

Mite Allergens

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There is an increasing awareness of the health implications of mite sensitivity, as it is closely related to asthma. Mite allergy constitutes a complex worldwide problem, with sanitary and economical implications. Not only are mite species present in house dust, producing potent allergens, but other, less studied species are also responsible for significant allergic reactions in occupational settings. In this review, we focus on the growing number of mite species that are implicated in allergic cutaneous and respiratory diseases in humans. Mite allergy is not restricted only to the human “indoor” environment, because numerous reports clearly demonstrate that many species that can induce sensitization and symptoms are encountered in occupational settings. An important component of allergy research is the evaluation of the allergenic cross-reactivity to verify to what extent different mite species have unique, species-specific, or cross-reactive allergens. The results of these investigations have important clinical consequences for the diagnosis and treatment of allergic diseases. Internationally standardized mite extracts are needed to compare sensitization rates around the world and clearly establish risk factors associated with sensitization and asthma. In spite of recent controversial results, a significant reduction in the exposure to mite allergens continues to be an important challenge and one of the main goals in the treatment of mite-induced respiratory symptoms. In many cases, this reduction must be achieved in the workplace as well as in the home environment.

Introduction

Mites belong to a large group of arthropods that have colonized most habitats of the world. They exhibit different feeding habits. Some are phytophagous and live on plants, some are fungivorous and live in the soil or on stored food products, some are predators of other mites, or insects, and some are parasites of vertebrate and invertebrate animals. Mites constitute one of the main groups of animals, owing to their diversity and their biomass. They are an essential component of the food and nutrient

chains. Mites are commonly present in human habitats, where they can be parasites of domestic animals or live in human dwellings in carpets, mattresses, sofas, furniture, and stored food [1•].

Among the many mite species that are implicated in human health, those that induce respiratory allergies play an important role. From the beginning of the 20th century (1920s), and especially after the initial use of skin testing, the inhalation of “house dust” was suspected as a relevant cause of respiratory symptoms. Therefore, the composition of house dust was studied in great detail [2,3]. The results of some of these investigations indicated that mites present in house dust could be responsible for the positive skin tests produced by house dust extracts. In 1964, Voorhorst *et al.* [4] demonstrated that house dust may contain large quantities of highly allergenic mites. In 1966, Fain [5] identified one of these species as *Dermatophagoides pteronyssinus*. The other main species, identified in Japan, was *D. farinae* [6,7].

Mites of Allergenic Importance in the Home Environment

From the early 1960s, much literature has been published concerning the taxonomy, biology, immunochemistry, and control of mites implicated in allergic reactions. Numerous species have been described that are the source of allergens capable of sensitizing and inducing allergic symptoms in sensitized and genetically predisposed individuals. Allergic diseases that can be triggered by mite allergens include allergic rhinoconjunctivitis, asthma, atopic dermatitis, and other skin diseases.

The most studied species, because of its abundance and allergenic importance, is the group of the house dust mites that belong to the family Pyroglyphidae, especially *D. pteronyssinus*, *D. farinae*, and *Euroglyphus maynei*. Other species of this group, such as *D. microceras*, *D. siboney*, and *Gymnoglyphus longior*, are also considered allergenic, although their study is more limited, owing to their less frequent presence in house dust. Other genera from the Pyroglyphidae family present in house dust are *Hirstia* and *Malayoglyphus*. House dust mites are commonly present in human dwellings, where they thrive on human dander. They are especially abundant in mattresses, sofas, carpets, and blankets.

In recent years, many mite allergens have been purified, sequenced, and cloned. A list of the different purified mite allergens, separated by groups of homology, is shown in

Table 1. Mite allergen groups

Group	Species	Function	kDa
Group 1	<i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>D. microceras</i> , <i>E. maynei</i> , <i>B. tropicalis</i>	Cysteine protease	25
Group 2	<i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>E. maynei</i> , <i>T. putrescentiae</i> , <i>G.</i> <i>domesticus</i> , <i>L. destructor</i>	?	14
Group 3	<i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>B. tropicalis</i>	Trypsin	28-30
Group 4	<i>D. pteronyssinus</i> , <i>B. tropicalis</i>	Amylase	60
Group 5	<i>D. pteronyssinus</i> , <i>B. tropicalis</i> , <i>L. destructor</i>	?	14
Group 6	<i>D. pteronyssinus</i> , <i>B. tropicalis</i>	Chymotrypsin	25
Group 7	<i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>L. destructor</i>	?	24-31
Group 8	<i>D. pteronyssinus</i>	Glutathione transferase	
Group 9	<i>D. pteronyssinus</i>	Serina collagenolítica	
Group 10	<i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>B. tropicalis</i> , <i>L. destructor</i>	Tropomyosin	33-36
Group 11	<i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>B. tropicalis</i>	Paramyosin	98-110
Group 12	<i>B. tropicalis</i>		
Group 13	<i>A. siro</i> , <i>B. tropicalis</i> , <i>L. destructor</i> , <i>T. putrescentiae</i>	FABP (fatty acid binding protein)	14
Group 14	<i>D. pteronyssinus</i> , <i>D. farinae</i> , <i>E. maynei</i>	Apolipophorin	177
Group 15	<i>D. farinae</i>	Chitinase	98
Group 16	<i>D. farinae</i>	Gelsolin-villin	53
Group 17	<i>D. farinae</i>	Calcium binding protein	53
Group 18	<i>D. farinae</i>	Chitinase	60
Group 19	<i>B. tropicalis</i>	Antibacterial peptide homologue	7.2
Group 20	<i>D. pteronyssinus</i>	Arginine kinase	40

*Includes purified and sequenced allergens published in the list of allergens by the subcommittee of Allergen Nomenclature of the International Union of Immunological Societies—www.allergens.org
A.—*Acarus*; B.—*Blomia*; D.—*Dermatophagoides*; E.—*Euroglyphus*; G.—*Glycyphagus*; L.—*Lepidoglyphus*.

Table 1. The allergens from the *Dermatophagoides* species have been studied in greater detail than those from other families and genera. In many cases, their allergenicity has been demonstrated by in vivo (skin testing) and in vitro studies (specific IgE determinations).

An important group of mites, referred to as “storage mites,” comprises mainly members of the Acaridae and Glycyphagidae families. Besides their allergenic importance, these mites also have an economical significance, because they can destroy large crops of grains and other stored products.

There has been a change in the nomenclature of the mite species that are capable of inducing specific IgE-mediated respiratory or cutaneous diseases. Currently, all mite species present in the home environment and capable of inducing IgE-mediated sensitization are called “domestic mites” [8]. However, the name “storage mites” is still used to designate mite species found in house dust that do not belong to the family Pyroglyphidae. Approximately 150 storage mite species are known [9], although only about 20 can be considered to be important from an economic and sanitary perspective. From this group, the most studied species is *Blomia tropicalis*, owing to its abundance in tropical and subtropical regions of the world, and *Lepidoglyphus destructor* because of its frequent presence in barns. Other storage mite species are present in relatively small quantities in human dwellings

(mattresses and carpets), although they can be found in larger quantities in kitchen floor dust, cupboards, and pantries. In some cases, and especially in humid homes, these species can also be found in mattresses. Their preferred habitat is stored food. They can be an important plague with economical transcendence, as they cause occupational respiratory allergies in farmers and other occupationally exposed individuals. The most important genera are *Lepidoglyphus*, *Glycyphagus*, *Acarus*, *Tyrophagus*, *Aleuroglyphus*, *Suidasia*, *Chortoglyphus*, and *Cheyletus*. The main storage mite species, which can produce allergic reactions, is shown in Table 2.

Mites of Allergenic Importance in Agricultural and Occupational Settings

The allergenicity of several mite species present in agricultural settings (horticulture), either as crop pests or as a control tool (predator mites) to reduce mite infestations, has been studied. Among the mites present in horticultural environments, the following have clinical importance: phytophagous mites belonging to the family Tetranychidae [10–20] (genera *Tetranychus* and *Panonychus*) [21–26], and predator mites belonging to the families Phytoseiidae (genera *Phytoseiulus* and *Amblyseius*), Dermanyssidae (genus *Hypoaspis*) [27,28,29•], and Hemisarcopidae (genus *Hemisarcopetes*) [30].

Table 2. Main families and species of storage mite that have been described as allergenic

Family	Species
Glycyphagidae	<i>Glycyphagus domesticus</i>
	<i>G. privatus</i>
	<i>Gohieria fusca</i>
	<i>Lepidoglyphus destructor</i>
Echimyopodidae	<i>Blomia tropicalis</i>
	<i>B. kulagini</i>
	<i>B. tjiobdas</i>
Chortoglyphidae	<i>Chortoglyphus arcuatus</i>
Ebertiidae	<i>Suidasia medanensis</i>
Acaridae	<i>Tyrophagus putrescentiae</i>
	<i>T. longior</i>
	<i>Acarus siro</i>
	<i>A. farris</i>
	<i>Thyreophagus entomophagus</i>
	<i>Aleuroglyphus ovatus</i>
Cheyletidae	<i>Cheyletus eruditus</i>
	<i>Ch. tenuipilis</i>
	<i>Ch. malaccensis</i>

The main symptoms associated with sensitization and exposure to Tetranychidae mites (red spiders) are rhinoconjunctivitis and asthma. The incidence is greater in greenhouse than in outdoor workers [31]. In populations at risk, such as agriculture workers dealing with fruit trees or greenhouse vegetables, the sensitization rates are high, in the range of 36% [13] to 100% [32]. Epidemiologic studies have also demonstrated high rates of sensitization in the surrounding population, which is not occupationally exposed to apple trees [21] or citrus trees [24–26]. Significant differences in the rate of sensitization to these mites have also been identified between children residing in rural or urban areas [33]. A study by Delgado *et al.* in Seville, Spain [15], confirmed a high rate of sensitization to *Tetranychus urticae* in agricultural workers; 66% were sensitized by skin prick test and specific IgE determination. Bronchial provocation tests were conducted with mite-infested plant materials, producing a positive reaction in 12 out of 16 patients [15]. Positive conjunctival challenges with two species of Tetranychidae, namely *T. urticae* and *Panonychus citri*, were described in 48 out of 54 occupationally exposed individuals [13]. There is now ample evidence that suggests that these mite species are potent sensitizers in occupationally exposed, agricultural workers, and that the inhalation of their allergens can induce allergic respiratory symptoms.

Parasitic and Ectoparasitic Mites with Allergenic Importance

Several parasitic mite species, belonging to various families and genera, are in frequent contact with human beings and domestic animals. A classic example is *Sarcoptes scabiei*, which causes skin lesions and IgE-mediated sensitization

in parasitized individuals [34–36]. Ticks (*Ixodida*) belonging to the families Ixodidae [37–40] and Argasidae [41,42] have several proteins in their saliva that can induce IgE-mediated reactions. Several cases of anaphylaxis after tick bites have been reported [43]. The allergenic composition of these mites has been analyzed [44], and an important allergen of *Argas reflexus* has recently been cloned [45••].

Other parasitic mites that have been involved in allergic reactions in humans are *Varroa* (a bee parasite) [46] and *Diplaegidia* (feather mites of domestic birds) [47]. Other genera and species that can induce cutaneous problems are phytophagous mites of the family Tydeidae (*Pronematus davisii*) [48], parasites of insects of the family Pyemotidae (*Pyemotes*) [49], parasites of birds or rodents, such as *Ornithonyssus*, *Dermanyssus*, and *Androlaelaps* [50], parasites of mammals (Trombiculidae, Cheyletiellidae, and Psoroptes) [51,52], and parasites of human hair follicles, such as *Demodex* spp. [53]. However, it is not clear whether the response to these mites is always mediated by specific IgE [54,55•]. A list of the main mite species that can produce allergic problems, and do not belong to the house dust or storage mite groups, is shown in Table 3.

Clinical Significance of Sensitization to Domestic Mites

The clinical relevance of sensitization to *D. pteronyssinus* and *D. farinae* has been demonstrated in numerous publications. However, the clinical relevance of sensitization to other mite species is not as well established, and more studies are clearly needed using standardized extracts. As part of these investigations, several cross-reactivity studies have been conducted to establish to what extent nonrelated mite species share common epitopes. Recently, there has been an increasing interest in the study of storage mites as a cause of respiratory symptoms. A high prevalence of positive skin tests has been detected in farmers [56–59] as well as in urban dwellers [60]. Studies conducted with German farmers have shown a prevalence of positive skin tests to different storage mites of approximately 40% [61,62]. A higher prevalence has been detected in the tropics, where the mite fauna is richer in species [63–65].

Sensitization to different storage mites has been described in several regions of Spain. Armentia *et al.* [66] evaluated the prevalence of sensitization to different mite species in grain workers and detected a prevalence of 38% for *L. destructor* and *Tyrophagus putrescentiae*, of 34% for *B. kulagini*, and of 24% for *Acarus siro* and *Chortoglyphus arcuatus*. A study conducted in Galicia in 469 adult patients residing in rural and urban areas demonstrated a rate of sensitization of 34.4% for *L. destructor* and/or *T. putrescentiae* [67]. In Cartagena, Murcia, in an urban population of adult *Dermatophagoides* spp. sensitized patients, the authors detected a prevalence of sensitization to *Blomia* spp. of 56.6%, to *L. destructor* of 65.7%, and to *T. putrescentiae* of 47% [68].

Table 3. Other mite families and species of allergenic mites, excluding house dust and storage mites

Family	Species
Plant parasites	
Tetranychidae	<i>Tetranychus urticae</i> <i>Panonychus ulmi</i> <i>Panonychus citri</i> <i>Pronematus davisii</i>
Tydeidae	
Predator mites	
Phytoseiidae	<i>Amblyseius cucumeris</i> <i>Phytoseiulus persimilis</i> <i>Hypoaspis miles</i> <i>Hemisarcopetes cooremani</i>
Hypoaspidae	
Animal parasites	
Varroidae	<i>Varroa</i> sp.
Sarcoptidae	<i>Sarcoptes scabiei</i>
Analidae	<i>Diplaegidia columbae</i>
Ixodidae	<i>Ixodes pacificus</i> <i>I. holocidus</i> <i>I. ricinus</i> <i>Rhipicephalus</i> sp.
Argasidae	<i>Argas reflexus</i>

We have recently analyzed the prevalence of sensitization to *C. arcuatus* and *Glycyphagus domesticus* in Galicia [69]. A total of 138 consecutive allergic patients were analyzed; 40.7% lived in a rural area and 59.3% were city dwellers. Skin prick tests were conducted with the following mite species: *D. pteronyssinus*, *L. destructor*, *T. putrescentiae*, *C. arcuatus*, and *G. domesticus*. The percentage of patients with a positive skin test reaction to *D. pteronyssinus* was 94.2%; to *G. domesticus*: 89.6%; to *L. destructor*: 89.1%; to *T. putrescentiae*: 87% (1 monosensitized); and to *C. arcuatus*: 58% (2 monosensitized). A significant correlation was established between sensitization to *D. pteronyssinus*, *G. domesticus*, *T. putrescentiae*, and *L. destructor* ($P < 0.05$). However, the correlation was not significant between *C. arcuatus* and the rest of the mites. There were no differences in the sensitization rate of rural or urban dwellers. There was a significant correlation between the number of mites to which the patient was sensitized and the years of evolution of the disease ($P < 0.05$). This study demonstrated that there is a high prevalence of sensitization to storage mites in the humid region of Galicia, and there is a significant positive correlation between the years of evolution of the disease and the number of mites to which the patients become sensitized.

In Las Palmas de Gran Canaria, in the subtropical Canary Islands of Spain, the prevalence of positive skin tests to several storage mite species has also been investigated [70]. Sensitization rates of 46% for *G. domesticus*, of 44% for *A. siro*, of 28% for *Goheria fusca*, of 18% for *L. destructor*, and of 12% for *T. putrescentiae* were established in allergic patients attending an allergy service. In the

neighboring island of Tenerife, similar results were also obtained [71].

Cheyletus eruditus is a mite species frequently identified in house dust, especially in rural environments, where it feeds on storage mites. This species is also used as a pest control agent to reduce mite populations in infested crops [72]. Only a few studies have evaluated the allergenicity of *Cheyletus* spp. [73,74]. We have recently demonstrated that *C. eruditus* is capable of sensitizing exposed individuals. We investigated a population of mite-allergic individuals from Martinique, France, and established, by skin testing, a prevalence of sensitization to *C. eruditus* of 37.8% [75]. Further studies are needed to confirm the allergenicity of this mite species, and if it has any clinical implications.

Few reports have analyzed the clinical significance of sensitization to storage mites using provocation tests. It is noteworthy that positive skin tests to storage mites do not conclusively prove that the inhalation of allergens released by these mites are the cause of allergic respiratory symptoms in sensitized individuals [76,77]. One of the better studied mite species in this sense is *L. destructor* [78,79]. Davies *et al.* [80] performed a bronchial provocation test to one farmer with his own grain contaminated with *L. destructor*. The patient experienced an immediate and late-phase response. Conjunctival challenges have also produced positive results [81]. In the Canary Islands, Álvarez *et al.* [82] induced a positive bronchial reaction in an asthmatic patient sensitized to *L. destructor*. High levels of tryptase, eosinophils, and epithelial cells were detected in the induced sputum. In Sweden, bronchial provocation tests conducted in farmers with asthma were positive, in all cases, with *L. destructor*, suggesting the clinical relevance of this mite species in allergic farmers in this country [83]. The inhalation of *L. destructor* has also induced a late-phase reaction in a cereal worker, who did not previously experience an immediate reaction [84].

Most of these studies confirm the etiologic role and clinical implication of *L. destructor* in occupationally exposed patients. However, less information is currently available on individuals who are not occupationally exposed to *L. destructor*. In these cases, the only suspected exposure is their home environment. Ferrer *et al.* performed nasal provocation tests with a standardized extract of *L. destructor* in nine *L. destructor*-sensitized patients who were not occupationally exposed to this mite species, and in one control. The provocation test was positive in six patients, and there was a good correlation with specific IgE levels and the results of the provocation results [85]. In this same study, nasal provocation tests were also conducted with a standardized extract of *T. putrescentiae* extract in three *T. putrescentiae*-sensitized individuals. All the reactions were positive. Furthermore, one of the patients had a negative reaction with *D. farinae* and was positive with *T. putrescentiae*.

Only a few studies have evaluated the allergenicity of *T. putrescentiae* using nasal challenges. Lelong *et al.* [86]

reported eight positive nasal challenges in a group of 12 children with allergic rhinitis *T. putrescentiae*. Although more studies are clearly needed, sensitization to *T. putrescentiae* seems to be relevant in some sensitized individuals, including those who are not occupationally exposed. Other species of *Tyrophagus* frequently encountered in stored food and grains are *T. longior* and *T. palmarum*. Ingram *et al.* [87] reported positive bronchial provocation tests with a mixture of *T. longior* and *L. destructor* extracts in four farmers with rhinoconjunctivitis and asthma. Other studies have also shown positive reactions with *A. siro* and *G. domesticus* [88].

Allergenic Importance of *B. tropicalis*

B. tropicalis is a very common mite present in the home environment in many homes in subtropical and tropical regions of the world. Due to its wide distribution and clinical relevance, *B. tropicalis* is the best studied species of the genera *Blomia*. The prevalence of sensitization to *B. tropicalis* has been the subject of many studies in different geographic regions [89–92]. In Las Palmas de Gran Canaria, Sánchez Palacios *et al.* [93] identified a prevalence of positive skin tests to *B. tropicalis* of 50% in a group of patients evaluated at a local allergy service. The results in Tenerife were very similar. There are several reports of nasal and bronchial provocation studies using *B. tropicalis* extracts, especially in areas where this mite is abundant. Studies have been conducted in the Canary Islands [94,95], Brazil [96], United States (Florida) [97], and Singapore [98,99]. In Florida, Stanaland *et al.* [97] conducted nasal provocation tests in 19 patients with allergic rhinitis; 12 of these individuals were sensitized to *B. tropicalis* and the rest only to *Dermatophagoides* spp. The test was positive in 10 *B. tropicalis*-sensitized individuals and negative in those who were not sensitized, which suggests the specificity of the *in vivo* allergic response.

Several studies have included bronchial inhalation tests with *B. tropicalis*; two studies were conducted in the Canary Islands using *B. kulagini* and *B. tropicalis*. In one of these studies [94], the provocation test was positive, with *B. kulagini* in 18 patients sensitized to this species and negative in the controls. In the second study [95], bronchial provocations were conducted in a group of 15 patients with standardized extracts of *B. tropicalis* and *D. pteronyssinus*. The bronchial provocation test was positive in nine of the *B. tropicalis*-sensitized patients and negative in six individuals—two were skin test positive to *B. tropicalis*, and four were negative controls. The bronchial provocation test with *D. pteronyssinus* was positive in all patients, except in one, who had a positive reaction to *B. tropicalis*. In this study, conjunctival provocation tests with *B. tropicalis* were also conducted in 32 patients; 20 had a positive reaction to *B. tropicalis* (18 were sensitized to *B. tropicalis*), and 12 had a negative response—five were sensitized to *B. tropicalis*. The conjunctival provocation test was positive with *D. pter-*

onyssinus in all sensitized patients. In Brazil [96], nasal provocation tests were conducted in 10 children sensitized to *B. tropicalis* and *D. pteronyssinus*; six of these children had a positive response to *B. tropicalis* and nine to *D. pteronyssinus*. In Singapore [98,99], nasal provocation studies were also conducted in pediatric and adult patients with asthma and/rhinitis sensitized to *B. tropicalis*. An increase in nasal obstruction and symptoms, which was dose dependent, was measured. An increase from basal tryptase and leukotriene C4 [98] levels was also detected.

These studies clearly show that *B. tropicalis* induces an allergic response (bronchial, nasal, and conjunctival) in the target organ of sensitized patients. Based on these studies, there is minimal-to-moderate cross-reactivity between *B. tropicalis* and *Dermatophagoides* spp. The lack of studies using internationally standardized *B. tropicalis* extracts hampers, to a certain extent, the complete understanding and full analysis of these results [100,101]. The same concept is true for the rest of the mite extracts that have been used in population-based studies to establish sensitization rates.

Cross-reactivity of Mite Allergens

There has been considerable progress in the study of the molecular characteristics of mite allergens. Mite allergens have been purified from aqueous extracts or produced as recombinant proteins, from which nucleotide and amino acid sequences have been obtained. Molecular cloning provides an efficient way of obtaining pure polypeptides, in their native sources from complex mixtures, and are often present in very small amounts. The cloning of allergen provides pure proteins to map B-cell and T-cell epitopes and permits the identification of these binding sites. Sequence similarity searches have identified the biological function of many mite allergens. When sequence homologies with known proteins have not been found, the biological function of these allergens remains unknown. Sequence polymorphisms have been identified for several allergens. These polymorphisms influence antibody binding and T-cell recognition.

The number of purified allergens has increased significantly recently. Most of the well-characterized allergens have an ascribed biological function based on the similarity with other proteins of known functions. Most have been placed in groups based on their chronologic characterization and/or homology with previously purified *Dermatophagoides* allergens [102].

Mite-allergic individuals may be sensitized by various species. This could be, in part, due to cross-reactivity of common allergenic determinants. The study of allergen cross-reactivity has experienced important changes in recent years. Originally, cross-reactivity was studied using whole extracts and radioallergosorbent test (RAST) inhibition techniques. More recently, purified native or recombinant allergens, epitope mapping, and T-cell proliferation

techniques have been used [103]. Small peptides, with eight to 15 amino acids, are known as allergenic determinants, or epitopes, and are responsible for specific IgE binding and, to a large extent, for cross-reactivity between different allergens. Allergenic cross-reactivity occurs when different proteins have a certain degree of homology and contain identical or similar specific IgE-binding epitopes.

Cross-reactivity is a common feature among mite allergens, especially in those from taxonomically related species. The allergenicity of the house dust mite *D. pteronyssinus*, *D. farinae*, and *E. maynei* is well documented, but the extent to which their allergens are unique or cross-react with mite allergens or other genera has not been completely delineated. *E. maynei*, *D. pteronyssinus*, and *D. farinae* show significant allergenic cross-reactivity, in which several allergens are involved, including Der p 2 [104].

In vitro cross-reactivity studies between whole extracts of *B. tropicalis* and other mite species have demonstrated that these mites share common, as well as species-specific, allergens. Puerta *et al.* [105] demonstrated a greater degree of cross-reactivity between *B. tropicalis* and *L. destructor* than between *B. tropicalis* and *Dermatophagoides* spp. Arlian *et al.* [106] demonstrated that most allergens present in *B. tropicalis* are species-specific. Only three allergens are common with *D. farinae* body and feces extracts, two and one with body and feces extracts of *D. pteronyssinus*, respectively, using immunoelectrophoresis. Morgan *et al.* [107] demonstrated corresponding IgE-binding proteins of 105, 75, 57, 18, and 14 kDa in extracts of *E. maynei* and *B. tropicalis*. However, most IgE-binding proteins did not show corresponding bands in both extracts. The authors concluded that *E. maynei* and *B. tropicalis* are the source of both species-specific and cross-reactive allergens, and that most allergens in each extract were species-specific. In recent years, several allergens of *B. tropicalis* have been cloned and sequenced. Some of them have shown sequence homology with purified allergens of *D. pteronyssinus*, such as Blo t 5, a homologue of Der p 5; Blo t 13, a fatty acid binding protein; Blo t 11, homologous to paramyosin; Blo t 10, homologous to tropomyosin; and Der p 10—Blo t 3, a trypsin-like protease [18], and Blo t 1, homologous to cysteine proteases. All of these studies have confirmed a low-to-moderate degree of cross-reactivity. Several studies have focused on the in vitro cross-reactivity of purified Blo t 5 and Der p 5 [108,109], and Blo t 10 and Der p 10 (tropomyosin). Most group 5 studies demonstrated low-to-moderate cross-reactivity at the molecular level. Less information is available about group 10 allergens.

The allergenic cross-reactivity between *L. destructor* and *B. tropicalis* was initially demonstrated by specific IgE inhibition studies using whole allergen extracts. The participation of group 2 in the cross-reactivity between these two species has also been suggested [110]. Cross-reactivity among group 2 allergens from nonpyroglyphid mites, such as *L. destructor*, *T. putrescentiae*, and *G. domesticus*, is greater than with Der p 2. A homologous allergen

to Blo t 13 has also been identified in *L. destructor*. These allergens may also contribute to the high degree of cross-reactivity among nonpyroglyphid mites. Group 13 also seems to contribute to the cross-reactivity between *B. tropicalis* and *D. siboney*. Der p 10 and Blo t 10 share 95% of amino acid identity and have a significant degree of cross-reactivity. However, they have unique IgE-binding epitopes. The results suggest the potential deficiency of using only one of these highly conserved allergens as diagnostic or therapeutic reagents.

Dermatophagoides spp.—allergic individuals may experience allergic symptoms after consumption of crustacean and mollusks. Der f 10 and Der p 10 proteins with homology to tropomyosin from various animals are involved in the cross-reactivity among *Dermatophagoides* spp., mollusks, and crustaceans. The 36 kDa cross-reactive tropomyosin present in mites, various insects (chironomids, mosquito, and cockroach), and shrimp [111] is responsible for cross-reactivity among different arthropods [112]. In addition, a 25-kDa allergen present in several arthropod groups also seems to be involved in this cross-reactivity.

Immunochemical studies have demonstrated that allergens from snails, crustaceans, cockroaches, and chironomids cross-react with house dust mite allergens. However, house dust mites are usually the primary source of sensitizing allergens.

The nematode *Anisakis simplex*, a common fish parasite, can act as a hidden food allergen, inducing IgE-mediated reactions. Allergic cross-reactivity between this nematode and the domestic mites *A. siro*, *L. destructor*, *T. putrescentiae*, and *D. pteronyssinus* have been reported, in which tropomyosin seems to be involved. The clinical relevance of this cross-reactivity needs to be further investigated [113].

The feather mite *Diplaegidia columbae* is a major source of clinically relevant allergens for pigeon breeders. The results of RAST inhibition experiments suggest that this feather mite cross-reacts with *D. pteronyssinus* [114]. Arlian *et al.* [115] demonstrated that antigens of the parasitic mite *Sarcoptes scabiei* cross-react with antigens of *D. pteronyssinus*. More recently, proteins with homology to different groups of mite allergens have been identified by molecular cloning in the parasitic mites *S. scabiei* [116] and *Psoroptes ovis* [117].

Conclusions

The clinical relevance of all these phenomena of cross-reactivity is not well understood. However, it is well established that mites contain species-specific, as well as cross-reactive, epitopes. At the molecular level, mites may have very similar allergens, but small discrepancies in amino acid sequences can determine the recognition, or not, by an allergic patient. The intensity of the exposure to the allergen, its similarity, and the genetic background of an individual will condition the degree of cross-reactivity of two different mite allergens.

In the case of patients with positive skin tests to several species, provocation tests (conjunctival, nasal, or bronchial) may be needed for a more accurate diagnosis, or more effective treatment.

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