



Contents lists available at ScienceDirect

Allergology International

journal homepage: <http://www.elsevier.com/locate/alit>

Invited Review Article

Respiratory sensitization to insect allergens: Species, components and clinical symptoms

Yuma Fukutomi ^{a,*}, Yuji Kawakami ^{a,b}^a Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Kanagawa, Japan^b Laboratory of Integrated Pest Management, FCG Research Institute, Inc., Tokyo, Japan

ARTICLE INFO

Article history:

Received 18 March 2021

Available online xxx

Keywords:

Allergy

Asthma

Insect

Occupational allergy

Sensitization

ABSTRACT

Airborne insect particles have been identified as an important cause of respiratory allergies, including allergic asthma and rhinitis. In the literature, the significance of respiratory exposure to insect particles as a cause of occupational allergy has been well-documented. Indeed, many cases of occupational allergy have been reported including allergy to the larvae of flies and moths in anglers and occupationally exposed workers, to grain pests in bakers or other workers handling grains, and to crickets and/or locusts in researchers and workers in aquaculture companies. Furthermore, the prevalence of sensitization to insect allergens is considerably high among patients with asthma and/or rhinitis who are not occupationally exposed to insects, suggesting the clinical relevance of exposure to insects in indoor and outdoor environmental non-occupational settings. Exposure to cockroaches, a well-studied indoor insect, is associated with cockroach sensitization and the development and exacerbation of asthma. Booklice, another common indoor insect, were recently identified as a significant sensitizer of asthmatic patients in Japan and India, and potentially of asthma patients living in warm and humid climates around the world. Lip b 1 was identified as an allergenic protein contributing to the species-specific sensitization to booklice. Moths are considered a significant seasonal outdoor allergen and their allergens are considered to have the highest sensitization rate among Japanese patients. However, other than cockroaches, allergenic insect proteins contributing to sensitization have not been fully characterized to date.

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Introduction

Insects are a major source of allergens for humans. In the literature, cases of asthma or rhinitis related to respiratory exposure to insects were reported from as early as the 1920's and 30's.^{1–3} Insects are taxonomically positioned as an arthropod and the number of insect species exceeds one million. There is a large regional variation in the dominant insect species present in indoor and outdoor environments, which reflects the variations in climate globally. Insect allergy can be induced by bites, stings, inhalation, and ingestion. In this review article, we focused on the respiratory sensitization to insects and its effects on respiratory allergic diseases.

Respiratory sensitization to insect allergens in occupational settings

Large numbers of reports have identified insect particles as a cause of occupational respiratory allergies and various occupations are related to the occupational exposure to insects.⁴ One group of occupations involves people who work directly with insects that are reared for study, animal feed, or other commercial reasons. Another group of occupations involves persons who encounter insects in their work environment.⁴

Anglers and workers exposed to live fish bait

The larvae of flies and moths are commonly used as bait for angling or fish food. Previous studies have reported that live fish bait (LFB) is a well-documented causal agent for occupational allergy, including rhinitis, asthma, and immediate systemic allergic reactions, among anglers and occupationally exposed workers.⁵ Cases of allergy to the larvae of the bee moth (Lepidoptera- Pyralidae- *Galleria mellonella*),^{6,7} mealworm (Coleoptera- Tenebrionidae- *Tenebrio molitor*),^{8–10} common green bottle

* Corresponding author. Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, 18-1 Sakuradai, Minami-ku, Sagami, Kanagawa 252-0392, Japan.

E-mail address: fukutomi.yuma.da@mail.hosp.go.jp (Y. Fukutomi).

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2021.04.001>

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fly (Diptera- Calliphoridae- *Lucilia Caesar*), blue bottle fly (Diptera- Calliphoridae- *Calliphora vomitoria*),¹¹ blue-assed fly (Diptera- Calliphoridae- *Protophormia terraenovae*),^{12,13} and non-biting midge (Diptera- Chironomidae- *Chironomus thummi thummi*)^{14,15} have been documented. A study on occupationally exposed workers showed that 31.6% were sensitized to LFB, and that LFB sensitization was associated with work-related allergic symptoms.¹⁶ However, commercially available heat-treated larvae were reported to have reduced allergenicity.¹⁷

Workers handling insects in laboratories or aquaculture companies

Occupational allergy to crickets,¹⁸ locusts¹⁹ (Orthoptera), and Mediterranean Flour Moth (Lepidoptera- Pyralidae- *Ephestia kuehniella*)²⁰ have also been reported among researchers who handle them or workers in aquaculture companies. A study of 286 laboratory workers handling fruit flies (Diptera- Drosophilidae- *Drosophila melanogaster*) reported that 6% were sensitized to this insect with a clear relationship to the increased frequency/intensity of exposure.²¹ It was also reported that people who handle insects to feed pet reptiles and fish in non-occupational settings can develop allergic symptoms.²²

Sericulture workers

Asthma related to sericulture, which was once popular in Japan, was reported as an occupational insect allergy in Japan. Two processes associated with sericulture are related to the occurrence of respiratory symptoms: the gathering of cocoons (Lepidoptera- Bombycidae- *Bombyx mori*; chrysalis of the silk moth) from equipment and/or when adult silk moths are handled for mating. The causal agent for the former process was reported to be airborne particles of watery excrement derived from the worms²³ and the causal agent for the latter is the scales of the adult silk moth.²⁴ Occupational asthma among workers who process raw silk has also been reported in Sri Lanka.²⁵

Other occupations

Farmers are at high risk of developing occupational allergy to insects, including the housefly (Diptera- Muscidae- *Musca domestica*).²⁶ Occupational allergies in bakers and other workers handling

grains can be caused by allergies to beetles and lepidopteran insects that contaminate grain or wheat (commonly called grain pests).²⁷ Causal insect species for this disease entity include the Mediterranean Flour Moth (Lepidoptera- Pyralidae- *E. kuehniella*),^{28–30} Indian meal Moth (Lepidoptera- Pyralidae- *Plodia interpunctella*), Confused flour beetle (Coleoptera- Tenebrionidae- *Tribolium confusum*),^{31,32} and a species of shield bugs (Hemiptera- Scutelleridae- *Eurygaster austriaca*).^{29,30} Carmine (E-120) is a natural dye extracted from the dried females of the cochineal (Hemiptera- Dactylopiidae- *Dactylopius coccus*). Carmine dye is frequently used in the cosmetic and food industries, and can also induce allergic reactions after oral or respiratory exposure.³³ A study of 25 workers at a natural dye processing factory reported prevalence rates of 42% and 8% for sensitization and occupational asthma caused by carmine, respectively.³⁴

Distribution of insect allergens in indoor and outdoor environments

Respiratory exposure to airborne insect particles can also occur in indoor and outdoor environments during daily life in non-occupational settings, as well as in occupational settings. Numerous insects are present outdoors and airborne particles derived from these insects can become seasonal outdoor allergens. A seasonal increase in the levels of allergens from moths, caddis flies (Trichoptera), and midges (Diptera- Nematocera; including species in several families of non-mosquito Nematoceran Diptera) in the outdoor air from spring to autumn have been documented.^{35,36} However, in most of these studies, radioallergosorbent test-inhibition assays using crude insect extracts and pooled sera of sensitized patients were used to estimate allergen levels in the air; therefore, the species-specific levels of each insect allergen might be inaccurate. Additionally, regional variations in the levels of outdoor insect particles and the dominant insect species present in the environment that produce these particles have not been studied to date.

Insects can invade houses from outdoors causing allergies in humans. An example of this is allergy to Asian lady beetles (Coleoptera- Coccinellidae- *Harmonia axyridis*) reported in the United States.³⁷ Other insects can live and increase their numbers indoors, inducing human allergies. A well-documented example of this is

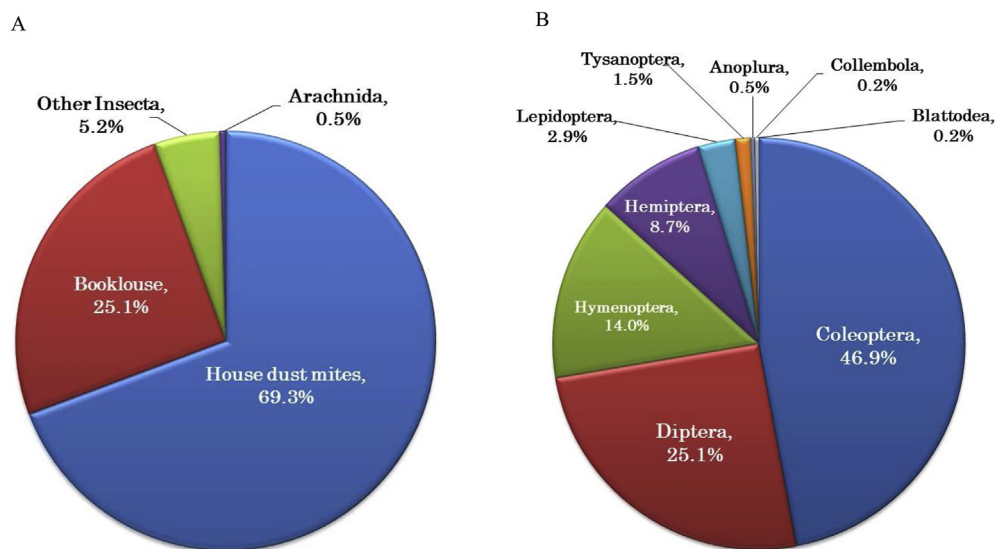


Fig. 1. Ratio of arthropods isolated from house dust according to the average number isolated per room (A), and the breakdown of other insects (B). Reprinted with permission from Reference.³⁸

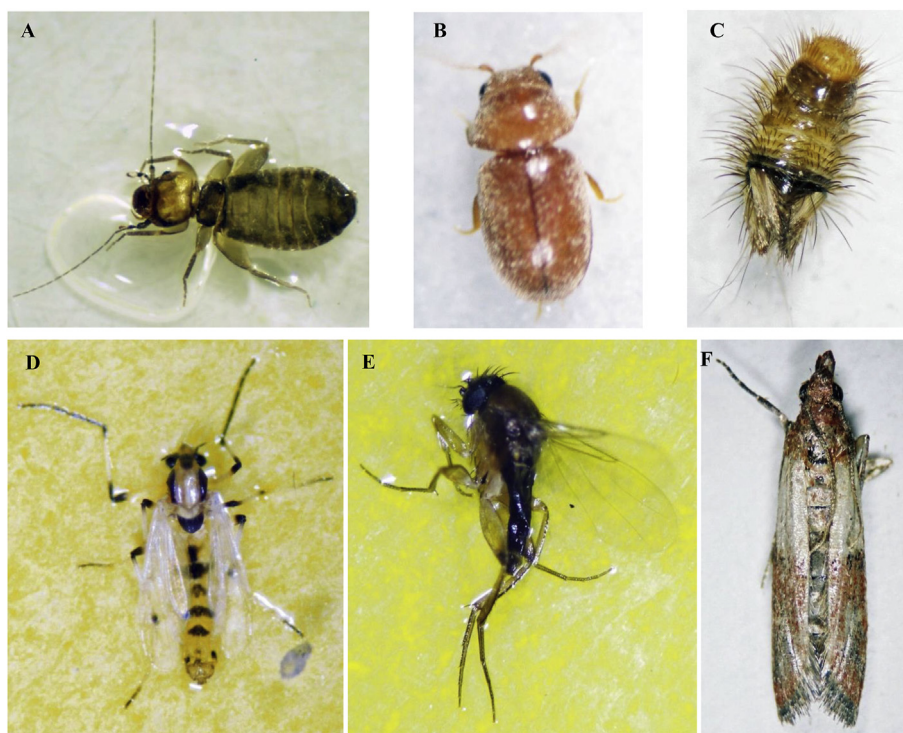


Fig. 2. Insects commonly found in house dust samples in Tokyo, Japan. **A:** Banded psocid, a common species of booklice (Psocodea-Liposcelidae-*Liposcelis bostrichophila*; body length, 1.0–1.3 mm), **B:** Cigarette beetle (Coleoptera-Anobiidae-*Lasioderma serricorne*; body length, 1.7–3.1 mm), **C:** Varied carpet beetle (Coleoptera-Dermestidae-*Anthrenus (Nathrenus) verbasci* (oligopod larva); body length, about 4 mm), **D:** Non-biting midge (Diptera-Chironomidae-*Cricotopus* sp.; body length, 2.5–3.0 mm), **E:** Scuttle fly (Diptera-Phoridae-*Dohrniphora cornuta*; body length, 1.5–2.4 mm), and **F:** Indian meal moth (Lepidoptera-Pyralidae-*Plodia interpunctella* body length, about 10 mm; opened wing length, 12–16 mm).

allergy to cockroaches (Blattodea). Furthermore, grain pests, causal insects for occupational asthma as mentioned above, can be found in houses in non-occupational settings.

Regarding the distribution of insects in indoor environments in Japan, we reported the results of an entomological survey performed on 20 houses in Tokyo in the summer and autumn of 2011.³⁸ In that study, an electric vacuum cleaner was used to collect house dust samples from the floors of living/dining rooms and bedrooms by suctioning for 5 min, and then the numbers of arthropods in the samples were counted. Figure 1 shows the ratio of arthropods in house dust according to the average number isolated per room. The number of detections was highest for house dust mites, followed by booklice (Psocodea), and the orders of Coleoptera and Diptera. Figure 2 shows pictures of insects commonly found in house dust in Japan. *Liposcelis bostrichophila* (Psocodea, Fig. 2A) is the most common species of booklice found indoors. Among the beetles (insects of the Coleoptera order), the cigarette beetle (Ptinidae-*Lasioderma serricorne*, Fig. 2B) and varied carpet beetle (Dermestidae-*Anthrenus (Nathrenus) verbasci* (oligopod larva), Fig. 2C), are relatively common in Japan. Many flies, non-biting midges and other insects belonging to the Diptera order are also present in houses in Japan. Figure 2D, E shows examples of non-biting midges (Chironomidae-*Cricotopus* sp.) and scuttle fly (Phoridae-*Dohrniphora cornuta*), respectively, which are frequently detected indoors. Indian meal moths (*P. interpunctella*) (Fig. 2F) are a grain pest, but can also live in the outdoor environment and invade houses in Japan. Some allergenic fungi, including *Aspergillus fumigatus* and *A. ochraceus* (*A. westerdijkiae*) are often attached to the surface of Cigarette beetles and Indian meal moths, indicating these insects are carriers of allergic fungi as well as sources of their own allergen.³⁹

Respiratory sensitization to environmental insect allergens

There is a large regional difference in the rate of sensitization to insect allergens, which might reflect differences in the numbers and types of insects dominant in the environment. Table 1 shows the prevalence of sensitization to house dust mites and various insects among atopic populations reported from various regions. The prevalence of sensitization to cockroaches shows large regional variations ranging from 4 to 52%. Generally, the prevalence of sensitization to cockroaches is higher in warmer regions and in contrast, in the northernmost region of Sweden, the prevalence of sensitization to cockroaches and mites is low (4%).⁴⁰ The higher prevalence of sensitization to insects including moths and cockroaches in southern warmer regions, and lower prevalences in northern cooler regions were reported in a nationwide study in Japan (data not shown).⁴¹

The prevalence of sensitization to cockroaches is not always the highest among insects (Table 1). In India, houseflies (*M. domestica*) is the most common insect allergen^{42,43} and moths is the most common insect allergen for patients in Ohio in the United States,⁴⁴ Brazil,⁴⁵ and Japan.⁴⁶ Sensitization to mosquitoes is most common in Iran.⁴⁷

Of note, the prevalence of sensitization to insects shown in Table 1 does not always reflect the genuine prevalence of species-specific sensitization to each insect. Insect allergen extracts contain various cross-reactive allergens, including tropomyosin, glutathione S-transferase, and arginine kinase, which frequently result in IgE cross-reactivity between extracts from different insect (and other arthropod) species.^{46,48–51} Therefore, the measurement of IgE to crude insect extract can result in the over-estimation of the actual prevalence of sensitization to each insect. Measuring the

Table 1

The prevalence of sensitization to insect allergens and house dust mites among allergic population in the literature.

Author/year	Country, city/town	Subjects	Type of IgE testing	House dust mite	Cockroach	Moth	Other insects
Gupta 1990 ⁴²	India, Deli	Allergic asthma (12–64 yrs)	Intradermal	NA	33%	19–25%	Housefly 43% Mosquito 27–34%
Lierl 1993 ⁴⁴	Unites States, Ohio	Allergic asthma (2.5–17.2 yrs)	In house ELISA	NA	NA	43%	Housefly 23% Cricket 19% Grasshopper 19%
Perzanowski 2000 ⁴⁰	Sweden, Northernmost region	Asthma (7–8 yrs)	CAP-FEIA	3%	4%	NA	NA
Dowaisan 2000 ⁶²	Kuwait	Rhinitis (6–64 yrs)	CAP-FEIA	32–39%	48%	NA	NA
Montealegre 2004 ⁶³	Puerto Rico, Ponce	Dermatitis/rhinitis/asthma (childhood to adult)	SPT	94%	42%	NA	NA
Smith 2005 ¹²⁸	United States, West Virginia	Asthma (childhood to adult)	SPT	39%	37%	7%	Caddis fly 14% Housefly 18% Mayfly 19%
Bemanian 2012 ⁴⁷	Iran, Yazd	Rhinitis	SPT	7–8%	14%	26%	Mosquito 33%
Fukutomi 2012 ⁴⁶	Japan, Sagamihara	Allergic asthma	In house ELISA	73%	16%	35%	Housefly 27% Booklouse 22% Mosquito 18%
Raj 2013 ⁴³	Northern India	Asthma (5–18 yrs.)	SPT	8%	18%	NA	Housefly 37%
Araujo 2014 ⁴⁵	Brazil, Curitiba	Asthma and/or rhinitis (6–15 yrs)	CAP-FEIA	87%	48%	61%	NA
AlKhater 2017 ¹²⁹	Eastern region of Saudi Arabia	Asthma (5–14 yrs)	SPT	45–48%	26%	NA	NA
Luo 2020 ¹³⁰	Southwest China	Suspected atopic diseases	CAP-FEIA	26%	27%	NA	NA
Kwizera 2020 ¹³¹	Uganda, Kenya, Ethiopia	Severe asthma (12–70 yrs)	SPT	66%	52%	NA	NA
Ishak 2020 ¹³²	Egypt	Asthma (3–55 yrs)	EAST	8–14%	19%	NA	NA

NA, not assessed; ELISA, enzyme-linked immuno sorbent assay; CAP-FEIA, CAP-fluorescent enzyme immunoassay; SPT, skin prick test; EAST, enzyme allergosorbent test; Yrs, years.

levels of IgE to allergen components specific for each insect species can solve this problem.⁵² However, species-specific allergen components have not been well-characterized for most insect species other than cockroaches.

Clinical significance in different insects

Cockroaches (*Blattodea*)

Cockroaches are a well-studied respiratory insect allergen. Although many species of cockroaches are associated with allergies, studies have concentrated on the German cockroach (*Blattodea-Ectobiidae- Blattella germanica*) and the American cockroach (*Blattodea-Blattidae- Periplaneta americana*).

Epidemiological studies performed on subjects in metropolitan inner-city areas in the United States have shown the relationship between exposure to cockroaches and cockroach sensitization, and the onset and worsening of asthma. One study performed on inner-city children with moderate-to-severe asthma showed that 69% were sensitized to this insect.⁵³ Many studies have shown that environmental cockroach allergen levels are associated with cockroach sensitization.^{54–56} Additionally, in a study on children with asthma in the Baltimore metropolitan area, African-American race and low socioeconomic status were identified as significant risk factors for cockroach allergen sensitization.⁵⁷ Furthermore, cockroach allergen exposure is a very strong risk factor for the development of asthma. A two-year cohort study of children under the age of five years in Boston, United States, reported that children in homes with high levels of cockroach allergens were 26 times more likely to develop asthma than children in homes with no detections.⁵⁸ Furthermore, cockroach allergy is an important exacerbating factor for asthma. In particular, asthma patients with cockroach sensitization and exposure have been shown to have a higher frequency of acute exacerbations of asthma.^{53,59} Among inner-city children with atopic asthma, an individualized, home-based, comprehensive environmental intervention was reported

to decrease exposure to indoor allergens, including cockroach and dust-mite allergens, resulting in reduced asthma-associated morbidity.⁶⁰ Several studies have demonstrated the greater effectiveness of integrated pest management (IPM) compared with routine chemical interventions in apartment buildings and the benefit of cockroach allergen reduction using IPM.⁶¹

As shown in Table 1, there are large regional differences in the rate of sensitization to this insect among allergic populations. In general, the prevalence of sensitization seems to be higher in warmer regions.^{62,63} Furthermore, living in the inner city is a risk factor for exposure and sensitization to this insect.⁶⁴ High rates of the detection of cockroach allergens was reported in houses in the southern and tropical regions in China,⁶⁵ and schools⁶⁶ and houses⁶⁷ in Iran. However, a relatively low rate of cockroach allergen detection was reported in Korea⁶⁸ and inland areas of China.⁶⁵ In Europe, a high rate of detection of cockroach allergens was reported in a study on low-cost public housing in Strasbourg, France.⁶⁹ A study in Poland also showed that 24% of children with asthma were sensitized to cockroaches and that cockroach allergens were detected in 55% of house dust samples from the houses of children with cockroach sensitization.⁷⁰ However, a study in Dresden, Germany showed a relatively low rate of sensitization and exposure to cockroaches.⁷¹

However, information on the clinical significance of cockroach allergens is relatively limited in Japan.⁷² The most common cockroach in houses in Japan is Smoky-brown cockroach (*Periplaneta fuliginosa*), which is a species closely related to American cockroach (*P. americana*). In contrast, German cockroach (*B. germanica*) is not commonly found in ordinary households in Japan and its distribution is limited to restaurants and densely populated areas of cities. A study of 10 houses in the suburbs of Tokyo performed in the 1990's reported the detection of Per a 1 (cross-reactive with group 1 allergens from *P. fuliginosa*) in dust samples from the kitchens of 8 houses.⁷³ However, its levels are much lower than those of house dust mites, suggesting that its clinical significance on the pathogenesis of respiratory allergy among Japanese may be much lower than that of house dust mites.

Table 2

Allergenic proteins from insects of the order of Blattodea approved by the WHO/IUIS Allergen Nomenclature Sub-committee.

Species	Allergen	Biological activity	Molecular weight
<i>Blattella germanica</i>	Bla g 1	Major allergen Bla g 1.0101, nitrile specifier, microvilli-like protein with unknown function	46 kDa
	Bla g 2	inactive aspartic protease	36 kDa
	Bla g 3	Hemocyanin, arylphorins/TO Arthropod hemocyanins	78.9 kDa (by mass spectrometry)
	Bla g 4	Calycin, lipocalin	21 kDa
	Bla g 5	Glutathione S-transferase	23 kDa
	Bla g 6	Troponin C	21 kDa
	Bla g 7	Tropomyosin	33 kDa
	Bla g 8	Myosin, light chain	21 kDa
	Bla g 9	Arginine kinase	40 kDa
	Bla g 11	Alpha-amylase	57 kDa
	Bla g 12	Chitinase	58 kDa
<i>Periplaneta americana</i>	Per a 1	Major allergen Per a 1.0101, nitrile-specifier, microvilli-like protein with unknown function	45 kDa
	Per a 2	Aspartic protease-like and inactive aspartic protease-like	42 kDa
	Per a 3	Arylphorins/TO arthropod hemocyanins	72 kDa
	Per a 5	Glutathione S-transferase	23 kDa
	Per a 6	Troponin C	17 kDa
	Per a 7	Tropomyosin	33 kDa
	Per a 9	Arginine kinase	43 kDa
	Per a 10	Serine protease	28 kDa
	Per a 11	Alpha-amylase	55 kDa
	Per a 12	Chitinase	45 kDa
	Per a 13	Glyceraldehyde-3-phosphate dehydrogenase	36 kDa
	Copt f 7	Tropomyosin	35.4 kDa
<i>Coptotermes formosanus</i>	Copt f 7	Tropomyosin	35.4 kDa

Many allergenic proteins have been identified and approved by the World Health Organization and International Union of Immunological Societies (WHO-IUIS) Allergen Nomenclature Sub-committee (Table 2). Sensitization profiles of these allergens are unique to each patient⁷⁴ and are different between populations. Unlike Der p 1 and Fel d 1 for mite and cat allergies, no immunodominant allergens have been identified for cockroach allergy.⁷⁴ Bla g 1 and Bla g 2 allergens are secreted from the digestive system and excreted in fecal particles, whose levels in dust samples are considered good makers of cockroach allergen exposure.⁷⁵ Threshold levels of exposure for sensitization and asthma symptoms in a susceptible population were reported to be 2 and 8 U/g of dust.⁷⁵ At the same time, IgE to Bla g 1 and Bla g 2 are considered markers for detecting genuine sensitization to cockroaches in patients co-exposed to mites and cockroaches,⁷⁵ although the prevalence of sensitization to these allergen components, even if they are combined, are not sufficiently high among patients with cockroach allergy.⁷⁴ Bla g 4 is a lipocalin⁷⁶ and is considered an important allergen for cockroach allergy.⁷⁴ Bla g 7 is pan-allergen tropomyosin, which contributes to cross-reactivity between cockroaches and other arthropods. Bla g 5, a glutathione S-transferase, and Bla g 9, an arginine kinase, are also allergens with cross-reactivity to the allergens of other insects and arthropods.^{48,77} Cockroach allergen extract also exhibits protease activity, and it can damage the epithelium leading to the increased penetration of allergens and activation of innate immune cells.⁷⁸ A recent study also showed a role for cockroach allergen-associated glycans in allergen-induced immune reactions.⁷⁹ Chitins are part of the exoskeleton of arthropods, and they have complex and size-dependent effects on innate and adaptive immune responses, including the accumulation in tissues of innate immune cells associated with allergy.^{80–82}

Moths (Lepidoptera)

Moths and butterflies belong to insects of the Lepidoptera order. The first cases of asthma due to inhaled moth and butterfly

allergens were reported by Parlato *et al.* in 1932.^{3,83} In most early cases with asthma related to Lepidoptera sensitization,^{3,84,85} their exposure to the insect was related to an occupation or hobby. However, as shown in Table 1, sensitization to moths is also relatively common among the general (non-occupational) asthma population worldwide. Therefore, the exposure and sensitization to this insect in indoor and outdoor environments are also considered clinically relevant. Because scales from their wings can easily become airborne, they are considered a major vector of airborne exposure.⁸⁶ Furthermore, moths and butterflies are mainly present outdoors and so exposure to them occurs mainly outdoors. However, some species are present in indoor environments because they invade houses.

The most commonly-sensitized respiratory insect allergen in Japan is the moth.^{41,87} The rate of sensitization to moths is higher in the southern part of Japan,⁴¹ which may reflect regional differences in environmental exposure to moths and butterflies related to climate. Kino *et al.* reported the results of several studies showing the clinical significance of moth and butterfly allergens for Japanese patients with asthma. Their early study in the 1970s reported a high rate of sensitization to moths among adults with general asthma randomly selected from outpatients: the rate of positivity by intradermal test and serum IgE test to moths was 56.1% and 30%, respectively.⁸⁸ Positivity by bronchial provocation testing using moth or butterfly extracts was also observed for sensitized patients who experienced asthma symptoms most frequently from April to October, which corresponds to the active periods of moths and butterflies.⁸⁸ Kino *et al.* also showed that the wing components of the silkworm were a more common sensitizer than its body components, and that there was a strong cross-reactivity between extracts from silkworm wings, moths, and butterflies.⁸⁶ Furthermore, they also showed the presence of insect-related particles including moths in dust collected from the air at 18.6 m above ground level, with two peaks a year, one in the spring and one in the autumn.³⁵ Another study on Japanese patients with allergic rhinitis showed that more than 30% were sensitized to moths, with a higher prevalence of sensitization among patients with more severe rhinitis.⁸⁷

Table 3

Allergenic proteins from insects of the order of *Lepidoptera* approved by the WHO/IUIS Allergen Nomenclature Sub-committee.

Species	Allergen	Biological activity	Molecular weight
<i>Bombyx mori</i> (Silk moth)	Bom m 1 [†]	Arginine kinase	42 kDa
<i>Plodia interpunctella</i>	Plo i 1	Arginine kinase	40 kDa
(Indian meal moth)	Plo i 2	Thioredoxin	12 kDa
<i>Thaumetopoea pityocampa</i>	Tha p 1 [‡]	Protein with	15 kDa
(Pine processionary moth)		unknown function	
	Tha p 2 [‡]	Protein with	15 kDa
		unknown function	

[†] Identified as a food allergen.

[‡] Identified as a contact allergen.

The significance of moths as an environmental (non-occupational) inhaled allergen was also reported by researchers in the United States. Cases with respiratory allergy to the Miller moth (*Lepidoptera*- *Noctuidae*- *Acrionicta leporina*) invading the home from the outdoors in May and June were reported.⁸⁹ Wynn and colleagues showed seasonal changes in the outdoor levels of *Lepidoptera* in southeastern Minnesota using an immunochemical method. Analysis of airborne particles collected using an air sampler located 1.5 m above ground on a prairie indicated moth proteins peaked in June and August to September, which was compatible with the total number of moths captured in light traps.⁹⁰ They also found that relatively small particles sized 0.8–1.4 µm, which had moth–allergen activity, accounted for 43% of the total particles collected by the air sampler.

Studies of the allergenic proteins from *Lepidoptera* have been relatively limited (Table 3).⁹¹ Plo i 1 is an arginine kinase from the Indian meal moth identified by using sera from patients with allergic symptoms and sensitized to this insect. Of note, it has high sequence similarity with homologue proteins from other arthropods.⁴⁸ IgE to Plo i 1 are recognized by 25% of moth-allergic patients.⁴⁸ Bom m 1 is also an arginine kinase from silkworms.⁹² Plo i 2 is thioredoxin from Indian meal moths identified using sera from patients with an indoor allergy and IgE to moths, which was demonstrated in 8% of patients.⁹³ Both Tha p 1⁹⁴ and Tha p 2⁹⁵ were identified as contact allergens in a study using sera from patients with cutaneous reactions after contact with pine processionary caterpillars. A recent study using Western blot analysis of sera from patients sensitized to silkworm moths showed IgE reactivity to many other silkworm moth proteins in more than 50% of the patients tested, suggesting the major allergenic proteins in silkworm moths have not been identified to date.⁹¹

Chironomid (*Chironomidae*)

Chironomidae, commonly known as “non-biting midges”, are an abundant family of the insect order *Diptera*.⁹⁶ They can appear in vast quantities in water rich areas when water contains a certain proportion of organic material. Previous studies reported respiratory allergies to Chironomidae have two clinical phenotypes: respiratory allergy to environmental adult Chironomidae^{97–99} and an occupational allergy to larvae of Chironomidae used as fish food.¹⁰⁰

Since the 1920s, Chironomidae have been associated with widespread hypersensitivity in people living close to the Nile, in Sudan.^{101,102} The dominant species is Green nimitti (*Diptera*- *Chironomidae*-*Cladotanytarsus lewisi*) and an increase in its numbers is probably a result of increased working in the dam. In Japan, a higher rate of sensitization to *Chironomus yoshimatsui* (21.2%) was documented among adult patients with asthma living around the Lake Suwa area compared with those living distant to a lake.¹⁰³ In addition, a study performed in Toyama City, Japan, showed that the

number of chironomid antigens in airborne dust collected using an air sampler located near a paddy field was increased from spring to autumn, with a peak in the summer (86). Furthermore, chironomid sensitized asthma patients experienced more asthma attacks in August (86).

Larvae of the Chironomidae are commonly called “blood worms”, which are frequently used as bait for fishing and the farming of fish. Fishermen and other occupationally exposed persons who are frequently exposed to blood worms can develop occupational allergies, including asthma, rhinitis, and systemic allergic reactions.^{14,100} Chi t 1, a hemoglobin from the larvae of *Chironomus thummi thummi* (which is also the causative agent for the red color of the larvae) was identified as the major causative allergenic protein for this occupational allergy.^{96,100,104,105} In another study, 33 out of 43 patients with this symptomatic occupational allergy were sensitized to Chi t 1¹⁰⁵. However, hemoglobin degrades after its emergence and its levels are decreased in mature adults.¹⁰⁶ In a serological study examining the levels of IgE Ab to various Chironomidae using sera from Japanese, Taiwanese, and Swedish atopic asthma patients, the sensitization rate to Chi t 1 was low (4.1%). However, the rate of sensitization to the larvae of *Cricotopus sylvestris*, which does not contain hemoglobin, was the highest (nearly 40%) among four species of Chironomidae larvae studied,¹⁰⁷ suggesting that allergens other than hemoglobin are also involved in respiratory sensitization to Chironomidae in the environment. Finally, cross-reactivity between *Chironomus yoshimatsui* and silk moths (*B. mori*) was reported in a study using sera from Japanese asthma patients.¹⁰⁸

Booklice (*Psocodea*- *Troctomorpha*)

Booklice, alternatively called psocids, are a common household insect pest belonging to the Psocodea order. Despite their name, given because they infest old books, sheets of paper and stored food products in homes, they are not lice and do not feed on living animals. Members of Psocodea are distributed in all geographical regions, from the tropical to subarctic zones.⁴⁶ Particularly in Japan, booklice are a commonly found insect in house dust.³⁸ Banded psocid (*Troctomorpha*- *Liposcelididae*- *L. bostrichophila*), a common species of booklice found in house dust, is brownish, soft-bodied and 1.0–1.3 mm long when fully grown.⁴⁶ Recently, increasing numbers of reports have suggested the clinical significance of this insect as an indoor respiratory allergen.^{46,109}

The primary food source of booklice is mold. Therefore, booklice prefer warm, damp conditions and are abundant in homes in the summer and autumn.⁴⁶ Our previous environmental survey of houses in Tokyo showed a significant increase in the number of booklice in the summer and autumn (Fig. 3).¹¹⁰ Our other environmental survey also showed an increased number of booklice in house dust samples from apartment houses compared with detached houses, bedrooms compared with living rooms, in sunless rooms, and rooms containing carpets or Japanese tatami mats.³⁸ These findings indicate that, although the main source of exposure to mite allergens for humans is dust from mattresses, the most important source of booklice allergens is floor dust in dim bedrooms with carpets or tatami mats.

Our previous study on Japanese patients with atopic asthma showed the frequency of serum IgE positive for *L. bostrichophila* was 22%.⁴⁶ Additionally, using tatami mats or carpets in bedrooms is associated with IgE positivity for booklice,⁴⁶ which was compatible with residential risk factors related to the presence of booklice observed in our environmental survey³⁸ as discussed above. IgE-inhibition analysis using serum samples from booklice-sensitized asthma patients showed that specific sensitization to this insect, not explained by cross-reactivity from other insect allergens,

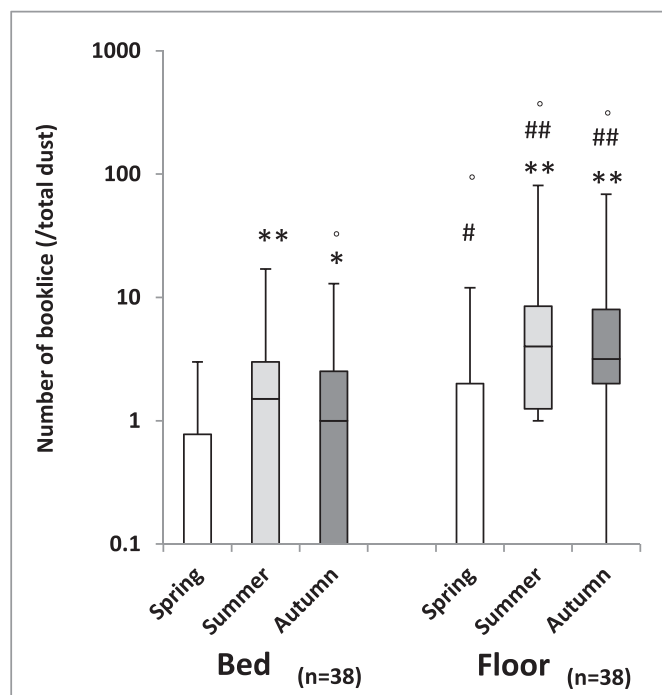


Fig. 3. Seasonal variations in the numbers of booklice isolated from bedding and floors. * $p < 0.05$, ** $p < 0.01$: compared with those collected in the spring using the Steel–Dwass test # $p < 0.05$, # $p < 0.01$: compared with beds using the Wilcoxon signed-rank test. Reprinted with permission from Reference 110.

occurred in one-third of patients sensitized to this insect,⁴⁶ suggesting the significance of this insect as a respiratory allergen involved in species-specific sensitization. An allergenic protein related to the species-specific sensitization to this insect was identified and named Lip b 1⁴⁶. Lip b 1 is a protein of unknown function with a molecular weight of about 26 kDa.¹¹¹ The results of a BLAST search of the amino acid sequence of Lip b 1 indicated no identical or highly homologous proteins, suggesting this is a novel protein.¹¹¹

Booklice are considered a predominant indoor insect worldwide, especially in warm and humid climates. The presence of booklice in indoor environments or cases with respiratory allergies to this insect was also reported in countries other than Japan, including India,¹⁰⁹ China,¹¹² Iran,¹¹³ France,¹¹⁴ and Spain.¹¹⁵ In an environmental study performed in Beijing, China, booklice specimens were found in 55.3% of all homes.¹¹² In a study in Mumbai, India, booklice were identified in 25% of house dust samples from the homes of patients with respiratory allergies and 20% of patients with respiratory allergies are sensitized to this insect.¹⁰⁹ Occupational allergic asthma induced by *Liposcelis decolor* (Liposcelidae), which was present in granaries where barley grains were harvested, was reported in Spain.¹¹⁶ A case of anaphylaxis after the ingestion of oats and rice infected with *L. bostrichophila* was also recently reported.¹¹⁷ Other species of booklice including *L. corrodens*, *L. entomophila*, *L. pearmani* are also relatively common in indoor environments and are thought to be significant indoor allergens, although the allergenicity of these booklice species has not been studied to date.

Other environmental respiratory insects

Respiratory allergies to silverfish (Thysanura- Lepismatidae- *Lepisma saccharina*),^{118–121} pharaoh ants (Hymenoptera- Formicidae- *Monomorium pharaonic*),¹²² and carpet beetles (insects

belonging to the *Dermestidae* family)^{123,124} present in indoor environments have also been reported. In India, the high rate of sensitization to mosquitos and the presence of air-borne mosquito allergens was also documented.^{125,126} Allergies to Asian lady beetles (*H. axyridis*) have been a problem since the late 1980's in the United States.^{37,127} Ladybugs were introduced from Asia to Europe and the United States at the beginning of the 20th century for the purpose of the ecological control of aphids. However, they invaded houses in the early autumn, and hundreds to thousands of beetles were present during the winter months. Therefore, individuals can become sensitized to this insect and develop allergic symptoms, including asthma and rhinitis.

Conclusion

Exposure to inhaled insect particles has been identified as a cause of respiratory allergy. Cockroaches are a well-documented allergenic insect that is mainly present indoors. Other indoor insects, including booklice, might be a source of clinically relevant indoor allergens, although evidence supporting this is relatively limited. Airborne particles from insects including moths and midges were also identified as seasonal outdoor allergens. Finally, other important environmental insect allergens might not have been identified yet, because insect species dominant in the environment have large regional variations. More research is needed to clarify the clinical relevance of the sensitization to these environmental insect allergens on the pathogenesis of respiratory allergies whilst considering regional differences.

Conflict of interest

The authors have no conflict of interest to declare.

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