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Edible insects and food safety: allergy

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Abstract

Edible insects are a unique food source, requiring extensive allergenic risk assessment before its safe introduction in the food market. In a recent systematic review, crustacean allergic subjects were identified as a risk group due to cross-reactivity mainly mediated by tropomyosin and arginine kinase. Immunologic co-sensitisation to house dust mites (HDM) was also demonstrated, but its clinical significance and molecular mechanisms were unclear. Furthermore, case reports of food allergy to insects were also analysed but lack of contextual information hindered the analysis. The main goal of this review is to provide an update of new information regarding food allergy caused by insects, covering relevant topics considering the guidelines for allergic risk assessment in novel foods. Newly published studies have further confirmed the role of tropomyosin as a cross-reactive allergen between edible insects and crustaceans, although there are some questions regarding the immunoglobulin E (IgE)-reactivity of this allergen in mealworm species. Furthermore, only specific treatments (enzymatic hydrolysis combined with thermal treatments) were able to eliminate IgE-reactivity of edible insects. Primary sensitisation (e.g. to *Tenebrio molitor*) has also been shown to be an important pathway for the development of food allergies, with responsible allergens being dependent on the route of sensitisation. However, more studies are necessary to better understand the potential of primary sensitisation causing cross-reactivity with other insect species, crustaceans or HDM. The clinical significance and molecular mechanisms involved in cross-reactivity between edible insects and HDM are still unclear, and a major focus should be given to better understand which allergens cause co-sensitisations between HDM and edible insects and what is the risk of HDM-only allergic subjects consuming edible insects. Contextual information about the reported cases of allergic reactions to insects have further demonstrated that insect-rearing workers and subjects with allergic diseases (in particular, food allergy to crustaceans) are the major risk groups.

Keywords: case reports, cross-reactivity, entomophagy, primary sensitisation, tropomyosin

1. Introduction

Immunoglobulin-E (IgE)-mediated food allergy can be described as an adverse reaction of the immune system to specific proteins in foods which are usually harmless (De Gier and Verhoeckx, 2018; Messina and Venter, 2020). It is estimated that 3-10% of adults and 8% of children worldwide have a food allergy, with most reactions being caused by milk, egg, peanut, tree nuts, fish, soy, wheat or crustaceans (Boyce *et al.*, 2010; Messina and Venter, 2020). These IgE-mediated reactions occur after the consumption of the food product with an onset of up to 2 hours after the consumption, with their presentations ranging from isolated cutaneous or abdominal symptoms to potential fatal reactions such as anaphylaxis (Wang and Sampson, 2011). Food allergies are developed in two phases. Firstly, in the sensitisation phase, susceptible individuals are exposed to an allergen (usually through

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consumption) and produce specific IgE antibodies to that allergen. Afterwards, following repeated exposure to the same allergen, IgE antibodies on the surface of mast cells recognise the specific allergen, cross-link, and activate an immunologic response (Muraro *et al.*, 2014). However, reactions can also occur due to cross-reactivity, which is defined as when IgE antibodies originally raised against one allergen bind to another structurally-related allergen. Cross-reactivity occurs frequently between allergens from taxonomically related species due to the existence of pan-allergens (proteins that are highly preserved from an evolutionary point of view, and capable of inducing allergic responses in related species) (García and Lizaso, 2011; Migueres *et al.*, 2014). In order to confirm cross-reactivity it is usually necessary to perform inhibition assays, otherwise it is recommended to use the term co-sensitisation, which consists on the simultaneous presence of different IgEs that bind to allergens that may not necessarily have common structural features (Migueres *et al.*, 2014).

Allergic reactions subsequent to insect consumption can be associated to cross-reactivity. This reaction may occur due to the phylogenetic relationship of insects with common allergen sources such as crustaceans or house dust mites (HDM) (Pennisi, 2015). In fact, cross-reactivity with crustaceans has been demonstrated to be clinically relevant, with the main cross-reacting allergens identified being the arthropod pan-allergens tropomyosin and arginine kinase (AK). On the other hand, co-sensitisation between edible insects and HDM has been shown, but the underlying molecular mechanisms and clinical significance remain unclear. Allergic reactions to edible insects can also be associated to primary sensitisation (either through environmental (Pomés *et al.*, 2017) or occupational (Stanhope *et al.*, 2015) exposure) – several allergens have been already identified and characterised, namely AK (cockroaches, silkworm and indianmeal moth), tropomyosin (cockroaches, mosquito, termite, silverfish), aspartic protease, hemocyanin, glutathione S-transferase, troponin C, myosin light chain, serine protease and α-amylase (cockroaches). Moreover, edible insect allergens were reported to have similar behaviours to crustacean allergens in response to enzymatic and thermal treatments (De Gier and Verhoeckx, 2018; Jeong and Park, 2020; Ribeiro *et al.*, 2018). While epidemiological data and even case reports are still scarce, and often lacking in contextual information (De Gier and Verhoeckx, 2018; Ribeiro *et al.*, 2018), there have been reports indicating that insects are responsible for 4.2-19.4% of cases of food allergies in Asian countries (Ribeiro *et al.*, 2018), and that silkworm pupae is a major culprit of food allergies in China (Ji *et al.*, 2008) and Korea (Jeong and Park, 2020).

The legal status of edible insects as a novel food (Belluco *et al.*, 2017) prompts the need for an in-depth risk assessment – including the allergenic risk – so that they can be commercialised in the European Union food market. Although there is not any established protocol for allergenicity assessment of novel foods, the current guidelines are based on weight-of-evidence approach, taking into account such different issues as: (1) the history of allergic reactions to the novel food; (2) the taxonomy of the novel food (to identify possible relations with known allergic sources); and (3) the identification and characterisation of proteins of the novel food (with assessment of their allergenic potential through bioinformatics assays, comparing them to known allergens). In addition, the IgE-binding capacity of the novel food has also to be assessed, using serum form individuals allergic to other sources (for cross-reactivity) or serum from individuals sensitised to the novel food (primary sensitisation). It is also important to identify possible IgE-binding proteins and to determine the biological activity of such proteins (if they can activate an immunologic response), either through functional tests (such as basophil activation tests; BAT) or food challenges. Further tests also include the evaluation of thermal and chemical (e.g. resistance to enzymatic digestion) treatments on the allergenic properties of a novel food.(Mazzucchelli *et al.*, 2018; Verhoeckx *et al.*, 2016; Westerhout *et al.*, 2019).

The relative novelty of this theme implies that new information is being constantly published, and that the state of the art needs to be updated frequently. Therefore, in this study, we aim to update our previous review (Ribeiro *et al.*, 2018), assessing the new scientific developments related to the allergic risks of insects as food. Specifically, we aimed to cover all the relevant topics related to allergic risk assessment of edible insects including the mechanisms and allergens implied both in primary sensitisation and in cross-reactivity with crustaceans or HDM and the effects of food processing on edible insects' allergenicity. In addition, we aimed to assess epidemiological studies and case series/reports of allergic reactions following insect consumption.

2. Methods

The methodology applied in this study was based on the previous systematic review performed by the authors (Ribeiro *et al.*, 2018). In brief, a systematic search was conducted on three online databases (PubMed/Medline, Scopus and Web of Science) on May 2020 using the same query – (insect OR mite* OR carmine OR cochineal OR cockroach OR arthropod OR crustacea* OR silkworm OR locust OR grasshopper OR cricket OR mealworm OR moth OR beetle) AND (allerg* OR hypersensitiv* OR anaphyla* OR crossreactiv*) AND (food OR edible OR consumption OR entomophagy OR ingesti* OR occupati* OR consum* OR eat*). In order to avoid obtaining previously reviewed papers, only articles published since 2017 were retrieved on this database search. References of included studies and review papers concerning entomophagy were also screened.

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Inclusion and exclusion criteria

In accordance with our aims, in this systematic review we sought to cover all the relevant topics regarding edible insects allergenicity according to current guidelines for novel food allergenic risk assessment. Therefore, we included original studies that assessed cross-reactivity or co-sensitisation between edible insects and crustaceans or HDM, as well as the molecular mechanisms in food primary sensitisation to edible insects. Moreover, articles identifying and characterising (including effects of food processing techniques) food allergens from edible insects were also included. Additionally, case reports describing allergic reactions following the intentional ingestion of insects, and studies assessing the prevalence of such reactions were also included.

We excluded articles that only assessed other types of insect allergies (e.g. respiratory allergy or reactions subsequent to stings or bites) as well as articles characterising allergens from non-edible insects (e.g. cockroaches). Additionally, articles included in our previous systematic review were also excluded.

Study selection and data extraction

After duplicates removal, the retrieved studies were firstly screened by title and abstract, and then by full-text reading. The full texts of studies meeting the inclusion criteria were analysed, and information was retrieved on May 2020.

The whole process for study selection and data extraction was independently performed by two authors, and any disagreement was solved by consensus.

3. Results

A total of 20 articles were included in this systematic review – 19 obtained through database research and 1 (Jiang *et al.*, 2016) obtained through screening of the references of included studies (although it was published in 2016, it was included since it was not present in our previous review) (Figure 1).

Of these 20 articles, 8 studied cross-reactivity or co-sensitisation with either crustaceans or HDM (Barre *et al.*, 2019; Beaumont *et al.*, 2019; Broekman *et al.*, 2017a; Hall *et al.*, 2018; Kamemura *et al.*, 2019; Pali-Scholl *et al.*, 2019; Palmer *et al.*, 2020; Sokol *et al.*, 2017), 5 focused on primary sensitisation (Broekman *et al.*, 2017a,b; Francis *et al.*, 2019; Jeong *et al.*, 2017; Nebbia *et al.*, 2019), 1 evaluated allergenic potential of insect tropomyosin (Klueber *et al.*, 2020), 3 studied the effects of food processing techniques on insects' allergenicity (Hall *et al.*, 2018; Hall and Liceaga, 2020; Pali-Scholl *et al.*, 2019), 4 were case reports or case series (Beaumont *et al.*, 2019; Gadisseur *et al.*, 2019; Nebbia *et al.*, 2019; Sokol *et al.*, 2017), 3 assessed the frequency of food allergies or food anaphylaxis caused by insects (Jiang *et al.*, 2016; Lee *et al.*, 2019; Rangkakulnuwat *et al.*, 2020) and 2 assessed the prevalence of allergic reaction among insect-eaters (Chomchai *et al.*, 2020; Taylor and Wang, 2018).

Mechanisms of immunologic co-sensitisation or cross-reactivity with crustaceans

In our previous review (Ribeiro *et al.*, 2018), we pointed that immunologic co-sensitisation or cross-reactivity to edible insect species (such as mealworms, crickets, locusts and grasshoppers) had been shown for individuals allergic to crustaceans (or to crustaceans and HDM). The main allergens responsible for this cross-reactivity included arthropod pan-allergens tropomyosin and AK, although minor arthropod allergens (e.g. glyceraldehyde 3-phosphate dehydrogenase, myosin light chain, fructose-biphosphate aldolase, actin, α-tubulin, β-tubulin or hexamerin) were also recognised as IgE-binding proteins. Additionally, a double-blind placebo controlled food challenge further confirmed the clinical significance of the cross-reactivity between crustaceans and *Tenebrio molitor* (Broekman *et al.*, 2016).

Since then, immunologic co-sensitisation between edible insects and crustaceans was demonstrated for the first time for the following species: *Galleria mellonella*, *Hermetia illucens* (Broekman *et al.*, 2017a), *Acheta domesticus*, *Locusta migratoria* (Broekman *et al.*, 2017a; Pali-Scholl *et al.*, 2019), *Gryllodes sigillatus* (Hall *et al.*, 2018), and *Schistocerca gregaria* (Pali-Scholl *et al.*, 2019). Moreover, new reports have re-confirmed immunologic co-sensitisation for *T. molitor* (Barre *et al.*, 2019; Broekman *et al.*, 2017a; Pali-Scholl *et al.*, 2019), *Zophobas morio*, *Alphitobius diaperinus* (Broekman *et al.*, 2017a) and *Gryllus bimaculatus* (Kamemura *et al.*, 2019). Furthermore, functionality of the co-sensitisation in *T. molitor* was demonstrated through the application of BAT (Barre *et al.*, 2019; Broekman *et al.*, 2017a), while inhibition studies were used to confirm cross-reactivity with crustaceans (particularly shrimp) involving *G. bimaculatus* (Kamemura *et al.*, 2019) and *Sphenarium mexicanum* (Sokol *et al.*, 2017).

Concerning the allergens responsible for co-sensitisation or cross-reactivity, tropomyosin – whose role as an arthropod pan-allergen capable of causing cross-reactivity has been extensively reported (Wai *et al.*, 2020; Wong *et al.*, 2019) – has been identified as a cross-reacting allergen through immunoblotting in *T. molitor* (Barre *et al.*, 2019; Klueber *et al.*, 2020; Pali-Scholl *et al.*, 2019), *G. sigillatus* (Hall *et al.*, 2018), *G. bimaculatus* (Kamemura *et al.*, 2019), *S. mexicanum* (Sokol *et al.*, 2017), *S. gregaria* and *A. domesticus* (Pali-Scholl *et al.*, 2019). Moreover, Kamemura *et al.* (2019), identified the high molecular

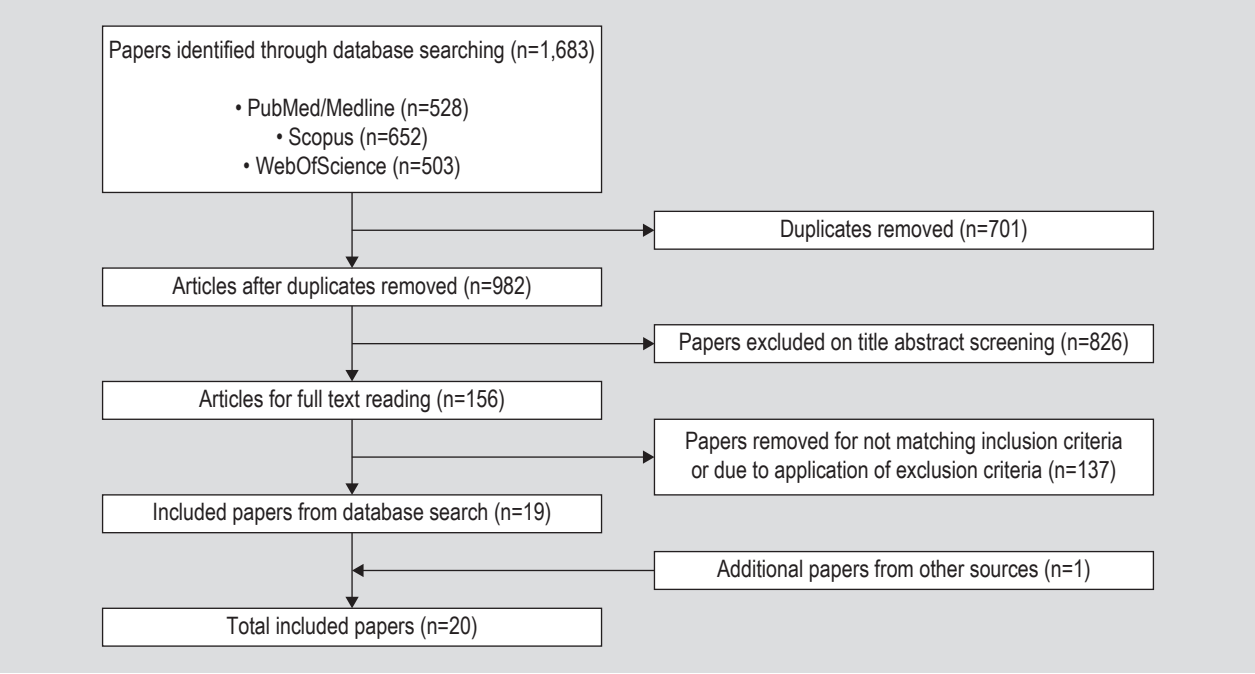

Figure 1. Flow chart of study selection process.

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weight isoform of tropomyosin of *G. bimaculatus* as the antigen that induced shrimp-specific IgE, and it was additionally shown that this isoform had great sequence homology with both other insects species and shrimp tropomyosins. Nonetheless, there has been some conflicting information on *T. molitor* tropomyosin allergenicity – for example, Klueber *et al.* (2020) reported that this protein was capable of causing similar immunologic response (as measured by β-hexosaminidase release from rat basophilic leukaemia cells expressing the human high-affinity IgE receptor) to shrimp tropomyosin while Palmer *et al.* (2020) reported that in three mealworm species (*T. molitor*, *G. mellonella* and *Z. morio*) tropomyosin had lower IgE-reactivity than tropomyosin from *A. domesticus* or *H. illucens*. This variation in mealworm tropomyosin IgE-reactivity may possibly be explained by individual patients characteristics, since Broekman *et al.* (2017a) reported that some shrimp-allergic patients had lower IgE-reactivity with mealworm tropomyosin than with tropomyosin from other insect species. Another possible explanation concerns small regionalised differences in protein sequence (most likely in IgE binding epitopes), since both the abundance of tropomyosin or overall sequence homology could not explain the verified diminished IgE-reactivity. Further research should be performed in order to assess if the molecular mechanisms of mealworm cross-reactivity are different from other insect species.

New studies have confirmed the role of other proteins which had been previously reported as involved in cross-reactivity with crustaceans or HDM. Such proteins include heat shock protein 70, AK (Barre *et al.*, 2019), and α-amylase (Barre *et al.*, 2019; Pali-Scholl *et al.*, 2019). In addition, larval cuticle protein, which has been identified as playing a major role in primary sensitisation to *T. molitor* (Broekman *et al.*, 2017b), was also identified as a cross-reacting protein (Barre *et al.*, 2019). Furthermore, novel IgE-binding proteins have been identified. Such proteins were apolipophorin-III and 12 kDa haemolymph protein, which have similar functions (binding and transport of hydrophobic ligands) (Barre *et al.*, 2019). Apolipophorin has already been identified as a potential allergen in mealworms (Broekman *et al.*, 2017a*)* due to its sequence homology with Der p 14, an allergen of HDM (Epton *et al.*, 2001). Regarding the 12 kDa haemolymph protein, it has been reported as one of the most abundant proteins in *T. molitor* supernatant (Yi *et al.*, 2016), but its allergenicity had never been previously reported.

Mechanisms of immunologic co-sensitisation or cross-reactivity with house dust mites

In our previous review, we reported that only one study (Van Broekhoven *et al.*, 2016) had used sera from patients solely allergic to HDM to assess cross-reactivity between edible insects and HDM. Sera from these patients was able to IgE-bind to extracts from mealworm species, and several cross-reacting proteins were identified (paramyosin, α-amylase, actin, larval cuticle protein, hexamerin and myosin heavy chain). This suggests that the molecular mechanisms of cross-reactivity between edible insects and HDM are different from the ones regulating cross-reactivity between crustaceans and HDM (with the latter being mostly related to tropomyosin) (Wong *et al.*, 2016).

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Newly published studies have added additional insight into co-sensitisation between edible insects and HDM. The level of co-sensitisation to edible insects appears to be different in subjects only allergic to HDM when compared to those that are also allergic to crustaceans (or which are solely allergic to crustaceans). In fact, Barre *et al.* (2019) tested the sera of 13 HDM-allergic participants with *T. molitor* extracts, observing only 2 positive reactions. On the other hand, Pali-Scholl *et al.* (2019) reported that HDM-allergic patients had different patterns of IgE-reactivity to insects, which differed according to the tested species and body parts: there was no IgE-reactivity to *T. molitor* and to the bodies of *A. domesticus*, *L. migratoria* and *S. gregaria*; on the other hand, IgE-reactivity was found for the extremities (wings and legs) of the tested species.

Regarding allergens responsible for co-sensitisation, in a HDM-allergic patient that suffered food allergy to *T. molitor*, Beaumont *et al.* (2019) identified two allergens (tropomyosin and hexamerin 2A) by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) while other cross-reacting proteins (larval cuticle proteins A1/A2, pupal cuticle protein G1A, α-amylase and tubulin) were also possibly present (visible in 2D-Western Blot). Of these allergens, hexamerin, α-amylase and larval cuticle protein had been previously identified as cross-reacting proteins between HDM and mealworm species (Van Broekhoven *et al.*, 2016). Interestingly, hexamerin has also been described as a cross-reacting allergen between HDM and shellfish (Giuffrida *et al.*, 2014). However, it is also important to note that, although tropomyosin was detected as a cross-reacting protein, such was based on the assessment of a subject which was not sensitised to shrimp or HDM tropomyosin, rendering unlikely that this allergen is responsible for cross-reactivity (Beaumont *et al.*, 2019).

The scarcity of studies performed with HDM-only allergic patients hinders our knowledge concerning the allergens involved in this cross-reactivity and its clinical significance. Future research should be focused on HDM/edible insects cross-reactivity, especially considering the role that HDM-sensitisation has on the development of shellfish allergy (Wai *et al.*, 2020; Wong *et al.*, 2016).

Primary sensitisation

Concerning primary sensitisation, in our previous review, we reported on studies which had been performed with individuals sensitised or with allergies to silkworm (Jeong *et al.*, 2016; Liu *et al.*, 2009; Wang *et al.*, 2016; Zhao *et al.*, 2015; Zuo *et al.*, 2015). These studies have identified a wide array of IgE-binding elements, such as AK (Liu *et al.*, 2009), chitinase (Zhao *et al.*, 2015; Zuo *et al.*, 2015), paramyosin (Zhao *et al.*, 2015), 27-kDa heat-stable glycoprotein (Jeong *et al.*, 2016), thiol peroxiredoxin (Wang *et al.*, 2016), vitellogenin, 30 K protein, triosephosphate isomerase, heat shock protein and chymotrypsin inhibitor (Zuo *et al.*, 2015). Of these, AK, paramyosin and chitinase were hypothesised to play a role in cross-reactivity with other arthropods (such as cockroaches or HDM), or even with shrimp due to their high sequence homology with known allergens of these species.

Newly published studies have focused on the detection and characterisation of allergens from *T. molitor* responsible for primary sensitisation and subsequent food allergy (Broekman *et al.*, 2017b; Nebbia *et al.*, 2019). Broekman *et al.* (2017b) identified larval cuticle proteins as major allergens of both respiratory and food allergy to *T. molitor*. On the other hand, Nebbia *et al.* (2019) hypothesised that cockroach allergen-like protein was the primary allergen in both respiratory and food allergies since it was present in extracts from *T. molitor* larvae and faeces (which authors proposed as the main route of sensitisation). These differences in the detected allergens could be explained by different routes of sensitisation, since the subjects reported by Nebbia *et al.* (2019) were mainly sensitised to *T. molitor* faeces while the subjects in the work by Broekman *et al.* (2017b) were not only domestic breeders of mealworm but also regular consumers of this insect. In addition, in both studies, arthropod pan-allergens such as tropomyosin, AK, myosin light and heavy chain (Broekman *et al.*, 2017b), 86 kDa early-staged encapsulation protein, and troponin C (Nebbia *et al.*, 2019) were detected as IgE-binding proteins.

However, it is still uncertain if primary sensitisation to edible insects can cause food allergies to crustaceans through cross-reactivity. In fact, Broekman *et al.* (2017b) observed that all subjects with primary sensitisation to *T. molitor* had negative oral challenges to shrimp, while the participants in the study by Nebbia *et al.* (2019) were not sensitised to shrimp or tropomyosin from other arthropods. Of note, Linares *et al.* (2008) had already previously described an individual with primary sensitisation and respiratory allergy to different species of crickets, but who had no detectable specific-IgE (sIgE) to allergic tropomyosins, and no cross-reactivity for crustaceans or mites. This lack of tropomyosin IgE-reactivity was also demonstrated in subjects allergic to silkworm pupa (Jeong *et al.*, 2017). These results seem to point out that tropomyosin might not play a major role in primary sensitisation to edible insects, which might explain the lack of cross-reactivity between individual primarily sensitised to edible insects and other arthropods. Nonetheless, it is known that there is a high degree of co-sensitisation/cross-reactivity between cockroaches and shellfish, with tropomyosin playing a major role (Wai *et al.*, 2020; Yang *et al.*, 2018), although its clinical significance is not yet established (Wong *et al.*, 2019)

Importantly, it is also possible that primary sensitisation can be somewhat species-specific, as observed in shrimp species (Jirapongsananuruk *et al.*, 2008). In a study performed with

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four subjects who were primarily sensitised to *T. molitor* (with respiratory and/or food allergies), it was shown that subjects had variable reactivity and sensitisation to several insect species (*Z. morio*, *A. diaperinus*, *G. mellonella*, *H. illucens*, *A. domesticus*, *L. migratoria*) (Broekman *et al.*, 2017a). Conversely, in the same study, most of shrimp-allergic patients were co-sensitised to all the tested insect species. Interestingly, two subjects that have had an allergic reaction to *T. molitor* consumption reported no clinical symptoms after consuming other insect species (namely greater wax moths, black soldier flies and crickets) (Nebbia *et al.*, 2019). However, some controversies remain on this question – in fact, Francis *et al.* (2019) reported that AK from *T. molitor* and from *A. domesticus* had weak conservation/homology, with apparent no cross reactivity between these species. On the contrary, Liu *et al.* (2009) not only identified AK as a major allergen of *Bombyx mori*, but also that it cross-reacts with AK from cockroaches.

Effects of food processing technologies

Some effects of food processing on edible insects' allergenicity had already been reported in our previous review. Overall, co-sensitisation between edible insects and crustaceans was reported not to be significantly diminished by thermal treatment (Broekman *et al.*, 2015; Van Broekhoven *et al.*, 2016), although the latter was described to have an impact on the intensity and types of allergens that are detected (Phiriyangkul *et al.*, 2015). Furthermore, *in vitro* digestion had been shown not to eliminate IgE-binding capacity of mealworm tropomyosin (Van Broekhoven *et al.*, 2016).

Food processing technologies are suggested to influence allergenicity of edible insects, and the effects of enzymatic hydrolysis (Hall *et al.*, 2018; Pali-Scholl *et al.*, 2019), microwave-assisted enzymatic hydrolysis (Hall and Liceaga, 2020), and heat treatment (Pali-Scholl *et al.*, 2019) on edible insects allergenicity have been assessed. Hall *et al.* (2018) assessed the allergenicity behaviour of tropomyosin from cricket species *G. sigillatus* and found that only a degree of hydrolysis superior to 50% with alcalase® was able to eliminate its IgE-binding capacity to shrimp-allergic sera. In a follow-up work (Hall and Liceaga, 2020) with the same species, IgG-reactivity of tropomyosin was lower with microwave-assisted enzymatic hydrolysis (also performed with alcalase and a degree of hydrolysis greater than 50%) than with just heat treatment (water bath or microwave) or water bath with enzymatic hydrolysis. These results are in line with previous studies, which had also suggested that insects' tropomyosin was able to maintain its allergenicity even after most thermal or enzymatic treatments (Broekman *et al.*, 2015; Van Broekhoven *et al.*, 2016). This behaviour is also present in shellfish tropomyosin, which has been described as resistant to most thermal treatments and even enzymatic hydrolysis (e.g. simulated gastric fluid and simulated intestinal fluid digestion systems) (Khan *et al.*, 2019), although potentially susceptible to combinations of processing techniques (Mejrhit *et al.*, 2017).

On the other hand, heat-treatment (water bath at 80 and 100 °C for 10 minutes or autoclaving at 121 and 138 °C for 20 minutes) or enzymatic hydrolysis (flavourzyme, papain, alcalase, neutrase) eliminated IgE-reactivity to *L. migratoria* in whole protein extracts of subjects with allergy to both shrimp and HDM (Pali-Scholl *et al.*, 2019). One possible explanation for these different results can be related to the protein extraction technique that was applied, which could have impacted the solubility and detection of the allergens, as shown in the work by Broekman *et al.* (2015).

Prevalence of food allergy to insects

The prevalence of allergic reactions caused by insect consumption has been assessed either through questionnaires directed to consumers of edible insects (Chomchai *et al.*, 2020; Taylor and Wang, 2018) (Table 1) or through retrospective analyses of series of patients assessed for food allergy or for anaphylaxis (Jiang *et al.*, 2016; Lee *et al.*, 2019; Rangkakulnuwat *et al.*, 2020) (Table 2).

Two studies assessed the prevalence of allergic reactions among consumers of edible insects. Such studies were performed in Thailand, and relied on self-reported symptoms following the consumption of insects. Chomchai *et al.* (2020) performed an Internet survey, where it was observed that 18 out of 140 assessed subjects (12.9%; 95% confidence interval [CI]=7.3-18.5%) reported allergic reactions following the consumption of insects, of whom 4 (22.2%; 95%CI=3.0-41.4%) reported severe symptoms. Furthermore, the occurrence of an allergic reaction to insects was found to be associated with a history of other allergies, including food allergy to seafood. Taylor and Wang (2018) assessed the characteristics of insect-consumers in the North-Eastern region of Thailand through a cross-sectional survey delivered in public schools and hospitals, and reported that 14.7% (95%CI=13.1-16.3%; 288 of 1,956) of insect consumers reported the occurrence of a single symptom after consuming insects, and 7.4% (95%CI=6.2-8.6%; 146/1,956) reported multiple symptoms. Furthermore, 72.3% (95%CI=61.4-83.2%; 47/65) of those reporting pre-existing food allergies, reported at least a single symptom following the consumption of insects. Severe reactions had allegedly been experienced by 150 participants (7.6%, 95%CI=6.3-8.7%; 150/1,956); however, the study does not clearly specify how such reactions were defined.

A previous study performed in Laos had reported lower frequencies of allergic reactions (81/1,059; 7.6% 95%CI=6.0-9.2%) (Barennes *et al.* (2015) (Supplementary Table S1). These differences reflect not only different consumption habits, but also different sampling methods – while

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Table 1. Description of studies assessing prevalence of food allergy amongst consumers of edible insects.

Reference/Study	Country	Methodology	Total number of subjects – n	Number of self-reported allergic reactions – n (%; 95%CI)	Species (number of cases)	Other information
Taylor and Wang (2018)	Thailand	cross-sectional survey assessing, amongst others, the occurrence of side effects after eating insects	1,956	434 (22.2%; 20.4-24.0%)	water bugs – 42.9% scorpions – 30.0% grasshoppers – 22.3% crickets – 21.6% bamboo worms – 17.1% red ants – 17.0% silkworms – 16.7% red ant eggs – 11.4%	14.7% (95%CI=13.1-16.3%; 288/1956) reported the occurrence of a single symptom and 7.4% (95%CI=6.2-8.6%; 146/1956) reported multiple symptoms; 72.3% (95%CI=61.4-83.2%; 47/65) of those reporting pre-existing food allergies, reported at least a single symptom following the consumption of insects
Chomchai *et al.* (2020)	Thailand	internet-based cross-sectional survey of people who practiced entomophagy	140	18 (12.9%; 7.3-18.5%)	silkworm larva (8 – 44.4%) grasshopper (4 – 22.2%) cricket (3 – 16.7%) bamboo caterpillar (3 – 16.7%)	allergic symptoms after insect consumption were associated with a history of respiratory allergy, skin allergy and seafood allergy

Table 2. Description of studies which retrospectively analysed food allergic reactions, and which included cases caused by insects.

Reference	Country	Methodology	Total number of cases of food anaphylaxis/ allergy	Number of cases caused by insects – n (%; 95%CI)	Species (number of cases)	Other information
Jiang *et al.* (2016)	China	retrospective review of outpatients diagnosed with 'anaphylaxis' or 'severe allergic reactions' in the Department of Allergy, Peking Union Medical College Hospital, from January 2000 to June 2014	1,501	5 (0.3%; 0.02-0.6%)	locusts (2) cicada (2) silkworm chrysalis (1)	
Lee *et al.* (2019)	Korea	retrospective review of the medical records of 812 Korean adult patients with suspected food allergy and who visited the Allergy Asthma Centre of a tertiary hospital in Korea from January 2014 to December 2018	415	13 (3.1%; 1.4-4.8%)	silkworm pupa (13	46.2% (6/13; 95%CI= 19.1-73.3%) also had food allergy to shellfish
Rangkakulnuwat *et al.* (2020)	Thailand	retrospective review of electronic medical records of patients who attended the outpatient and emergency departments at Chiang Mai University Hospital from January 2007 to December 2016	209	17 (8.1%; 4.4-11.8%)	fried insects, namely grasshopper, crickets, silk worms, and bamboo worms (n not specified)	

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Barennes *et al.* (2015) and Taylor and Wang (2018) performed their studies on populations where entomophagy is common, Chomchai *et al.* (2020) recruited participants through posters and ads in websites which could mean that people who suffered allergic reactions were more predisposed to participate in the survey. Furthermore, all these studies assessed self-reported reactions, which can also lead to an overestimation of food allergy cases. For instance, in the study performed by Taylor and Wang (2018), many of the cases classified as food allergy could be instead cases of food poisoning or allergic reaction to poison, since water bugs (*Lethocerus indicus*) (which are mostly eaten without cooking) and scorpions (*Heterometrus longimanus*) were the species that were reported to cause most allergic reactions, despite being two of the least consumed species by the participants. In fact, food poisoning – which is out of scope of this review – due to insect consumption is not rare, with several described reports of outbreaks of histamine poisoning (Chomchai and Chomchai, 2018). Histamine poisoning, also designed scombroid poisoning, is a foodborne illness that occurs due to toxic levels of histamine (caused by histidine decarboxylase formed by histamine-producing bacteria) mainly in spoiled fish and whose symptoms are very similar to IgE-mediated food allergy (Wu *et al.*, 1997).

Concerning the retrospective analyses of cases of food allergy or anaphylaxis, three different studies (Jiang *et al.*, 2016; Lee *et al.*, 2019; Rangkakulnuwat *et al.*, 2020) have been performed in Asia. Lee *et al.* (2019) retrospectively analysed medical records of 415 adult patients with suspected food allergy, reporting that 13 confirmed cases (3.1%; 95%CI=1.4-4.8%) were caused by consumption of silkworm pupae. Additionally, six of those 13 patients (46.2%; 95%CI= 19.1-73.3%) also had food allergy to shellfish. The other studies (Jiang *et al.*, 2016; Rangkakulnuwat *et al.*, 2020) have focused on retrospective analysis of cases of food anaphylaxis and found that insect consumption caused 0.3% (5/1,501; 95%CI=0.02-0.6%) (Jiang *et al.*, 2016) and 8.1% (17/209; 95%CI=4.4-11.8%) (Rangkakulnuwat *et al.*, 2020) of food anaphylaxis cases. Previous studies (Supplementary Table S2) have reported widely different values of food anaphylaxis caused by the consumption of insects – 5.2% (1/24; 95%CI=0.0-12.2%) (Jirapongsananuruk *et al.*, 2007), 17.6% (63/358; 95%CI= 13.6-21.4%) (Ji *et al.*, 2009), and 19.4% (7/36;95%CI=6.5-32-3%) (Piromrat *et al.*, 2008). These differences in values and in the species causing most reactions can mirror the consumption habits of the regions where the studies were performed. Nonetheless, it is noteworthy to mention that there are studies assessing the prevalence of food allergy in Asia and that do not mention insects as causative agents of food allergy (Le *et al.*, 2019; Lee *et al.*, 2013). This can happen because entomophagy is a more common practice in specific regions and rural areas (Manditsera *et al.*, 2018) which can lead to several cases going unreported at national levels.

Case reports and case series

In our previous review, we were able to retrieve 29 cases reports of food allergies caused by insects' consumption (Supplementary Table S3). Most of the cases occurred in Asia and Africa, with the causative species mostly reflecting regional consumption habits. For example, the reported reactions that occurred in China (Ji *et al.*, 2008) were due to silkworm pupae, while the reactions occurring in Botswana were caused by mopane worms (Kung *et al.*, 2011, 2013; Okezie *et al.*, 2010). In most cases (18/29), the reactions occurred after consuming the insect for the first time, suggesting that these reactions could have occurred due to cross-reactivity with crustaceans or HDM. In fact, two of the subjects had previous history of allergic reactions to shellfish (Choi *et al.*, 2010; Piatt, 2005), while other nine had subjects were either sensitised to common aeroallergens or had an history of allergic diseases (Broekman *et al.*, 2017b; Choi *et al.*, 2010; Freye, 1996; Ji *et al.*, 2008; Kung *et al.*, 2011, 2013). Furthermore, in three cases (Broekman *et al.*, 2017b; Freye, 1996) the mechanism for food allergy was probably primary sensitisation since it occurred in subjects which were constantly exposed to the species.

In this review, we identified 16 new cases of food allergy caused by the consumption of insects (Table 3; Beaumont *et al.*, 2019; Gadisseur *et al.*, 2019; Nebbia *et al.*, 2019; Sokol *et al.*, 2017). These cases occurred in France (Beaumont *et al.*, 2019), United States of America (Sokol *et al.*, 2017), Italy (Nebbia *et al.*, 2019) and Niger (Gadisseur *et al.*, 2019). The species that caused the allergic reactions were *chapulines* (*S. mexicanum*) (Sokol *et al.*, 2017), *T. molitor* (Beaumont *et al.*, 2019; Nebbia *et al.*, 2019), and crickets (Gadisseur *et al.*, 2019).

The five cases that occurred in Western countries (Beaumont *et al.*, 2019; Nebbia *et al.*, 2019; Sokol *et al.*, 2017) represent three of the different pathways involved in food allergy to edible insects: cross-reactivity with crustaceans/HDM (Sokol *et al.*, 2017), cross-reactivity with HDM (Beaumont *et al.*, 2019), and primary sensitisation (Nebbia *et al.*, 2019). The two patients in the cases reported by Sokol *et al.* (2017) had previous history of food allergy to shellfish while also being sensitised to common aeroallergens (including HDM). The patient in the case reported by Beaumont *et al.* (2019) only had previous history of respiratory allergy to HDM and was not sensitised to shrimp. Furthermore, in these three cases, the allergic reactions occurred after consuming the insect species for the first time, as observed in most of the previously reported cases (Ribeiro *et al.*, 2018). This further suggests that these reactions occurred through cross-reactivity to HDM and/or crustaceans.

Additionally, two of the reported cases (Nebbia *et al.*, 2019) occurred due to primary sensitisation to the causative species (*T. molitor* larvae). These two cases are very similar

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Table 3. Description of reported cases of allergy to insects' consumption.[1,2]

Reference	Age/sex/ nationality	Species	Clinical symptoms	Clinical history of allergies	Other characteristics
Sokol *et al.* (2017)	43/M/American	*Chapulines* (*Sphenarium mexicanum)*	I, S (lips and tongue), UC, AP, D	history of allergic rhinoconjunctivitis, bronchial asthma and food allergy to shellfish	Reaction occurred after consuming *chapulines* for the first time Positive SPT and sIgE to grasshopper, *chapulines*, crickets, cockroach, mites, shellfish, cat and dog sIgE inhibition with *chapulines* to grasshopper, crickets, cockroach, mites, shellfish Identification of tropomyosin in immunoblot
Sokol *et al.* (2017)	50/F/American	*Chapulines* (*S. mexicanum)*	I (mouth, throat, generalised), S (face, lips, perioral tissue, throat), DSw, DSp, Sy	history of allergic rhinoconjunctivitis, bronchial asthma, intermittent urticaria, moderately severe atopic dermatitis and food allergy to shellfish	Reaction occurred after consuming *chapulines* for the first time Positive SPT and sIgE to grasshopper, *chapulines*, crickets, cockroach, mites, shellfish, cat and dog sIgE inhibition with *chapulines* to grasshopper, crickets, cockroach and shellfish Identification of tropomyosin in Immunoblot
Beaumont *et al.* (2019)	31/M/French	Yellow mealworm (*Tenebrio molitor*)	U, A, Dys, N	rhinitis and mild asthma	Positive SPT and sIgE to dust mites and mealworm Positive sIgE to Der p 1, Der p 2 and Der p 23. Negative sIgE to Pen a 1 and Der p 10 Identification of IgE-binding proteins: tubulin α-chain, α-amylase, tropomyosin, hexamerin, pupal cuticle protein G1A and larval cuticle protein
Nebbia *et al.* (2019)	24/M/Italian	Yellow mealworm (*T. molitor*)	OAS – P (oral), T (throat)	rhinoconjunctivitis, itching and contact erythema when exposed to *T. molitor*	Consumed other species (greater wax moth, black soldier fly and crickets) without developing allergic reactions Reaction occurred after *T. molitor* hamburger for the first time Positive SPT to grass Positive SPT and BAT to *T. molitor* Identification of cockroach allergen-like protein, Troponin C and 86 kDa early-staged encapsulation protein as IgE-binding proteins
Nebbia *et al.* (2019)	27/M/Italian	Yellow mealworm (*T. molitor*)	OAS, P (oral), T (throat)	rhinoconjunctivitis, itching and contact erythema when exposed to *T. molitor*	Consumed other species (greater wax moth, black soldier fly and crickets) without developing allergic reactions Reaction occurred after *T. molitor* hamburger for the first time Positive SPT to *Alternaria* Positive SPT and BAT to *T. molitor* Identification of cockroach allergen-like protein, Troponin C and 86 kDa early-staged encapsulation protein as IgE-binding proteins
Gadisseur *et al.* (2019)	31/M/Nigerien	Crickets	OAS, U, A, GI, V	allergy to shrimp and HDM	Sensitised (positive SPT and/or sIgE) to shrimp, HDM, cockroach and cricket. Positive sIgE to HDM allergens (Der p 1, Der p 2, Der f 1, Der f 2)

Table 3. Continued.

Reference	Age/sex/ nationality	Species	Clinical symptoms	Clinical history of allergies	Other characteristics
Gadisseur *et al.* (2019)	26/F/Nigerien	Crickets	OAS, Dys, HT, V, A	allergy to shrimp	Sensitised (positive SPT and/or sIgE) to shrimp and cricket Positive sIgE to Der p 10 (HDM tropomyosin), Pen a 1, Pen m 1 (shrimp tropomyosin), Bla g 7 (cockroach tropomyosins) and HDM allergens (Der p 1, Der p 2, Der f 1, Der f 2)
Gadisseur *et al.* (2019)	26/F/Nigerien	Crickets	OAS, U, A, R, C, GI	allergy to shrimp and cockroach	Sensitised (positive SPT and/or sIgE) to shrimp, cockroach and cricket Positive sIgE to Der p 10 (HDM tropomyosin) Pen a 1, Pen m 1 (shrimp tropomyosin), Bla g 7 (cockroach tropomyosins), Pen m 2 (shrimp AK)
Gadisseur *et al.* (2019)	36/M/Nigerien	Crickets	OAS, U, A	allergy to shrimp	Sensitised (positive SPT and/or sIgE) to cockroach and cricket
Gadisseur *et al.* (2019)	44/M/Nigerien	Crickets	U, OAS, GI, V	allergy to shrimp	Sensitised (positive SPT and/or sIgE) to shrimp, cockroach and cricket
Gadisseur *et al.* (2019)	55/F/Nigerien	Crickets	OAS, U	no previous history of allergies	Sensitised (positive SPT and/or sIgE) to shrimp, HDM, cockroach and cricket Positive sIgE to Der p 10 (HDM tropomyosin), Pen a 1 (shrimp tropomyosin) and Pen m 2 (shrimp AK)
Gadisseur *et al.* (2019)	39/M/Nigerien	Crickets	U, GI, V	allergy to shrimp and cockroach	Sensitised (positive SPT and/or sIgE) to shrimp, cockroach and cricket Positive sIgE Pen a 1, Pen m 1 (shrimp tropomyosin), Pen m 2 (shrimp AK) and Pen m 4 (shrimp Sarcoplasmic Calcium-Binding Protein)
Gadisseur *et al.* (2019)	8/F/Nigerien	Crickets	OAS, U	allergy to cockroach	Sensitised (positive SPT and/or sIgE) to shrimp, cockroach and cricket Positive sIgE to Pen m 2 (shrimp AK)
Gadisseur *et al.* (2019)	20/M/Nigerien	Crickets	U	allergy to HDM	Sensitised (positive SPT and/or sIgE) to shrimp, HDM, cockroach and cricket Positive sIgE to HDM allergens (Der p 1, Der p 2, Der f 1, Der f 2) and Pen m 2 (shrimp AK)
Gadisseur *et al.* (2019)	14/F/Nigerien	Crickets	GI	allergy to cockroach	Sensitised (positive SPT and/or sIgE) to shrimp, cockroach and cricket Positive sIgE to Bla g 1
Gadisseur *et al.* (2019)	31/M/Nigerien	Crickets	OAS	allergy to shrimp	Positive SPT to dust mites and mopane worm Positive sIgE to Der p 10 (HDM tropomyosin), Pen a 1 (shrimp tropomyosin), Pen m 2 (shrimp AK) and Bla g 5 (cockroach Glutathione S-transferase)

[1] Clinical symptoms: A = angioedema; AP = abdominal pain; BAT = Basophil Activation Test; C = conjunctivitis; D = diarrhoea; DSp = difficulty speaking; DSw = difficulty swallowing; Dys = dyspnoea; GI = gastrointestinal trouble; HT = hypotension; I = itchiness; N = nausea; OAS = oral allergy syndrome; P = pruritus; R = rhinitis; S = swelling; sIgE = Specific IgE; SPT = skin prick test; Sy = syncope; T = tightness; U = urticaria; UC = unconsciousness; V = vomiting.

[2] List of allergens (WHO/IUIS, 2020): Der p 1 = cysteine protease from the European house dust mite *Dermatophagoides pteronyssinus*; Der p2 = Niemann-Pick proteins of class C2 family from *Dermatophagoides pteronyssinus*; Der p 10 = tropomyosin from *Dermatophagoides pteronyssinus*; Der p23 = peritrophin-like protein domain (PF01607) from *Dermatophagoides pteronyssinus*; Der f 1 = cysteine protease from the American house dust mite *Dermatophagoides farinae*; Der f 2 = Niemann-Pick proteins of class C2 from *Dermatophagoides farinae*; Pen a 1 = tropomyosin from brown shrimp *Penaeus aztecus*; Pen m 1 = tropomyosin from the black tiger shrimp *Penaeus monodon*; Pen m 2 = arginine kinase from *Penaeus monodon*; Pen m 4 =Sarcoplasmic calcium binding protein from *Penaeus monodon*; Bla g 1 = microvilli-like protein with unknown function from the German cockroach *Blattella germanica*; Bla g 7 = tropomyosin from *Blattella germanica*.

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to two other previously reported by Broekman *et al.* (2017b), since the patients were constantly exposed to *T. molitor* on their work and had no previous history of food allergy to shellfish or sensitisation to shrimp. Additionally, in both cases reported by Nebbia *et al.* (2019), the subjects also had respiratory allergies to *T. molitor*, while in the report by Broekman *et al.* (2017b) only one subject developed, respiratory allergies although he had previous history of allergies caused by HDM.

Furthermore, Gadisseur *et al.* (2019) assessed the sensitisation profile of a entomophagous population in Niger who displayed symptoms of allergy to insects and/or crustaceans/HDM. This study described 11 subjects with cases of food allergy following the consumption of crickets. In most cases (10 of 11), subjects had previous history of allergic diseases with the most common being food allergy to shellfish (7/11; 64%). Regarding sensitisation to allergens, sIgE to tropomyosin was detected in 5 individuals (5/11; 45%), while sIgE to AK was detected in 6 (6/11; 55%) subjects, respectively. It is also noteworthy to mention that, in the same study, 3 subjects who consumed crickets without developing any symptoms of food allergy were all sensitised to crickets, shrimp and cockroach. Additionally, in these subjects, sIgE was only detected for Bla g 1 (cockroach nitrile specifier), Der p 1 (mite *Dermatophagoides pteronyssinus* cysteine protease) and Der f 1 (mite *Dermatophagoides farinae* cysteine protease). These cases illustrate that sensitisation (such as positive skin prick test or sIgE to common arthropod allergens) alone is not an indication that a clinical reaction can happen.

Providing contextual information about cases of food allergy to insects' consumption is essential to better understand the mechanisms that regulate those reactions. In our previous review (Ribeiro *et al.*, 2018), lack of contextual information hindered our analysis of reported cases and only 12 of 29 individuals with food allergies to insects (41%) had previous allergic diseases or were primarily sensitised to the culprit species. On the other hand, in cases reviewed in this work, these situations occurred in 15 of 16 individuals (94%). Current literature of reported cases highlights that individual allergic to crustaceans or that are constantly exposed to edible insects appear to be the two major group risks for developing food allergies to insects. Nonetheless, several cases occurred in individuals which were sensitised to HDM or had history of allergic diseases (e.g. allergic rhinitis) which emphasises that individuals allergic to HDM may also be a risk group of food allergies to insects.

4. Conclusions

In conclusion, the current literature points that the two major risk groups for development of food allergy to insects' consumption are subjects allergic to crustaceans and individuals constantly exposed to edible insects. For subjects allergic to crustaceans, reactions to edible insects may occur due to cross-reactivity, which seems to be mainly mediated through tropomyosin, with tropomyosin from *T. molitor* being able to produce an allergic response in an animal model. However, other minor allergens (e.g. AK and α-amylase) may also play a role and previously unreported IgE-binding proteins (apolipophorin and 12 kDa haemolymph protein) were identified. The allergenicity of edible insects seems to be resistant to thermal treatments and digestion with enzymes (unless very specific conditions are applied), a similar behaviour to crustaceans' allergens.

On the other hand, it has also been demonstrated that individuals constantly exposed to *T. molitor* can become sensitised and subsequently develop a food allergy to this insect. Different allergens (larval cuticle protein and cockroach allergen-like protein) were identified depending on the route of sensitisation. Significantly, tropomyosin has not been identified as a significant allergen in primary sensitisation to *T. molitor or* silkworm. Additionally, it is still uncertain if this sensitisation is species-specific or if it can lead to co-sensitisation with other insect species or crustaceans.

On the other hand, co-sensitisation has been shown between HDM and edible insects, but it seems to be different from co-sensitisation between edible insects and crustaceans – a relatively small number of HDM-allergic patients are sensitised to edible insects, and IgE-binding to edible insects only occurs in specific body parts. Additionally, the clinical relevance of such co-sensitisation is not yet defined, and the underlying molecular mechanisms remain unclear (although hexamerin has been consistently identified in all studies), especially considering the apparent lack of involvement of tropomyosin.

Although substantial work has been performed within the topic of edible insects' allergenicity, there are still gaps in our current knowledge. Concerning cross-reactivity with crustaceans, future studies should assess the allergenicity of other species besides *T. molitor*, and a comparison of the molecular mechanisms between different species should be performed, namely by using extracts from different species and serum from the same patients. One of the focal points of future research should be performing studies with individuals monosensitised to HDM in order to have a better understating of HDM-edible insects cross-reactivity. The clinical significance of this co-sensitisation is still unclear and biological assays (preferably food challenges) should be performed.

One of the major flaws when studying food allergy to edible insects is the lack of reliable epidemiological data, since there still is a lack of reported cases/series of food allergy to edible insects. Prevalence studies performed in Asian countries have reported that 0.3-19.4% of food anaphylaxis/

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allergy cases were caused by insects' consumption. Furthermore, studies performed with populations of insect-eaters haver reported that 7.6-22.2% of individuals suffered allergic reactions after consuming insects (although these rates could be overestimated because they were bases on self-reported reactions). Despite these high prevalences, we were only able to retrieve a total of 45 cases in both reviews. This can happen because the regions where insects are consumed are mostly rural (possibly leading to sub-notification), or because several cases may have only been published in local literature (e.g. Chinese). Given the large pool of subjects allergic to the consumption of insects in these areas, it is of extreme importance for these cases to be reported so that we can better understand the characteristics of food allergy to insects, including their severity and epidemiological association with other allergy diseases. In fact, it is expected that an increasing number of cases of food allergy will be reported, due to the introduction of edible insects in the food market of Western countries. This impact is already evident, as food allergy cases have already been reported in subjects who work with *T. molitor* (Broekman *et al.*, 2017b; Nebbia *et al.*, 2019), although the number of reported cases (4) is still very small. These types of cases are essential to have a better understanding of primary sensitisation to edible insects, namely regarding the major allergens involved and whether such sensitisation is species-specific.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material can be found online at https://doi.org/10.3920/JIFF2020.0065.

Table S1. Description of studies assessing prevalence of food allergy amongst consumers of edible insects, included in both systematic reviews (current article and Ribeiro *et al.* 2018).

Table S2. Description of studies included in both systematic reviews (current article and Ribeiro *et al*. 2018), which retrospectively analysed food allergic reaction, including cases caused by insects.

Table S3. Description of reported cases included in both systematic reviews (current article and Ribeiro *et al*. 2018) of allergy to insects' consumption.

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