is, however, not sufficient in helping the therapeutic decision (i.e., allergen avoidance) and could lead to over-intervention reducing the patient's quality of life. Practical consequences drawn from the current knowledge on this topic are summarized in Table 7.

When combining the immunological and clinical data with population studies, the highest informative value should be aimed at. The clinical descriptions should include features such as age, symptomatology, geographical regions, and the quality of the diagnosis. It has been beyond the resources of this working group to grade all published works on cross-reactivity between inhalants and foods, but it is conceivable that when more large-scale epidemiological studies become available, a ranking such as outlined below could be used to create databases categorizing the evidence for cross-reactivity. Only when such validated databases become available, data-mining for elucidation of the patient's risk profile will be possible.

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Author contributions

Stefan Vieths and Thomas Werfel initiated this task force within the EAACI Interest Group Food Allergy which was later taken over and finalized by Thomas Werfel and Karin Hoffmann-Sommergruber. Several face-to-face meetings and telephone conferences were organized to prepare this document. Riccardo Asero, Barbara Ballmer-Weber, Kirsten Beyer, Ernesto Enrique, Andre Knulst, Adriano Mari, Antonella Muraro, Markus Ollert, Lars Poulsen, and Margitta Worm contributed to this manuscript with their expertise. All the authors participated in the discussion and phrasing of the recommendations and approved the final version of this position paper.

Conflict of interest

T. Werfel, R. Asero, A. Mari, E. Enrique, A. Muraro, M. Worm, L.K. Poulsen, and A. Knulst have no conflict of interests. B. Ballmer-Weber reports financial support from EAACI, during the conduct of the study, and personal fees from ThermoFisher, outside the submitted work. K. Beyer reports grants and personal fees from ThermoFisher Diagnostics, and grants from Hycor, outside the submitted work. In addition, Dr. Beyer has a patent Cor a 9 issued to Mount Sinai School of Medicine. K. Hoffmann-Sommergruber reports lecturing honoraria from ThermoFisher outside the submitted work. Dr. Ollert reports others from PLS-Design GmbH, Hamburg, Germany, outside the submitted work.

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