

ARTHROPOD ALLERGENS IN URBAN HOMES

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Dust mites, cockroaches, and pets (cats, dogs) are common in homes worldwide, and many species are the source of potent allergens which cause allergic diseases. These diseases are influenced by genetic predisposition and environmental exposure. Generally, the levels of house dust mite (Der p 1 and Der f 1) and cockroach (Bla g 1, Bla g 2) allergens are used as markers of indoor exposure to arthropods.

This article reviews the findings of allergens Der p 1, Der f 1, and Bla g 1 in randomly selected urban households in Zagreb (Croatia) measured from 2006 to 2010 and compares them with exposure to arthropod allergens in other countries. In short, house dust mite allergen levels in Croatian homes are low, but exposure is common; Der p 1 was found in 73 % and Der f 1 in 83 % of the households. By contrast, exposure to cockroach allergen Bla g 1 was both low and uncommon (13 %). Exposure to multiple allergens associated with sensitisation and asthma was not frequent in urban homes in Croatia. However, further studies should include monitoring of both arthropod and pet allergens in high-risk populations in inland and coastal Croatia. They should also investigate a complex dose-response relationship between exposure and sensitisation/asthma development, especially in early childhood.

KEY WORDS: *Bla g 1, Der f 1, Der p 1, house dust mites, ELISA, indoor allergens*

INDOOR ALLERGENS

Exposure to indoor allergens brings the risk of sensitisation and symptoms of asthma in atopic individuals (1, 2). The major biological sources of aeroallergens in homes are arthropods (dust mites and cockroaches), furred pets (primarily cats and dogs), moulds, and pollen (3-5). Table 1 shows common allergens used for indoor exposure assessment. House dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are a particularly important source of allergens in homes in the temperate climate (6), Der p 1 and Der f 1 in particular (6). The cockroach species *Blattella germanica* (German cockroach) and *Periplaneta americana* (American cockroach) are also the source of potent allergens that can trigger allergic reactions. The primary source of dust mite and cockroach allergens has been identified in faecal

material, and they present a source of inhaled aeroallergens (7). Furthermore, the increasing number of pets (especially cats and dogs) has raised the level of exposure to the allergens produced by these domestic animals in residential and public places (8, 9). While the major cat allergen (Fel d 1) is present mainly on the fur, the primary source of dog allergen, Can f 1, has been identified in the saliva and urine (10). The distribution of all indoor allergens shows regional variations, mainly due to climate factors (11-14).

Allergic diseases are common chronic diseases, and their prevalence is increasing in Croatia and in many European countries (6, 15-18). The gene-environment interactions have a significant role in the sensitisation and exacerbation of childhood asthma, particularly in urban households (2, 3, 11, 19). The outcome of these interactions may be influenced by

other environmental exposures. Indoor air pollution (NO₂ and ozone) and passive exposure to tobacco smoke may potentiate allergic sensitisation and exacerbate the existing asthma (20-22). In addition, outdoor pollution such as traffic-related air pollution and pollen allergens has been also associated with asthma attacks in children and adults in several European countries (23).

Table 1 Major house dust allergens

Source	Allergen
Hose dust mite	
<i>D. pteronyssinus</i>	Der p 1, Der p 2
<i>D. farina</i>	Der f 1, Der f 2
<i>B. tropicalis</i>	Bla t 5
Cockroach	
<i>B. germanica</i>	Bla g 1, Bla g 2
<i>P. americana</i>	Per a 1
Domestic animals	
<i>F. domesticus</i>	Fel d 1
<i>C. familiaris</i>	Can d 1

In this article, exposure to common allergens in households in Croatia has been presented and results were compared with our earlier investigations and with reported exposure in other countries.

CHARACTERISTICS OF ARTHROPOD ALLERGENS

Mite allergens have been well characterised and according to their biological function they are categorised in more than 20 groups of dust mite allergenic proteins (Table 2) (24). The major allergens of *D. pteronyssinus* and *D. farinae* (Der p 1 and Der f 1) are usually used as markers of exposure to house dust mites in the temperate climate. In the tropical climate, the dominant mite species is *B. tropicalis*, and its major allergen Blo t 5 has been used to assess indoor exposure (25).

Cross-reactivity between Der p 1 and Der f 1 is higher than 80 % (26). Another source of cross-reactivity is the group 10 mite allergen tropomyosin, also shared by cockroaches and invertebrates such as squid, crab, and lobster. Exposure to tropomyosin through food may lead to sensitisation to dust mites and vice versa (25). In contrast, allergens from *B. tropicalis* share low-to-moderate cross-reactivity to allergens of other dust mites (25).

Similar to mites, cockroaches produce potent allergens (6, 27). While *B. germanica* is common in Europe and North America, *P. americana* is dominant

Table 2 Categorisation and characteristics of common house dust mite allergens

Group	Allergens	Biological function
1	Der p 1, Der f 1, Blo t 1	Cysteine protease
2	Der p 2, Der f 2, Blo t 2	Niemann-Pick C2 homologue
3	Der p 3, Der f 3, Blo t 3	Trypsin
4	Der p 4, Blo t 4	Amylase
5	Der p 5, Blo t 5	Unknown
6	Der p 6, Der f 6	Chymotrypsin
7	Der p 7, Der f 7	Unknown
8	Der p 8	Glutathione-S-transferase
9	Der p 9	Collagenolytic protease
10	Der p 10, Der f 10, Blo t 10	Tropomyosin
11	Der p 11, Der f 11, Blo t 11	Paramyosin
12	Blo t 12	Unknown
13	Blo t 13	Fatty-acid binding protein
14	Der p 14, Der f 14	Vitellogenin-apolipoprotein like
15	Der f 15	Chitinase
16	Der f 16	Gelsolin
17	Der f 17	Calcium binding protein
18	Der f 18	Chitinase-like
19	Blo t 19	Antimicrobial peptide
20	Der p 20	Arginine kinase
21	Der p 21, Blo t 21	Unknown

Der p, *Dermatophagoides pteronyssinus*; *Der f*, *Dermatophagoides farinae*; *Blo t*, *Blomia tropicalis*

in the tropical countries (6). Cockroach allergens are found in its saliva, faeces, secretions, and dead body. Up to now, 10 cockroach proteins have been identified as allergens in both cockroach species (24). Among them, Bla g 1 and Bla g 2 are the major allergens and they have been commonly used as markers of exposure to cockroach allergens. Bla g 1 and Per a 1 (*P. americana*) are cross-reactive, while Bla g 2 is species-specific (24). Bla g 7 and Per a 7 are tropomyosin, a major allergic component accounting for the cross-reactivity between dust mites and cockroaches (24).

AERODINAMIC DIAMETER OF INDOOR ALLERGENS

Table 3 shows the aerodynamic properties of common indoor allergens. Arthropod allergens have different aerodynamic diameters and distribution than the allergens of pet dander, moulds, and pollen (17, 28). Mite allergens are mostly associated with large particles (25 µm in diameter), which are not respirable. However, a small portion of Der p 1 is associated with particles smaller than 10 µm, which are respirable and may cause airway inflammation in the lung. Similarly, about 80 % of cockroach allergens Bla g 1 and Bla g 2 are carried on relatively large particles (range 5 µm to 40 µm in diameter) (29, 30).

Cat (Fel d 1) and dog (Can f 1) allergens are associated with both large and small particles (Table 3). About 75 % of Fel d 1 is carried on particles >9 µm in diameter. However, a considerable amount of Fel d 1 is associated with fine particles of <5 µm in diameter, that are respirable and remain airborne for a long time (28, 10, 31). Bioaerosol settling is influenced by environmental and physical parameters

such as (temperature, relative humidity and air currents) (32). Allergens in settled dust become airborne by human activity (vacuum cleaning) and air currents (17, 31).

DETECTION OF ALLERGENS

Threshold values for indoor allergens

The dose-response relationship between allergen exposure and sensitisation has well been described in the literature (3-6). Figure 1 shows the generally accepted threshold values (for sensitisation and disease) for common indoor allergens in settled dust. Exposure to mite allergens Der p 1, and Der f 1 of 2 µg g⁻¹ and 10 µg g⁻¹ of dust has been regarded as a risk factor for sensitisation and asthma, respectively. However, in sensitised individuals with mild asthma, repeated exposure to low allergen level may lead to chronic asthma (18).

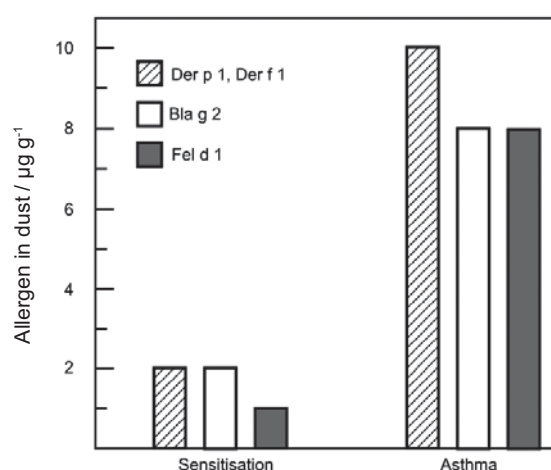


Figure 1 Allergen exposure thresholds for sensitisation and allergic diseases

Table 3 Aerodynamic properties of common indoor allergens

Source	Allergen	Particle size	Ref.
Mite	Der p 1, Der f 1	Large particles, 25 µm	7, 29
Cockroach	Bla g 1, Bla g 2		
Cat	Fel d 1	Large particles >10 µm (75 %) Small particles <5 µm (25 %)	10, 28, 62
Dog	Can f 1		
Moulds	Alt a 1	Large particles, 10 to 40 µm	77
<i>A. alternata</i> <i>A. fumigatus</i>	Asp f 1	Small particles <5 µm	
Grass pollen	Phl p 5	Small particle, 0.5 to 2.5 µm	78
	Lol p 5	Larger particles >7.2 µm	

Allergen sampling

Allergens of mites and cockroaches have usually been quantified in reservoir dust (floors, carpets, or beds) due to their extremely low air concentration. In contrast, cat and dog allergens are measured both in air-borne and dust-borne samples (33-35).

ELISA measurement

Currently, capture enzyme-linked immunosorbent assay (ELISA) is the gold standard for indoor allergen analysis (3, 4, 36, 37). In our previous studies, we used the following monoclonal antibodies (mAb) for capture: anti Der p 1 (clone 5H8), anti Der f 1 (clone 6H8), and anti-Bla g 1 (clone 10A6). Der p 1 and Der f 1 were detected using biotinylated mAb 4C1, while Bla g 1 was detected using the polyclonal rabbit serum anti-*B. germanica*. Several years ago, a fluorescent multiplex array was developed for simultaneous

measurement of six indoor allergens from a single sample (38). This array is especially suitable for large epidemiological studies involving hundreds of samples analysed for multiple allergens.

EXPOSURE TO ARTHROPOD ALLERGENS

Mites

Most homes in the temperate climate are inhabited by multiple mite species (39). *D. pteronyssinus* and *D. farinae* dominate the inland and coastal Croatia. However, the coastal areas also report *Blomia* spp, *Lepidoglyphus* spp., and *Glycyphaus* spp (about 10 %), mainly due to higher air temperature (14). Table 4 shows the median Der p 1 and Der f 1 in living room dust samples of the general population in inland Croatia (Zagreb). Mite allergens are common in Zagreb; however, their levels are low (36). In the coastal Croatia, Der p1 level is significantly higher than inland, which suggests that exposure to mite allergens varies with climate (14). Similar inter-regional differences in mite populations and allergen levels were observed in Spain (40). The population dynamic of dust mites is influenced by temperature, humidity, and housing characteristics (heating, ventilation) (14, 41, 42).

Table 5 shows exposure profiles to mite allergens in floor dust (uncarpeted) in different geographic locations worldwide. There are large qualitative and quantitative differences in mite allergen levels between countries. Even though exposure to mite allergens is extremely low in Iceland, sensitisation is higher than expected (9 %) (43). The highest levels of Der p 1 were reported in Australia and New Zealand (Table

Table 4 Distribution of mite and cockroach allergens in household dust (Zagreb, Croatia)

Allergen	Number of samples / %	Median	Ref
Der p 1		0.32 µg g ⁻¹	36
Detectable	73		
> 2 µg g ⁻¹	13.3		
> 10 µg g ⁻¹	3.3		
Der f 1		0.35 µg g ⁻¹	36
Detectable	83		
> 2 µg g ⁻¹	6.6		
> 10 µg g ⁻¹	10		
Bla g 1		0.74 U g ⁻¹	37
Detectable	13.3		
> 2 U g ⁻¹	3.3		
>8 U g ⁻¹	0		

Table 5 Mite allergens (µg g⁻¹) in floor dust samples (median or geometric mean)

Der p 1	Der f 1	Population, n	City, Country	Ref
<LOD	<LOD	General, 197	Reykjavik, Iceland	43
0.035	0.27	General, 578	Hamburg, Germany	53
0.15	0.83	General, 44	Pavia, Italy	46
0.26	0.75	High-risk, 750	Northeastern United States	79
0.77		High-risk, 369	Barcelona, Spain	40
0.94		High-risk, 76	The Netherlands	80
1.36		High-risk, 624	Ashford, United Kingdom	40
1.59		General, 40	Hong Kong, China	51
9.04		High-risk, 481	Menorca, Spain	40
9.37		High-risk, 590	Sydney, Australia	44
17.2		High-risk, 447	Melbourne, Australia	45

LOD, limit of detection

5). In parts of the coastal Australia, concentrations of Der p 1 exceeded the higher threshold of $10 \mu\text{g g}^{-1}$ in about 80 % of homes (44, 45). In Croatia by contrast, Der p 1 and Der f 1 exceeded this threshold in less than 10 % of homes (36). Similarly, about 10 % to 15 % of homes in the United Kingdom and Italy exceeded this threshold (46, 47). The distribution of dust mite species differs between tropical and temperate areas. *B. tropicalis* dominates in tropical and sub-tropical climates. High level of Blo t 5, a major allergen of *B. tropicalis*, was reported in Singapore house dust (48).

In addition, several studies have shown that mite allergen levels were higher in carpeted bedrooms than in uncarpeted rooms in the same dwelling (49). Antens et al. (50) reported six to fourteen times lower dust mite allergen concentrations in uncarpeted than carpeted floors. In addition to floor dust, mite allergens have also been determined in mattress dust (12, 51) and beds (52).

Cockroaches

German cockroach (*B. germanica*) is the dominant species in Croatia. Our previous study showed low exposure to Bla g 1, a major allergen of the German cockroach, in the general population of Zagreb (37). In most samples Bla g 1 was below the limit of detection, and only 3.3 % of the samples had Bla g 1 above the sensitisation threshold of 2 U g^{-1} . Similarly low exposure to cockroach allergens has been reported in Germany (53) and in Canada (20). In contrast, Bla g 1 or Bla g 2 levels were considerably higher in residential dust samples collected in the homes of asthmatic children of low socioeconomic status in the US (6, 54). Bla g 1 was the predominant indoor allergen and a major risk for children with asthma in urban homes in the US (55-59). The frequency of allergy to cockroach in the asthmatic population of the US is much higher (about 50 %) than in Germany (4.2 %) (60) and Croatia (9.6 %) (61). Therefore, rare allergies to cockroach in these European countries correspond to low Bla g 1 and Bla g 2 levels in house dust samples.

EXPOSURE TO CAT AND DOG ALLERGENS

Cat allergens can be found in cat-free homes, public places, and workplaces ($>1 \mu\text{g g}^{-1}$) where they are brought by their owners (8, 34, 62). Generally, the

levels of airborne cat allergens in cat-free homes can suffice to cause sensitisation and symptoms in atopic individuals (62). As expected, the levels of cat and dog allergens (Fel d 1 and Can f 1, respectively) in houses with cats and dogs is much higher ($>100 \mu\text{g g}^{-1}$) than in cat- or dog-free environments (34, 62). Parvaneh et al. (34) found a moderately strong correlation between airborne and dustborne Fel d 1 levels in homes with cats. Generally, exposure to cat and dog allergens in homes and public places is much higher than exposure to mite and cockroach allergens. For example, in homes with cats, the level of Fel d 1 was found to be about 100 times higher than the level of Der p 1 (34, 62).

ENVIRONMENTAL CONTROL

Environmental control is a part of a wide strategy to treat allergic patients and to reduce the severity of asthma (28). Allergen avoidance makes part of the primary prevention for infants at high risk of developing allergic diseases and secondary prevention for patients with established sensitisation and diseases (28). HEPA air cleaners have a beneficial role in patients sensitised to pet allergens, as they efficiently capture the relatively small particles carrying pet allergens (63). However, air cleaners are not efficient in reducing exposure to house dust mite allergens (10). Other measures are used instead, including encasing mattresses and pillows with impermeable covers, removing the carpets, minimising upholstered furniture, vacuuming with a HEPA filter, and washing all bedding in the hot cycle ($60 \text{ }^\circ\text{C}$) (28).

In combination with these avoidance measures, keeping the humidity below 50 % and increasing bedroom ventilation can also help to reduce the levels of indoor allergens (12). However, cockroach allergens may be more difficult to remove from homes even if the cockroach population has been substantially downsized (27). Measures for reducing indoor reservoir allergens and for asthma prevention have been described in detail elsewhere (4, 12, 19, 28, 49, 63-65).

CLINICAL ASPECTS

Indoor allergens and asthma

A dose-response relationship between the level of exposure to dust mite allergens and sensitisation has

been well documented (66) (Figure 1). Particularly high levels of dust mite allergens ($>10 \mu\text{g g}^{-1}$) in early childhood have been associated with frequent and severe asthma development in atopic children (18, 66). Exposure to cockroach (19, 57, 59) and cat (45) allergens has also been associated with sensitisation in genetically predisposed children. All this suggests that infancy may be a critical time for exposure to common indoor allergens and later development of asthma. However, although the relationship between allergen exposure and asthma is widely accepted, several recent studies challenge this dose-response concept (67-70). Tovey et al. (69) found a nonlinear relationship between high-level exposure ($>23.4 \mu\text{g g}^{-1}$) to Der p 1 and the prevalence of asthma and eczema. Exposure to high levels of this allergen is common in the coastal Australia. Similarly, Torrent et al. (40, 70) found a nonlinear relationship between exposure to Fel d 1 and sensitisation in small children. Some authors suggest that early high-level exposure to Fel d 1 ($>20 \mu\text{g g}^{-1}$) is associated with higher production of specific IgG4 antibody and decreased cat-specific IgE response, which could result in better protection against sensitisation (62, 71, 72). This induction of tolerance to Fel d 1 could actually reduce the risk of allergy development (11, 18, 71)

In addition to mite, cockroach, and pet allergens, mould and pollen allergens, viral infections, and especially tobacco smoke may contribute to the development of sensitisation and respiratory diseases (2, 10, 73).

Hygiene hypothesis

This so-called *hygiene hypothesis* suggests that increased exposure to bacterial endotoxins in early childhood protects against allergy and asthma by inhibiting Th2-type immune responses (1, 18). Although early endotoxin exposure may be protective against atopy, it can present a risk for wheeze in sensitive children (66). Gehring et al. (74), showed an inverse relationship between indoor endotoxin levels and the occurrence of asthma, but not for rhinitis (74). Domestic animals are usually a source of endotoxin, and keeping a cat or dog in the first year of life may reduce a child's risk of allergic disease (72). Similarly, other studies showed a lower prevalence of allergic diseases among rural adolescents raised on a farm with animals than among children growing up in urban environments without animals (75, 76). Platts-Mills et al. (71) suggested that endotoxin exposure may

prevent allergen-specific Th2 cytokine production and direct it toward a Th1-type response.

CONCLUSION

The incidence of allergic diseases has been increasing in many developed countries over the last few decades. Despite many advances in understanding the factors associated with the development of asthma, the natural history of asthma is not absolutely clear. A better characterisation of indoor allergens (molecular structures of allergens, biological functions) and investigations into the genetic susceptibility of atopics to these allergens could help to understand the complex gene-environment interactions and the basic mechanisms of allergy development.

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Sažetak**ALERGENI ARTROPODA U GRADSKIM STANOVIMA**

Prašinske grinje, žohari i kućni ljubimci (mačka, pas) česti su u stanovima širom svijeta, a mnoge vrste su izvor jakih alergena koji uzrokuju alergijske bolesti. Uzroci alergijskih bolesti su genetska predispozicija i utjecaj okoliša. Alergeni prašinskih grinja (Der p 1 i Der f 1) i žohara (Bla g 1 i Bla g 2) pokazatelji su izloženosti artropodima u kućanstvu. U ovom je radu prikazana izloženost alergenima Der p 1, Der f 1 i Bla g 1 u neselektivnim, urbanim kućanstvima u Zagrebu (Hrvatska) tijekom 2006.-2010. godine, a rezultati su uspoređeni s razinom alergena artropoda u drugim zemljama. Razina alergena grinja Der p 1 i Der f 1 u kućnoj prašini u općoj populaciji u Hrvatskoj je niska, ali su ti alergeni određeni u 73 do 83 % kućanstva. Nasuprot tome, izloženost alergenu žohara je rijetka (13 %), a razina izloženosti je također niska. Opća populacija u Hrvatskoj nije izložena višestrukim i rizičnim razinama alergena vezanim za razvoj senzibilizacije i astme. Buduća bi ispitivanja trebala uključiti mjerenje alergena artropoda i kućnih ljubimaca u kućanstvima visokorizičnih osoba na nastanak alergijskih bolesti u kontinentalnom i obalnom području Hrvatske. Nova istraživanja povezanosti razine alergena unutarnjih prostora i pojave senzibilizacije i astme naročito u ranom djetinjstvu (učinak ovisan o dozi), trebala bi rezultirati boljim tumačenjem te složene interakcije.

KLJUČNE RIJEČI: *alergeni unutarnjih prostora, grinje kućne prašine, Der p 1, Der f 1, Bla g 1, ELISA*

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