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Insect (food) allergy and allergens

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ABSTRACT

Insects represent an alternative for meat and fish in satisfying the increasing demand for sustainable sources of nutrition. Approximately two billion people globally consume insects. They are particularly popular in Asia, Latin America, and Africa. Most research on insect allergy has focussed on occupational or inhalation allergy. Research on insect food safety, including allergenicity, is therefore of great importance. The objective of this review is to provide an overview of cases reporting allergy following insect ingestion, studies on food allergy to insects, proteins involved in insect allergy including cross-reactive proteins, and the possibility to alter the allergenic potential of insects by food processing and digestion. Food allergy to insects has been described for silkworm, mealworm, caterpillars, *Bruchus lentis*, sago worm, locust, grasshopper, cicada, bee, *Clanis bilineata*, and the food additive carmine, which is derived from female *Dactylopius coccus* insects. For cockroaches, which are also edible insects, only studies on inhalation allergy have been described. Various insect allergens have been identified including tropomyosin and arginine kinase, which are both pan-allergens known for their cross-reactivity with homologous proteins in crustaceans and house dust mite. Cross-reactivity and/or co-sensitization of insect tropomyosin and arginine kinase has been demonstrated in house dust mite and seafood (e.g. prawn, shrimp) allergic patients. In addition, many other (allergenic) species (various non-edible insects, arachnids, mites, seafoods, mammals, nematoda, trematoda, plants, and fungi) have been identified with sequence alignment analysis to show potential cross-reactivity with allergens of edible insects. It was also shown that thermal processing and digestion did not eliminate insect protein allergenicity. Although purified natural allergens are scarce and yields are low, recombinant allergens from cockroach, silkworm, and Indian mealmoth are readily available, giving opportunities for future research on diagnostic allergy tests and vaccine candidates.

1. Epidemiology and immunology

1.1. Epidemiology and cases of insect food allergy

With an increasing world population and demand for sustainable food sources, insects are a promising alternative source of protein (Xiaoming et al., 2010; FAO, 2013; Rumpold and Schlüter, 2013; Mlcek et al., 2014). Almost 2000 insect species are consumed globally by approximately two billion people (FAO, 2013; Jongema, 2015). The top eight of most frequently consumed insect orders is shown in Table 1. Insects are consumed in Asia, Latin America, and Africa. Entomophagy is not yet common practice in the Western world (FAO, 2013; Caparros Megido et al., 2014). Nevertheless, people already unknowingly ingest approximately 500 g of insect traces per year (FDA, 2005).

Food allergic reactions are defined as ‘‘adverse reactions to an otherwise harmless food or food component that involves an abnormal response of the body's immune system to specific protein(s) in foods'' (FAO and WHO, 2001). In Europe, 0.1–5.7% of the children and 1–3.2% of the adults have a food allergy (Nwaru et al., 2014). Adverse reactions after eating insects are scarce and only two population studies report on the prevalence of food allergy to insects. Barennes et al. (2015) showed that 7.6% of entomophagists in Laos experienced allergic symptoms following the consumption of insects and Ji et al. (2009) reported that 18% of the reported cases of fatal anaphylaxis and anaphylactic shock to food in China was due to the ingestion of insects (Ji et al., 2009; Barennes et al., 2015). Allergy following ingestion of

Abbreviations: AK, arginine kinase; BAT, basophil activation test; BCT, bronchial challenge test; CAP, ImmunoCAP; DBPCFC, double-blind placebo controlled food challenge; ELISA, enzyme-linked immunosorbent assay; FAST, fluoroallergosorbent test; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HDM, house dust mite; IST, intradermal skin test; LHRT, leukocyte histamine release test; OOCT, open oral challenge test; PEF, peak expiratory flow recordings; PK test, Prausnitz-Kustner test; RAST, radioallergosorbent test; r*Bm*AK, recombinant *Bombyx mori* arginine kinase; RIA, radioimmunoassay; r*Pa*AK, recombinant *Periplaneta americana* arginine kinase; SBPCFC, single-blind placebo controlled food challenge; SPT, skin prick test

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Table 1
Top 8 most frequently consumed insect orders and number of case reports describing insect food allergy (FAO, 2013).

Number	Insect order	Percentage consumed	Number of case reports
1	Coleoptera (beetles)	31%	3
2	Lepidoptera (caterpillars)	18%	12
3	Hymenoptera (ants, wasps and bees)	14%	2
4	Orthoptera (locusts, grasshoppers and crickets)	13%	2
5	Hemiptera (leafhoppers, planthoppers, cicadas, scale insects and true bugs)	10%	11
6	Isoptera (termites)	3%	0
7	Odonata (dragonflies)	3%	0
8	Diptera (flies)	2%	0
	Other orders	5%	0

various (non) edible insects was also reported in a number of case studies.

More information exists on insect sting or inhalant allergies (Stanhope et al., 2015). Inhalant allergy to cockroach is the most frequently reported. Recently an extensive review on cockroach allergy has been published. For more in depth information on inhalant cockroach allergy we refer to the review by Pomés et al. (2017). For information on occupational insect allergy we refer to a systematic review by Stanhope et al. (2015) and for insect venom allergy we refer to chapter 17 of this special issue. Because insects will be consumed more frequently in the future, it is expected that the prevalence of insect food allergy will increase. This review will mainly focus on insect food allergy, but allergy to cockroach will also be touched upon.

For this review we included information from 30 case reports, which reported on the following insects; (larvae of) beetles (mealworm, sago worm, lentil weevil), larvae of moths (silkworm, mopane worm, pine processionary caterpillar, woolly bear caterpillar, *Clanis bilineata*), locusts, grasshoppers, cicadas, and bees (Table 2). Allergy was also reported following ingestion of carmine (E120), which is obtained from female *Dactylopius coccus* var. *Costa* and is used in the food industry as a color additive (Marmion, 1991; Acero et al., 1998; Dufossé, 2014). Of all insects, allergy to silkworm (7 articles) and the food additive carmine (9 articles) were most frequently described, and yet they are not the most commonly consumed insects. Silkworm is part of the Lepidoptera order and *Dactylopius coccus* var. *Costa* is part of the Hemiptera order, the second and fifth most frequently consumed insect order respectively (Table 1) (FAO, 2013).

Although most insects are consumed in Asia, Africa, and Latin-America, remarkably many insect food allergy reports were from Western countries (FAO, 2013). It is not clear if there is a lack of research or underreporting in non-Western countries that causes this difference. It must be noted that language-bias is definitely a contributing factor as some articles were only available in Chinese. Some original articles discussed in studies by Ji et al. (2008, 2009) and Lucas et al. (2001) could therefore not be verified.

The clinical manifestation of insect food allergy ranged from a mild localized reaction to a more severe systemic clinical presentation such as anaphylactic shock. Reported symptoms can be subdivided into skin (e.g. urticaria, pruritus, rash, flushing, angioedema), gastrointestinal (e.g. abdominal pain, nausea, vomiting, diarrhea) and respiratory (e.g. asthma, dyspnea). One particular case report by Yew and Ling Kok (2012) reported the development of Takotsubo cardiomyopathy three days after ingestion of sago worm. Due to the onset of allergic symptoms after three days not being common, it is debatable whether this truly was an allergic reaction or intolerance. Time until onset of symptoms in other cases ranged from a few minutes to 6 h.

From the case reports it can be concluded that patients who developed anaphylaxis after insect ingestion did not necessarily have an allergic history, which was the case for 54.3% (25/46) of the patients. This is in line with studies on other food allergies in which subjects did not necessarily have an allergic history (Oropeza et al., 2017; Alvarez-Perea et al., 2017). In addition, insect food allergy did not exclusively occur after first time ingestion, which is also seen with other food allergies (Sicherer, 2001; Stiefel et al., 2017). For example, the patient described by Okezie et al. (2010) did have an extensive history of ingestion of mopane caterpillar since childhood, but never had allergic symptoms following ingestion until the age of 36 (Okezie et al., 2010).

In cases where a food allergic reaction to insects occurs up on the first ingestion of the insects, cross-reactivity with other foods such as shrimp may play a role. Based on the investigated case studies it can be concluded that food allergy to insects is possible. Kung et al. (2011) found that a person who reacted to mopane worm was also sensitized to other allergenic species of the Arthropoda phylum, such as dust mites, cockroach, *Ascaris*, and anisakis. This may suggest a role for cross-reactivity in the development of insect food allergy (Kung et al., 2011).

1.2. Immunology

Allergy following ingestion of insects can be divided into primary sensitization to edible insects and cross-reactivity with other allergenic species. This paragraph discusses clinical and animal studies on primary (edible) insect sensitization and clinical studies addressing insect cross-reactivity.

1.2.1. Primary insect allergy

The possibility to induce sensitization to edible insects has been assessed in rats, mice and guinea pigs (Table 3). Tested insect species included Japanese rhinoceros beetle, mealworm, and cricket. Sensitization was only demonstrated to mealworm in a mouse model. IgE against arginine kinase, tropomyosin, myosin heavy and light chain, larval cuticle protein (A1A, A2B, A3A), Actin-87E, cuticular protein, chitin-binding protein, and troponin T was found (Broekman et al., 2017a). This indicates that sensitization to insect proteins is possible. However, clinically relevant evidence for sensitization in guinea pigs and rats was not detected.

Only a few studies were found on sensitization of edible insect species in humans (Table 4). Sensitization to a specific food allergen does not occur solely via oral exposure, but also the route via skin or lungs might be relevant. Sensitization via inhalation or skin contact is especially important in occupational allergy in entomologists or laboratory workers (Stanhope et al., 2015). Therefore we included studies investigating sensitization to (edible) insects in general, and not specifically in insect food allergic patients (Yoshida et al., 1995; Schlüter et al., 2017).

Silkworm allergic subjects were mainly sensitized to arginine kinase, paramyosin, and chitin (Liu et al., 2009; Zhao et al., 2015). Proteins with a molecular weight of 50, 110 and 120 kDa were recognized by IgE from silkworm allergic subjects (Liu et al., 2009). Mealworm allergic subjects recognized several allergenic proteins such as arginine kinase, tropomyosin and myosin light and heavy chain. The study from Broekman et al. (2017b) also revealed three novel mealworm allergens: larval cuticle protein A1A, A2B and A3A. In this study two mealworm breeders showed food allergic symptoms after eating mealworm snacks. The investigators ruled out cross-reactivity with shrimp by an open food challenge with shrimp and suggested that exposure different from ingestion (e.g. inhalation or skin contact) might also play a role in the onset of primary mealworm allergy. The allergens involved in primary mealworm allergy are possibly different from the allergens known to cause cross-reactivity (Broekman et al., 2017b).

Many reports can be found describing cockroach allergy. Although cockroach is an edible insect, these studies describe subjects who were sensitized to cockroach allergy via inhalation. None of these studies reported on allergy after ingestion of cockroach. Sensitisation to major