

Review article

Allergen cross-reactivity between house-dust mites and other invertebrates

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Introduction

House-dust mites (HDM) are important sources of indoor allergens (1–3). In the general population, the prevalence of HDM sensitization is 9–16% (4–6); for some groups, the prevalence may locally amount to 26–43% (2, 7). HDM sensitization may give rise to rhinitis in half of the cases (5), and it markedly increases the risk of asthma (2, 6, 7). Our understanding of the cross-reactivity between HDM allergens and other allergens is still limited; thus, particularly from a clinical point of view, it is of interest to know whether or how HDM sensitization changes patients' reaction to allergens from other sources. This will have consequences for the inter-

pretation of the skin prick test (SPT) and specific IgE in the individual patient as well as in epidemiologic studies.

Simultaneous sensitization to two or more allergens in a frequency higher than the chance expectation is termed "covariation of sensitization". The phenomenon may originate from cross-reactions or be caused by parallel sensitization. Cross-reaction occurs when an antibody originally raised against one allergen binds to a similar allergen from another source; the term "parallel sensitization" is to be used when a patient's different IgE antibodies bind to different allergens.

The discovery of possible cross-reacting allergens is often the result of epidemiologic studies or clinical observations of covariation of sensitization. Homology as shown by gene sequencing may also indicate possible cross-reacting allergens.

Cross-reactivity is mainly confirmed by immunochemical techniques, i.e., inhibition tests, primarily RAST inhibition (8), ELISA inhibition, and immunodot inhibition. Among other IgE-based techniques are

Abbreviations. CIE: crossed-immunoelectrophoresis; CRIE: crossed-radioimmuno-electrophoresis; ELISA: enzyme-linked immunosorbent assay; HDM: house-dust mite; IT: immunotherapy; mAb: monoclonal antibody; RAST: radioallergosorbent test; SDS-PAGE: sodium dodecyl sulfate-polyacrylamide gel electrophoresis; SPT: skin prick test.

CRIE, SDS-PAGE, and immunoblotting (Western blot). These semiquantitative systems are not suited for the monitoring of small variations in the concentration of an allergen. Techniques based on animal antibodies comprise electrophoresis or precipitation-in-gel methods, such as crossed immunoelectrophoresis (CIE) and ELISA-type sandwich assays. If cross-reacting allergens are identified by immunochemical tests with animal antibodies, we may hypothesize that the subjects possess a similar IgE-mediated cross-reacting immune response, but a proper demonstration has to include sera from such patients. If a cross-reaction with IgE in patient sera is shown, we may assume that the cross-reacting allergen causes allergic reactions, but this does not allow us to determine whether the reaction is of any clinical consequence for the patient. This may be determined by a provocation test or at least an unequivocal anamnesis.

HDM allergens have been proposed to cross-react with allergens from other invertebrates including other species of mites, insects, mollusks, and crustaceans. Their taxonomic relationships are indicated in Fig. 1.

Allergens from mites

Pyroglyphid mites

In *Dermatophagoides* species, 12 allergen groups, Der 1–11 and Der 14, have been identified (Table 1) (9–31). Due to microheterogeneity within and between species, the allergens are also referred to as groups. Allergens of groups 12 and 13 have been described for other mites (*Acarus siro* and *Blomia tropicalis*), and are thought to exist for *Dermatophagoides* as well (32). Unless otherwise stated, the term “HDM” will refer to the species *D. pteronyssinus* and *D. farinae*.

Although the genes for Der 1, 2, and 3 are present as single loci in the mite genome, the alleles show a high degree of polymorphism (9). This variation in mite allergens is revealed by geographic diversity, and by differences observed between mites from cultures and from the environment – and not least – in a diversity in results of tests for cross-reactivity. Der f 1 and Der p 1 induce both cross-reacting and species-specific antibodies (11, 33, 34). IgE antibodies to Der f 2 and Der p 2 are known to cross-react almost completely (33), or less intensively (35). The identification of Der 10, or HDM tropomyosin, has drawn special attention to the cross-reactivity between HDM and other invertebrates. Tropomyosin is a muscle protein present throughout the animal kingdom. Der f 10 and Der p 10 have 98% homology (36); therefore, cross-reactivity may be expected. In contrast, HDM tropomyosin and human tropomyosin have less than 56% homology (36). Extracts of

used culture medium may contain 1000 times less tropomyosin than whole-body extracts (26). Thus, in cross-reaction studies including tropomyosin, the source of the HDM extract should be taken into account.

The majority of HDM-allergic patients are co-sensitized to *D. pteronyssinus* and *D. farinae* (37). These are the most prevalent HDM, and allergens from both species are normally present in any sample of house dust from most of the temperate to the tropical zones. In theory, the cosensitization might be due to parallel sensitization, but it may also be a consequence of the existence of several cross-reacting allergens (38). IgE immunoblots to HDM are less heterogeneous in patients sensitized only to HDM than in patients also sensitized to other common inhalatory allergens (39). In children and in adults known to be sensitized in their childhood, reactivity to Der 2 and, to a lesser extent, to Der 1 predominates, with additional reactivity to one, two, or three other allergens; the latter occurs only in children older than 3 years of age (16). In contrast, lower IgE-binding to Der p 1 and 2 is seen in newly diagnosed adults (15), but with reactivity to a diverse array of other HDM allergens, including Der 3 and Der 4 (40, 41).

The *Dermatophagoides* species *D. siboney* is known from subtropical and tropical areas; but 100% of Swedish HDM-allergic patients, although, presumably, not exposed to *D. siboney*, are SPT-positive to this species (42). As parallel sensitization to *D. siboney* seems unlikely, this reaction is probably due mainly to cross-reactivity. A strong cross-reactivity exists between *D. siboney* and the three species of *Dermatophagoides* known to occur in Sweden, *D. farinae*, *D. microceras*, and *D. pteronyssinus*, and is most pronounced for proteins with molecular masses of 65, 62, 37, and 30 kDa (43).

Euroglyphus maynei is a less common pyroglyphid mite with an endemic pattern of occurrence. A significant relationship between specific-IgE concentration against HDM and *E. maynei* has been found (44, 45), and all of 250 suspected allergic patients positive in SPT with *E. maynei* also demonstrated positive SPT to HDM (45). In these two studies, HDM extract exerted a much higher degree of inhibition of the *E. maynei* system than *E. maynei* did of the HDM system. CIE has shown that *E. maynei* has from four to six antigens in common with HDM (46). Most *E. maynei* allergens, however, also possess species-specific epitopes (47). Sera from HDM-sensitized patients show IgE-binding to the majority of allergen bands from both HDM and *E. maynei* in Western blotting (48). The *E. maynei* group 1 allergen (Eur m 1) shows 85% sequence homology with Der p 1 (49), but there is only modest T-cell cross-reactivity with HDM (50). Der p 4 and Eur m 4 have nearly 90% identical amino-acid sequences, but,

Table 1. Known allergens of house-dust mites

Allergen	Homology %	kDa	Description	Prevalence of HDM allergics reacting to allergen(s) in %
Der p 1 Der f 1	80	24	Cystein proteases	40–100
Der p 2 Der f 2	88	14	Like epididymal protein	70–96
Der p 3 Der f 3	81	25	Trypsin-like	16–100
Der p 4 Der f 4	—	56–63	Amylase	25–50
Der p 5 Der f 5	—	14	—	40–60
Der p 6 Der f 6	75	25	Chymotrypsin	39–41
Der p 7 Der f 7	86	26–31	—	40–52
Der p 8 —	—	26	Glutathione-S-transferase	40–50
Der p 9 —	—	24–68	Collagenolytic enzyme	92
Der p 10 Der f 10	98	37	Tropomyosin	41–81
Der f 11 —	—	98	Paramyosin	61–88
Der p 14 Der f 14	—	190	Apolipoprotein	—

Der m 1 is also known. Its N-terminal end shows 70% homology with Der p 1 and 93% with Der f 1. Source: Thomas & Smith (9) and other works (10–31).

surprisingly, none of the HDM-sensitized patients with IgE against Der p 4 had IgE against Eur m 4 (51).

Sera from HDM-sensitized patients show IgE-binding to most allergen bands from fecal and body extracts of HDM and to the mite *Gymnophagus longior* in Western blotting (48). *G. longior* is closely related to *E. maynei* and is known from agricultural environments, but is only occasionally seen in house dust (52–54).

Storage mites

Storage mites are microbial grazers on decaying biologic matter in the open, but they are mainly known to us from their occurrence in stored products. A typical test panel comprises *Acarus siro*, *Tyrophagus putrescentiae*, *Lepidoglyphus destructor*, and *Glycyphagus domesticus*. Testing by one or more of these species along with HDM has provided contradictory results. Most investigations have found a positive covariation of sensitization to storage mite and HDM (55–66). In HDM-allergic patients, the sensitization to storage mite is in the range of 60–88% (66–68). Some studies, however, found no covariation (69–73).

Most reports confirm that HDM extracts inhibit storage-mite-specific IgE-binding (*A. siro*, *T. putrescentiae*, *L. destructor*) and vice versa (61, 62, 66, 67, 74–77); one study even found no cross-reactivity (73). HDM seem to cross-react more strongly to *A. siro* and *T. putrescentiae* than to *L. destructor* (61). Generally, HDM are stronger inhibitors of *A. siro*/*T. putrescentiae*-specific IgE-binding than vice versa (61, 62, 74, 76). *L. destructor* extract may show stronger inhibition of HDM allergens than vice versa (77); similarly, HDM extract seems to be a weak inhibitor of the binding of anti-L d mAbs to *L. destructor* antigen (78).

Results from CIE/CRIE indicate that HDM and *T. putrescentiae* have two similar allergens (79), and that

HDM and *A. siro* have one (76). A 25-kDa component is responsible for the cross-reactivity between HDM and *A. siro*/*T. putrescentiae* (74). A supplementary 16–18-kDa component, believed to be Der 2 for HDM, is involved in the cross-reactivity between HDM and *T. putrescentiae* (75). Der 1 is inhibited to the same extent by *D. pteronyssinus* and *L. destructor* extracts in inhibition tests, while the cross-reactivity between Der 2 and *L. destructor* was found to be less extensive (77). Other research did not find any Lep d 1 inhibition of HDM-specific IgE-binding (80). The amino-acid sequence homology of Der 2 and Lep d 2 is 43%. For Der p 2 and Tyr p 2, this figure is 41%; between Der f 2 and Tyr p 2, there is 43% sequence homology (81, 82).

Blomia tropicalis is known from house dust in subtropical and tropical areas. In Swedish HDM-allergic patients possibly not exposed to those tropical mites, 86% still had a positive SPT for *B. tropicalis* (42), in parallel to the findings for *D. siboney* mentioned above. However, in another group unexposed to *B. tropicalis*, only a few HDM-allergic patients had IgE to Blo t 5 (83). *B. tropicalis* extract was able, to a low to moderate degree, to inhibit HDM-specific IgE-binding and vice versa in atopic patients in Colombia and Singapore (66, 84). CIE/CRIE results suggested that HDM and *B. tropicalis* had two to four similar allergens (84, 85). Dot-plot inhibition studies indicated that the cross-reactive allergens are not closely related to Der p 1, Der p 2, and Der p 5, and only a moderate cross-reactivity was shown between the recombinant Der p 5 (rDer p 5) and rBlo t 5 (84). Sequence homology between Der p 5 and Blo t 5 was found to be 43% (83).

Positive covariation of sensitization was found between HDM and *Aleuroglyphus ovatus* (8), a storage mite similar to *A. siro*. There was slight to moderate cross-reactivity between HDM and *A. ovatus* (8, 86), *Chortoglyphus arcuatus* (86), and *Goiheria fusca* (67), while HDM extract was not able to inhibit *G. domesticus* (73).

Phylum ARTHROPODA

Subphylum Chelicerata

Class ARACHNIDA	
Order Sarcoptiformes	
Acaridae (F)	<i>Acarus siro</i> <i>Tyrophagus putrescentiae</i> <i>Aleuroglyphus ovatus</i>
Glycyphagidae (F)	<i>Glycyphagus domesticus</i> <i>Lepidoglyphus destructor</i> <i>Blomia tropicalis</i>
Chortoglyphidae (F)	<i>Chortoglyphus arcuatus</i>
Carpoglyphidae (F)	<i>Goiheria fusca</i>
Pyroglyphidae (F)	
Pyroglyphinae (SubF)	<i>Euroglyphus maynei</i> <i>Gymnoglyphus longior</i>
Dermatophagoidinae (SubF)	<i>Dermatophagoides farinae</i> <i>Dermatophagoides pteronyssinus</i> <i>Dermatophagoides microceras</i> <i>Dermatophagoides siboney</i>
Sarcoptidae (F)	<i>Sarcoptes scabiei</i>
Psoroptidae (F)	<i>Psoroptes cuniculi</i> <i>Psoroptes ovis</i> <i>Otodectes cynotis</i>
Order Trombidiformes	
Tetranychidae (F)	<i>Tetranychus urticae</i> <i>Panonychus citri</i>
Ereynetidae (F)	<i>Riccardoella limacum</i>
Cheletoidea (SuperF)	
Cheyletidae (F)	<i>Cheyletus eruditus</i>
Demodicidae (F)	<i>Demodex folliculorum</i>

Subphylum Antennata

Class CRUSTACEA	
Order Decapoda	
Suborder Natantia	<i>Penaeus aztecus</i> <i>Metapenaeus ensis</i>
Suborder Reptantia	<i>Palinurus strimponi</i> <i>Homarus americanus</i> <i>Charybdis feriatus</i>
Class INSECTA	
Order Thysanura	<i>Lepisma saccharina</i>
Order Blattaeformia	<i>Blattella germanica</i> <i>Periplaneta americana</i>
Order Diptera	
Chironomidae (F)	<i>Chironomus tummi</i>

Phylum MOLLUSCA

Class GASTROPODA	
Order Pulmonata	<i>Helix sp.</i>
Class LAMELLIBRANCHIA	<i>Mytilus sp.</i> <i>Ostrea sp.</i>

Phylum CHORDATA (vertebrate)

Homo sapiens

Figure 1. Taxonomic relationship of species referred to in this paper where cross-reactivity with house-dust mite was shown or suspected.

Mange and spider mites

Positive covariation between sensitization to HDM and sensitization to *Sarcoptes scabiei* is known (87–91). First-time scabies patients had a higher prevalence of HDM sensitization than a matched control group (87, 88); and HDM-sensitized patients with no history of scabies were seen to have a positive skin test to *Sarcoptes* more frequently than the controls (89). Both atopic and nonatopic patients were found to be HDM-IgE positive during the scabies infestation. One year after successful treatment, most of the nonatopic patients had no HDM IgE, whereas HDM IgE persisted in the sera of the majority of the patients with atopy (90).

IgE from scabies patients binds both species-specific and HDM-cross-reacting *Sarcoptes* allergens (91). Three to seven antigens, of which one to five are believed to be allergens, are involved in the formation of rabbit anti-HDM/*Sarcoptes* extract precipitates (92, 93). The responsible HDM allergens are not known.

This cross-reactivity may play an important role in susceptibility to scabies and thereby to its clinical manifestations. Severe skin reactions occur in HDM-sensitized patients suffering scabies infestation (87). Protection against scabies infestation in 71% of

rabbits after IgE immunization with HDM was seen in another study (94). The cross-reaction may also provide the basis for an overdiagnosing of HDM sensitization in patients with scabies months before.

All seven HDM-sensitized patients tested had a positive SPT to the cat and dog ear mite *Otodectes cynotis* (95). A slight cross-reactivity seems to exist between HDM and the rabbit mange mite *Psoroptes cuniculi*, the sheep mange mite *Psoroptes ovis*, and the predator mite *Cheyletus eruditus*, possibly related to the group 4 mite allergens and, for the mange mites, probably also to the group 12 (96, 97). Covariation in sensitization, as well as cross-reactivity, is found between HDM and the spider mites *Tetranychus urticae* and *Panonychus citri*, which are parasites of plants (98). We found no information on cross-reactivity between HDM and the mite *Demodex folliculorum*, an obligate parasite of the human skin and an obvious candidate for testing. *Demodex* is closely related to *C. eruditus*.

Inhalation allergens from insects

Cockroaches

Covariation between sensitization to cockroach and

HDM has been shown (99, 100), although this was less convincing or doubtful in other studies (101, 102). In areas with high cockroach load, sensitization to cockroach was higher than in areas with low density of cockroach, although sensitization to HDM was similar (102). Positive covariation of sensitization to cockroach and HDM might be partly explained by coexistence of the allergens in the environment. Thus, sensitization to HDM does not fully explain that to cockroach.

HDM and cockroach cross-react in inhibition tests in the majority of sera (103, 100), although they do not always do so (104). In such reactions, HDM turned out to be a stronger inhibitor of cockroach-specific IgE-binding than vice versa (103, 100). Cockroach reacts to mAbs raised against HDM tropomyosin (105), and this protein may therefore be involved in the cross-reaction. The homologous major allergens from the American cockroach *Periplaneta americana* (Per a 1) and the German cockroach *Blattella germanica* (Bla g 1) are not involved in the cross-reactivity (106, 107), but allergens other than tropomyosin are probably also involved (100). In our opinion, it is possible that part of the cross-reactivity may originate from irrelevant allergens in the cockroach cultures, as it is difficult to raise these insects without a contamination of storage mites. Mite contamination is known from extracts based on dog dander (108), cat dander (109), and hen's feather (110).

The clinical importance of the cross-reactivity between cockroach and HDM is unknown. Studies with provocation tests might be a way to approach the question, but this method is laborious and involves an element of risk for the patient. Probably the histamine-release assay could often replace the provocation test in estimation of the clinical relevance of the cross-reactivity between HDM and cockroach (111).

Silverfish and chironomids

Positive covariation of sensitization to HDM and both silverfish (*Lepisma saccharina*) and chironomids (Diptera, Chironomidae) is reported in some (65, 100, 112–114), but not all studies (115, 116).

HDM extracts inhibit chironomid- and silverfish-specific-IgE binding strongly in most sera, while these insects only partially can inhibit HDM-specific IgE-binding. In this context, tropomyosin seems to play only a minor role (100). No cross-reactivity was found between HDM and silverfish/chironomids in other studies (112, 117); similarly, HDM extract showed no reaction with sera from chironomid-immunized rabbits (118). However, mAb to shrimp tropomyosin reacted with chironomids as well as HDM (105). In comparison of chironomid-sensitized

patients with and without occupational exposure to chironomids, the exposed group was monosensitized to chironomids and primarily had IgE against the main chironomid allergen Chi t 1 (from *Chironomus thummi*), while the occupationally unexposed group had IgE against several protein bands from chironomids, HDM, shrimp, and mosquito. Proteins with masses of 25 and 35 kDa were often involved (119). These could represent glutathione S-transferase and tropomyosin. When HDM-induced T-cell clones were stimulated with chironomid extracts, 8% of the clones showed a significant proliferation. The cross-reactive epitopes were thought to be expressed on a HDM molecule of 45–53 kDa (120).

Food allergens from invertebrates

Crustaceans

Case reports have described patients with combined shrimp and HDM allergy (26, 121, 122). In a study of 48 patients allergic to “shellfish” (various species, but mainly shrimp), 82% appeared to be sensitized to HDM as well (121).

Inhibition tests show a multitude of reactions. Sometimes mite extract mainly inhibits shrimp-specific IgE-binding, and sometimes the opposite; this indicates different sensitizing agents (105, 122). Usually, tropomyosin seems to be the protein involved in shrimp–HDM cross-reactivity, and it may be the only allergen involved. Tropomyosin-depleted shrimp extract was 100-fold less potent an inhibitor of HDM-specific IgE-binding than was the normal shrimp extract (105). In shrimp-allergic patients, 82% reacted to tropomyosin, the only major allergen of shrimp (123). Tropomyosin as allergen is identified in the shrimp species *Penaeus aztecus* (Pen a 1) (124) and *Metapenaeus ensis* (Met e 1) (125), and a significant homology is found between them (125). The major allergens of the crab *Charybdis feriatus* (Cha f 1), the spiny lobster *Panulirus stimpsoni* (Pan s 1), and the American lobster *Homarus americanus* (Hom a 1) also show marked homology to Met e 1 (126, 127). Pen a 1 shows more sequence identity to HDM tropomyosin than to vertebrate tropomyosin (128).

In a longitudinal study of 17 HDM-patients receiving immunotherapy (IT), three had IgE against shrimp, and only the two of these having IgE against tropomyosin had oral allergy symptoms after ingesting shrimp. In one, the oral symptoms worsened during immunotherapy (IT) (26).

A clinically relevant cross-reactivity between HDM and at least some species of shrimps seems to exist, and tropomyosin often is the active allergen. The magnitude of the problem still has to be determined.

Snails

Positive covariation of snail and HDM sensitization has been demonstrated in some (129, 130), but not all tested populations (131).

Inhibition tests show that the IgE reactivity to snails generally is inhibited by extract from HDM, whereas IgE reactivity to HDM is not significantly inhibited by snail extracts. Such results imply that HDM usually is the sensitizing agent, and that the sensitization to snail is due to cross-reactivity (122, 131–134). This is further confirmed by clinical findings in those HDM-sensitized patients who have developed allergic reactions to snails while claiming never to have eaten them before (26, 134). Half of the patients with allergy to terrestrial snails also react to marine snails (129). Some terrestrial snails have a mite parasite, *Riccardoella limacum*, but it is not taxonomically close to HDM. SPT with *R. limacum* extract in snail-sensitized patients gave no skin reactions; thus, it is not likely to be responsible for the sensitization (129).

Most often, more than one allergen is involved in the HDM–snail cross-reactivity in a patient. Tropomyosin is involved in only a minority of cases, and here the patients are also sensitized to shrimps (26, 122). Candidate allergens are thermostable molecules not located in any particular organ of the snail (133). The HDM allergens responsible for the HDM–snail cross-reactivity may include Der p 4, Der p 5, Der p 7, and hemocyanin (26, 122, 133).

The eating of snails by HDM–snail-allergic patients may lead to severe symptoms: asthma, anaphylactic shock, generalized urticaria, and/or facial edema (122, 132, 133, 135, 136). In several reports of HDM–snail allergy, the patients had received IT for HDM, and, after snail ingestion, urticaria, erythema, and itch often appeared at the sites of previous IT injections (26, 122, 129, 132, 133, 135). IgE against snail seems to increase in these IT patients, while IgE against HDM remains unaffected (26).

Although clinically important HDM–snail cross-reactivity has been confirmed, the magnitude of the problem is still unknown. Sensitization to snail demonstrated by SPT appeared in 31% of HDM-allergic children in an unselected population (129). About 50% of these children had a positive open labial food challenge with snail, even though they all denied having eaten snails before (129). At the start of HDM IT, 76% of the patients showed sensitization to snail (compared with 13% in a group of *Parietaria*-allergic patients) (26). Furthermore, in 331 patients with respiratory symptoms tested by SPT for aero-allergens, 14 had positive SPT to snail; six of these recalled that they formerly had eaten snails, and four of them already had experienced anaphylactic reactions to snails (130). If these figures represent the

general trend, the HDM–snail cross-allergy might be a problem in countries where snails are a common ingredient in the food.

Bivalves

Covariation of sensitization to bivalves and HDM is known only from case reports of patients allergic to snail/shrimp and HDM who were sensitized to mussel as well (122, 134). Mussels and oysters can bind mAbs raised against HDM tropomyosin (105). Therefore, cross-reactivity between HDM and mussels and oysters is a possibility, but it has yet to be demonstrated adequately.

Conclusion

Cross-reactivity between HDM allergens and allergens from other invertebrates has been suspected to cause or worsen food allergy (snails and crustaceans), inhalation allergy (other mites and cockroach), and local skin reactions (scabies). The importance of such cross-reactivity could be evaluated by provocation tests in relevant organs. Allergens suspected to cause food allergy deserve special attention, and here the clinical relevance of a sensitization needs to be tested by double-blind, placebo-controlled food challenge (unless a record of severe anaphylactic reaction makes this unwise for safety reasons) (137, 138). Antibodies to the allergen to which the patient is primarily sensitized will probably have lower affinity for homologous allergens from other species. This is parallel to the cross-reaction to wheat observed in grass-pollen-allergic patients (139), where low-affinity cross-reacting antibodies may be determined by *in vitro* tests or in the skin, without any clinical symptoms to ingestion of wheat.

For both HDM allergens and the suspected cross-reacting allergens, the animal origin and the production methods of the extract used for testing may vary, as does the exposure of the population studied. This could explain why different centers have reported different results in *in vivo* as well as *in vitro* testing. Basically, allergens from snails, crustaceans, cockroaches, silverfish, chironomids, and other mites have been shown by immunochemical studies, to cross-react with HDM allergens. In the great majority of tests, HDM extract is a stronger inhibitor of the specific IgE-binding to the suspected HDM-cross-reacting allergen than vice versa, indicating that HDM usually is the primary source of sensitizing allergens. The cross-reacting species may have a few similar allergens in common with HDM, but mainly they possess their own unique allergens.

For snails, crustaceans, cockroaches, silverfish, chironomids, and various other mites, a covariation of sensitization to HDM often exists, while the clinical consequences of the cross-reactivity seem to be convin-

ingly documented only for snails, and merely indicated for shrimp and the scabies mite. It seems to be particularly important to know the clinical importance of cockroach and storage mite cross-reactivity with HDM, because of the high prevalence of sensitization to their allergens.

It is interesting that food-induced cross-reactions often seem to occur in HDM-sensitized patients receiving IT. During this treatment, allergens enter the body through an "unnatural" route, and at a higher concentration. This might result in (increased) IgE response to antigens that do not act as allergens under natural conditions.

HDM patients with possible symptoms from the

above-mentioned food and inhalant allergens may require special attention; but, in our opinion, the likelihood of reactions seems to be too low to issue special warnings to HDM-sensitized patients against the suspected allergens.

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