Allergo J Int (2022) 31:257–265
https://doi.org/10.1007/s40629-022-00200-1

Part II: Insect allergies—Inhalation and ingestion

A survey of the literature and our own cases

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Received: 10 September 2021 / Accepted: 27 December 2021 / Published online: 11 February 2022
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Summary
Background Allergies to insect stings and bites are common and were partly discussed in part I of this article series. Other mechanisms leading to allergen contact, sensitization, and potential allergy to insects or insects' compounds can be hard to suspect and diagnose due to their sometimes-hidden character in food or dust.
Aims We aim to provide an overview of allergic reactions to insects elicited by mechanisms other than sting or bite reactions.
Sources A PubMed search on allergy and insects apart from bees and wasps was conducted, articles were selected and included, and a series of relevant publications and cases of our outpatient units are used as examples.
Content and implications Allergies to insects following direct contact, inhalation, and accidental and deliberate ingestion are common and various insect species can elicit these allergies. Sensitization may occur transcutaneously, upon inhalation, and through ingestion. Allergic reactions to edible insects, such as grasshoppers and mealworms, as genuine allergies or as tropomyosin or other protein cross-reactivities in seafood or house dust mite allergic individuals are possible. In Europe, with the licensing of mealworms to be consumed as food and sold commercially in January 2021, allergies and cross-reactivity to insects or insect compounds as foods will become more common and relevant.

Keywords Beetles · Beetle dermatitis · Cockroach · Caterpillars · Moths · Edible insects

Availability of data and material (data transparency) All relevant data are included in this manuscript.

Part I of this article can be found under https://doi.org/10.1007/s40629-022-00199-5.

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Introduction

Part I of this article series discusses allergies to insect stings and bites. Part II discusses other forms and mechanisms of insect allergies, such as allergies to secretions and inhaled compounds of insects or entomophagy, and the associated allergic risks and considerations (Table 1).

Methods

Objectives We aim to offer a critical overview of allergologically relevant insects that lead to allergic reactions through direct skin contact, inhalation, and ingestion.

Search methods A literature search was conducted through May 1, 2021, using PubMed. The keywords

Table 1 Overview of allergologically relevant insects and clinical findings presented in this article

Order and family	Genus or species	Route of allergen exposure	Clinical manifestation	Disease transmission	Molecular allergen (WHO/IUIS)	Distribution	Reference
Coleoptera: Coccinellidae	Asian lady bird *(Harmonia axyridis)*	Inhalation of insect compounds including hemolymph. Bites rare	IgE-Anaphylaxis, rhinoconjunctivitis, asthma, urticaria, and angioedema	No	Har a 1-2	Native to Eastern Asia, introduced in North America and Europe as a pest control, now invasive	Nakazawa (2007) [1], Davis (2006) [2], Goetz (2007) [3], Goetz (2009) [4]
Coleoptera: Dermestidae	Skin or carpet beetle (e.g., *Dermestes maculatus*)	Inhalation of insect components in house dust, wool, fur and stuffed animals	IgE-Anaphylaxis, asthma, rhinoconjunctivitis, and late-type reactions	No	Not available	Worldwide	Cuesta-Herranz (1997) [5], Hoverson (2015) [6]
Coleoptera: Meloideae	Red-striped oil beetle (Berberomeloe majalis)	Direct skin contact with irritant body fluids	Toxic dermatitis	No	Not applicable	Mediterranean, northern Africa	Senel (2011) [7], Alexander (1984) [8], Zargari (2003) [9]
Coleoptera: Tenebrionidae	Mealworm (*Tenebrio molitor)*	Ingestion, airborne/inhalation	IgE-Anaphylaxis	No	Not available	Worldwide	Mankouri (2021) [10], Nebbia (2019) [11], Leni (2020) [12]
Blattodea: Ectobiidae	German cockroach (*Blattella germanica)* and American cockroach (*Periplaneta americana*)	Inhalation of insect compounds in dust	IgE-mediated respiratory disease	Contaminated food (feces and body parts) causing salmonellosis and typhoid fever, *Staphylococcus* infections, *Escherichia coli*	Bla g 1-12, Per a 1-13	Worldwide	Bernton (1964) [13], Arruda (1995) [14], Gore (2004) [15], Elgderi (2006) [16], Gao (2012) [17], Milligan (2016) [18], Pomés (2017) [19], Sookrung (2020) [20], Lee (2016) [21]
Diptera: Chironomidae	Chironomid midges	Inhalation of insect compounds	IgE-mediated respiratory disease, rhinoconjunctivitis	–	Not available	Worldwide	Broza (2008) [22], Baur (1992) [23], Hirabayashi (1997) [24], Cabrerizo (2006) [25]
Lepidoptera: Notodontidae	Oak processionary *(Thaumetopoea processionea)*	Direct skin contact with irritant or allergy-inducing setae	Lepidopterism	No	Not applicable	Central and southern Europe	Panzer (2020) [26], Maier (2003) [27]
Lepidoptera: Bombycidae	Silk worm (*Bombyx mori)*	Ingestion or inhalation	IgE-Anaphylaxis, asthma, rhinoconjunctivitis	No	Not available	China	Ji (2008) [28], Gautreau (2017) [29], He (2021) [30], Makatsori (2014) [31]
Orthoptera: Pyrgomorphidae	Grasshoppers (*Sphenarium*)	Ingestion	IgE-Anaphylaxis	No	Not available	Mexico, other species worldwide	Sokol (2017, 2020) [32, 33]
Hemiptera: Dactylopiidae	Cochineal lice (*Dactylopius coccus*)	Ingestion of carmine (red food dye, E 120), cosmetics	IgE-Anaphylaxis, asthma, contact urticaria, contact dermatitis	No	Not available	South America, Middle America, Mexico	Wüthrich (1997) [34], Suzuki (2021) [35], Takeo (2018) [36]
Hemiptera: Kerridae	Lac bug *(Kerria lacca)*	Accidental ingestion as citrus fruit wax, cosmetics	IgE-Anaphylaxis, contact dermatitis	No	Not available	Southeast Asia, India	Guillet (2021) [37], Veverka (2018) [38]

WHO/IUIS World Health Organization/International Union of Immunological Societies Allergen Nomenclature Sub-committee (http://www.allergen.org), *IgE-Anaphylaxis* IgE-mediated anaphylaxis

included "insect, allergy, beetle, Coleoptera, ladybird, lady beetle, *Coccinellidae*, carpet beetle, skin beetle, *Dermestidae, Meloidae, Oedemeridae, Staphylinidae*, beetle dermatitis, cockroach, *Blattodea, Orthoptera*, grasshopper, *Lepidoptera*, butterfly, moth, *Coleoptera*, mealworm, cochineal, *Dactylopius coccus, Kerria lacca*, shellac, lac bugs, tropomyosin, edible insect, novel food". Additional studies were found using bibliographical information of selected articles.

Case description Illustrative cases from our outpatient clinics are included.

Results

Inhalant insect allergies

Coleoptera—Beetles

Beetles comprise approximately 40% of all known insects, and about 370,000 species have been identified [39]. The following beetle species are of allergological and dermatological relevance.

Coccinellidae—Ladybirds Ladybirds or ladybird beetles (ladybugs in American English) are generally considered to be beneficial insects. The Asian

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Fig. 1 Ladybird (*Harmonia axyridis*). (André Mégroz, with permission)

lady beetle (*Harmonia axyridis*; Fig. 1), initially imported as a pest control in North America and Europe in the 1970s, has become an invasive pest in the last few decades. Ladybirds usually invade human homes in fall and winter, causing asthma, allergic rhinitis, and angioedema [40]. Specific IgE to two proteins (Har a 1 und Har a 2) were identified [1, 2, 4]. Hemolymph externalized during 'reflex bleeding' (a defensive behavior in some *Coleoptera* where a fluid is excreted when threatened) contains these allergens of *H. axyridis*. It may lead to the culprit allergen exposure through inhalation. Since there are no commercial ladybird extracts, diagnosis and specific immunotherapy are not standardized. However, there are reports of successful immunotherapy with whole-body extracts [3].

Case 1—Ladybird allergy *A 31-year-old woman presented with seasonal rhinoconjunctivitis and wheezing exacerbating during the heating period in winter. Milder symptoms occurred when working in her garden in the early summer months. Clinical signs were most pronounced inside her own house, especially in the dusty attic with partly open holes towards the outside. She owned a cat and two rabbits but reported no symptoms after contact with these pets. Hymenoptera stings did not cause any allergic reactions. An allergology workup with inhalant allergens showed positive skin prick tests to grass pollen, also detectable by specific IgE (gx3: 3.46 kU/l). All tests with pet and mite allergens (D. pteronyssinus, D farinae), mold (mx2), and honey bee and wasps (i1/i3) were normal. Specific IgE to German cockroaches was slightly positive (1.74 kU/l). Lung function in wintertime showed a mild obstruction (FEV1 72.3%). In spring and summer, the lung function was normal.*

As the patient reported an increase of symptoms in her attic, we performed scratch tests with house dust collected in various rooms. Dust from the attic resulted in a strongly positive skin test. The following spring, we performed a prick–to-prick test with minced ladybirds dissolved in saline, which was strongly positive. At that time, there was no commercial kit for the measurement of IgE to ladybird available. Therefore, we performed an IgE inhibition with cockroach IgE that showed inhibition of 80%. This pattern was interpreted as compatible with sensitization to ladybirds, as demonstrated earlier in another study [41]. *A diagnosis of seasonal allergic rhinoconjunctivitis and asthma due to ladybird sensitization and a mild grass pollen allergy. The attic was profoundly cleaned and isolated; from then on, the winter symptoms disappeared.*

Dermestidae—Carpet beetles *Dermestidae* are a family within Coleoptera, including 500–700 species. They can be found all over the world and in a wide variety of habitats. Most are scavengers and eat dead, dried animals and insect remains. These beetles can cause considerable damage to woolen fabrics, furs, and insect and animal collections. However, *Dermestes maculatus* is used intentionally by museums to clean soft tissue from animal skeletons. IgE-mediated allergy and asthma to dermestid larvae as part of house dust is possible [5]. Furthermore, Dermestidae may lead to T-cell mediated, late-type allergic reactions, as shown in a 2-year-old girl with negative skin prick test but positive skin patch test after 5 days [6]. Dermestidae can also cause histamine liberation and wheals on the affected skin area after contact with their toxic hair [42].

Blattodea—Cockroaches

Currently, over 460 genera with 4600 species of cockroaches are described worldwide. Cockroaches are common and highly adaptable insects with the ability to survive in various climates from Antarctica to the tropics. Cockroaches feed on human food and animal feed. They can transport and spread pathogenic germs on their surface. Cockroaches often trigger inhalant allergies, first demonstrated in New York in the 1960s [13, 16, 20]. Especially in developing countries, cockroach sensitization is associated with a high risk

Fig. 2 German cockroach (*Blatella germanica*). (ETH-Bibliothek Zürich, Bildarchiv/Photographer: Keller, Siegfried, CC BY-SA 4.0)

of asthma development. Especially in inner cities, children with asthma are very frequently sensitized to cockroaches [18, 19]. In the past 20 years, 12 cockroach allergens have been identified and are either excreted in feces or are found in the cockroach bodies [14, 15, 21]. In clinical practice, cockroach extracts and recombinant cockroach allergens can be used for in vitro and in vivo diagnostics. Therapeutically, specific immunotherapies can lead to the improvement of existing asthma ([43–45]; Fig. 2).

Diptera—Chironomidae

Many inhaled insect allergens are highly concentrated in the air when larvae living in water undergo a metamorphosis in high individual densities [46]. This is the case, for example, for chironomid midges (twitch flies), which occur locally in high concentrations in Japan and can frequently trigger asthma [23, 24]. Chironomid midges can also cause allergies in aquarium owners, as these larvae are often used for feeding fish [25].

Chironomid midges do not sting or bite and cannot directly transmit disease. However, egg masses of chironomids have been found to act as a natural reservoir of cholera bacteria ([22]; Fig. 3).

Insect allergies as occupational diseases

Occupational insect allergies were described in entomologists, laboratory workers, and farmers. Flour contaminated with insect components causes allergies in bakers and associated occupations. In general, insect-related occupational diseases are caused by direct and deliberate contact with insects or because the workplace is infested with insects [47].

In an American study in 1980, 60% of insect farmers were affected with an inhalant insect allergy [48]. In a recent study, 50% of greenhouse workers who use insects as pest control were sensitized to insects [49].

Scientists or laboratory workers working with *Drosophila* flies or *Locust* species sometimes also develop inhalant allergies [50, 51]. In bakers, various beetles contained in flour can cause inhalant allergies [46, 52–54]. In China, silk workers exposed to inhalant silk proteins of silk worm pupa *(Bombyx mori)* frequently develop immediate-type hypersensitivities [26, 31].

Direct toxic or allergic reactions on the skin

Meloidae, Oedemeridae, and *Staphylinidae*—Beetle dermatitis

Beetle dermatitis (or blistering beetle dermatitis [BBD]) is an inflammatory and non-allergic, blistering skin disorder, sometimes resembling contact dermatitis [55]. Skin lesions are caused by toxic body fluids (cantharidin or pederin) and occur hours after direct contact [39, 42]. Beetle dermatitis is a problem worldwide, especially in warmer climates with increasing incidence due to global warming [7, 55]. Typically, beetle dermatitis presents as toxic-irritative dermatitis with blistering eruptions, most frequently caused by *Meloidae, Oedemeridae*, and *Staphylinidae* [8]. Diagnosis of beetle dermatitis is made by the clinical history and typical cutaneous lesions, and sometimes histopathology provides additional diagnostic clues. To prevent beetle dermatitis, repellents and mosquito nets treated with insecticide can be used, and avoidance of crushing beetles on the skin reduces the risk of beetle dermatitis [9]. No specific treatment for beetle dermatitis exists, and the effect of topical corticosteroids or systemic antihistamines is limited. Sometimes even analgesics are needed because of severe pain [55].

Case 2—Blistering beetle dermatitis *A 52-year-old manual worker (maintenance of elevators) without a history of previous allergic or skin disorders traveled to Spain for professional reasons, staying in a middle-class hotel. One morning he awoke with painful and oozing vesicles, bullae, and erosions on the left side of his face and neck. A local pharmacist interpreted the symptoms as herpes zoster or a photo-aggravated*

Fig. 3 Chironomid midges, freshly hatched larva. (ETH-Bibliothek Zürich, Bildarchiv/Photographer: Keller, Siegfried, CC BY-SA 4.0)

Fig. 4 *Paederus littoralis*. (ETH-Bibliothek Zürich, Bildarchiv/Photographer/Keller, Siegfried, CC BY-SA 4.0)

Fig. 5 A 52-year-old man with eczematous skin on neck and face with honey-colored crusting. (Consent for publication of image given by patient to Peter Schmid-Grendelmeier)

contact dermatitis due to the wooden necklace the patient was wearing. He referred the patient to a local primary care physician who ruled out herpes zoster by PCR and diagnosed irritant dermatitis, most probably due to the locally endemic beetle Paederus littoralis (Family: Staphylinidae) [56]; Fig. 5). *Approximately 1 week later, the patient presented at our dermatology department with a widespread eczematous and rash on his face* (Fig. 4). *Again, microbial swabs (herpes, bacteria, and fungi) were negative, and we treated the patient with topical fusidic acid and hydrocortisone cream. Within 2 weeks, the rash had resolved. Patch testing performed later showed no contact sensitization to common allergens, including fragrances and plants.*

Lepidoptera and lepidopterism—Thaumetopoeinae

The Lepidoptera order includes different butterfly and moth species. An important subfamily of the Lepidoptera are the *Thaumetopoeinae*, commonly called processionary caterpillars in their larval stage (Fig. 6).

Fig. 6 Pine processionary (*Thaumetopoea pityocampa*). (Entomologie/Botanik, ETH Zürich/Photographer: Albert Krebs, CC BY-SA 4.0)

They are the typical triggers of lepidopterism. In lepidopterism, stinging hairs (setae) of caterpillars containing the protein thaumetopoein can be transmitted to the skin and mucous membranes by air and directly elicit toxic effects [26]. Epidemic-like outbreaks were described in cases of heavy infestation [27]. Different disease mechanisms, including irritant-toxic dermatitis, immediate and late-type hypersensitivity reactions, are thought to elicit symptoms ([26]; Fig. 6).

Insects as food

Insects consumed as food or insect compounds hidden in food can cause food allergies. Even though they do not (yet) play a relevant role as a direct food source in Western cultures, insects have been consumed for centuries in developing countries and form a cornerstone of a regular diet. Worldwide, more than 1600 different species are consumed [57]. With the world population growing, the question arises whether finite resources will be able to meet the food needs of so many people. Concerns about food security are directing research into alternative food sources for humans and feed for animals [58]. Edible insects could suit today's consumers seeking nutrient-rich and sustainable food sources. In Switzerland, three insect species can be used as food in processed form since May 2017, namely yellow mealworms *(Tenebrio molitor)*, house crickets (*Acheta domesticus*), grasshoppers (*Locusta migratoria*) [59]. In the EU, mealworms are permitted to be sold as food since January 2021 and are considered to be a "novel food".

There are two possibilities to develop allergies to insects. On the one hand, genuine insect allergies to various incompletely characterized insect allergens are possible. On the other hand, and probably much more frequent, a cross-allergy to edible insects must be expected in patients with seafood, crustacean, and potentially also house dust mite allergies [60]. Here, sensitizations to cross-reactive proteins like tropomyosin and also arginine kinase are in the foreground. Due to the large sequence homology within many invertebrate species, cross-reactivity can be expected and has already been described in smaller clinical studies [32, 61]. Fig. 7 shows commercially available, freeze-dried insects in Switzerland.

Orthoptera—Grasshoppers, locusts, crickets

Various Orthoptera species are consumed as food worldwide. Chapulines (genus *Sphenarium*), for example, are consumed after deep-frying, especially in Mexico [33]. In Asia, crickets (*Acheta domesticus*) are roasted, grilled, or fried and are nowadays considered to be one of the most promising insect species for global consumption because they have a beneficial nutritional profile. The farming of crickets requires little feed ("low feed conversion ratio") which makes them particularly attractive as "novel food" [62]. However, allergic reactions to *Orthoptera,* especially in

Fig. 7 Edible freeze-dried insects: **a** mealworm (*Tenebrio molitor*), **b** house cricket (*Acheta domesticus*), **c** grasshopper (*Locusta migratoria*). (Purchased from Essento®. Images from own stock)

seafood or house dust mite sensitized patients are possible and may be caused by tropomyosin cross-reactivity [32, 33, 63]. In principle, however, genuine food allergies and not only cross-allergies to Orthoptera are possible.

Coleoptera—Mealworms

Allergies to mealworms are of relevance especially in owners of animals who use them as animal feed or bait. After inhalative or transcutaneous sensitization, allergic symptoms such as rhinoconjunctivitis or respiratory symptoms may occur [46, 64, 65]. Tropomyosin-mediated cross-allergies to mealworms after ingestion as well as genuine mealworm food allergies are possible [10, 37, 66].

Lepidoptera—Silkworms

The use of *Lepidoptera* as food is especially common in China, where silk moth pupae (*Bombyx mori*) are grilled and eaten and can cause immediate type allergic reactions [28, 29, 46]. An allergic reaction after consuming mopane worms (*Imbrasia belina*) in Botswana was described [67]. In a recent study, a series of potential *Bombyx mori* allergens and potential cross-reactive species were identified [30].

Dactylopius coccus—Cochineal lice

Cochineal red (carmine, E120) is a dye obtained by drying and extracting scale insects of the genus *Dactylopius*. Carmine is approved for coloring various foods and is also used in cosmetics (e.g., blush) and paint colors. Allergic reactions to carmine are rare but often severe. Since the allergen often remains unrecognized for a long time, repeated episodes are characteristic [34]. For example, possible food products containing carmine include Campari (until 2006), fruit juices, and ice cream [34, 68].

Kerria lacca—Lac bug

Case 3: Orange anaphylaxis [37] *A 58-year-old, non-atopic, seafood-allergic woman presented to our outpatient allergy clinic after one episode of severe anaphylaxis that occurred 15 minutes after drinking orange juice and chewing on an unpeeled orange slice raising suspicion of immediate-type hypersensitivity to orange juice. She had not experienced a similar episode previously. Oranges of the same batch that had been consumed were used for allergy testing. The skin prick test was negative for orange juice and orange fruit pulp. Direct prick by prick test of orange peel was, however, strongly positive. Serologic testing revealed negative specific IgE autoantibodies to orange (<0.35 kUa/l). ISAC® Microarray test showed a strong sensitization to tropomyosins of various origins (nPen m1, rDer p10, aBlg g7, rAni s3). Since tropomyosins causing allergies are contained in invertebrate animal sources, the correlation of tropomyosin anaphylactic reaction after orange peel consumption was not obvious* [69]. *The patient denied having symptoms suggestive of house dust mite allergy and remembered having experienced an episode of oral itching, nausea, and vomiting shortly after eating shrimp in her youth and had since avoided eating seafood altogether. During the diagnostic workup, we learned that citrus fruit is coated in a protective wax after harvesting. This wax coating is applied as a seal to prevent the fruit from water loss and to enhance the shininess of the shell. Citrus fruit wax coatings usually contain shellac, a resin produced by the female lac bug (Kerria lacca)* [70]. *Chewing on the orange slice decorating the drink before the anaphylaxis episode probably led to the culprit allergen exposure. Since no other allergenic source could be identified in the orange peel, our diagnosis was an anaphylactic reaction due to insect compounds in fruit wax based on a tropomyosin sensitization.*

This case presents a severe allergic reaction to orange peel in a seafood allergic patient documented by a positive skin prick test. Sensitized to various tropomyosins, the patient has reacted to insect compounds, potentially tropomyosins, from the female lac bug (*Kerria lacca*) in the wax coating of the orange peel induced anaphylaxis. Multiple studies have reported delayed-type hypersensitivity (allergic contact dermatitis) to shellac but not immediate-type hypersensitivity [71]. We assume this is the first case of immediate type allergy to insect compounds in fruit wax.

Conclusion

Bees and wasps are the leading cause of insect-related immediate-type allergies worldwide. Other insect stings and bites may, however, also cause significant morbidity and were discussed in part I of this article series. However, insects are also a relevant cause of inhalant allergies in various settings, patient populations and professions. Direct toxic effects on the skin and immediate or late type allergic cutaneous reactions are all possible after contact with insects or insect parts, such as caterpillar setae. Allergic reactions and direct toxicities after intentional or unintentional ingestion of insects or insect compounds appear to be diverse yet are currently potentially underestimated or underdiagnosed.

Since food safety authorities are licensing insect species to be used in processed foods, and sustainable protein sources will be needed with the growing world population, food allergies involving insect products could become more common. Especially in tropomyosin sensitized patients, they will have to be considered due to cross-reactivity between tropomyosins [59, 60, 72]. It is, therefore, crucial to determine the allergenic potential of edible insects in detail and to investigate these allergies to "insects as novel food", and strategies must be developed to better assess the associated risks [73, 74].

Funding No funding to declare.

Author Contribution C. Guillet: Conception and design, acquisition of data, interpretation, drafting of the manuscript, final approval; O.Y. Martin: Conception and design, acquisition of data and visuals, drafting of the manuscript, critical revision of the manuscript for important intellectual content, final approval; C. Meincke: Critical revision of the manuscript for important intellectual content, final approval; L. Joerg: Acquisition of data, drafting and critical revision of the manuscript for important intellectual content, final approval, P. Schmid-Grendelmeier: Conception and design, acquisition of data and visuals, drafting of the manuscript, critical revision of the manuscript for important intellectual content, final approval.

Funding Open access funding provided by University of Zurich

Conflict of interest P. Schmid-Grendelmeier has acted as consultant or speaker for Bühlmann Laboratory, Euroimmun and Thermo Fisher; Research grants received from Bühlmann Laboratories and Thermo Fisher. C. Guillet, O.Y. Martin, C. Meincke and L. Joerg declare that they have no competing interests.

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