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Indoor Allergens

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Allergens found in house dust have been associated with asthma since the 1920s, when Kern¹ and Cooke² independently reported a high prevalence of immediate skin tests to house dust extracts among patients with asthma. Van Leeuwen³ showed that asthmatics who were admitted to a modified hospital room free of 'climate allergens' (thought to be bacteria and molds) showed clinical improvement: these were the first experiments that used allergen avoidance for asthma management. Allergists sought to explain how a heterogeneous material such as house dust could contain a potent allergen that appeared to be ubiquitous. The prevailing theory was that a chemical reaction occurred in dust resulting in synthesis of the 'house dust allergen'.⁴ Researchers extracted house dust with organic solvents to identify allergenically active compounds. The puzzle was finally resolved in 1967, when Voorhorst and Spieksma⁵ showed that the origin of house dust allergen was biologic rather than chemical. The allergenic potency of Dutch house dust extracts correlated with the numbers of house dust mites (Acari, Pyroglyphidae: *Dermatophagoides pteronyssinus* and *D. farinae*) in the samples. Extracts of mite cultures gave positive skin tests at dilutions of 10⁻⁶, and asthma symptoms correlated with seasonal variation in mite numbers. Exposure to 100 mites per gram of dust was associated with sensitization, and 500 mites per gram was associated with symptom exacerbation.

The prevalence of asthma has increased during the past 40 years. Current data suggest that approximately 10% of US children have asthma. Sensitization and exposure to indoor allergens, principally dust mites, cat, dog, mouse, cockroach (CR), and fungi, are among the most important risk factors.^{6,7} The two principal mite species, *D. pteronyssinus* and *D. farinae*, account for more than 90% of the mite fauna in US house dust samples. Other allergenic mites include *Euroglyphus maynei* and *Blomia tropicalis* (found in subtropical regions such as Florida, southern California, Texas, and Puerto Rico). Storage mites, such as *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, and *Acarus siro*, cause occupational asthma among farmers, farm workers and grain handlers. Childhood asthma is also strongly associated with sensitization to animal allergens, CR, and, to a lesser extent, mold allergens. Cat allergen (*Fel d 1*) has a ubiquitous distribution in the environment and can be found at clinically significant levels in houses that do not contain cats (similarly for dog allergen).^{8–10} Rodent urinary proteins have long been associated with occupational asthma among laboratory animal handlers. A high prevalence of sensitization and exposure to mouse allergen is a risk factor for asthma among inner-city children.^{11,12} Children living in urban areas are also at risk of developing CR allergy. Cockroach infestation of housing results in the accumulation of potent

allergens that are associated with increased asthma mortality and morbidity among US children, particularly African-American and Hispanic children, living in inner cities.^{6,13,14} Cockroach allergens appear to be particularly potent. Atopic individuals develop immunoglobulin E (IgE) responses after exposure to 10-fold to a 100-fold lower levels of CR allergens than to dust mite or cat.¹⁵

Investigation of the role of indoor allergens in asthma has involved the identification of the most important allergens and the development of techniques to accurately monitor allergen exposure. This chapter reviews the structure and biologic function of indoor allergens, methods for assessing environmental exposure and the clinical significance of indoor allergens.

Allergen Structure and Function

Allergens are proteins or glycoproteins of 10 to 50 kDa that are readily soluble and able to penetrate the nasal and respiratory mucosae. A systematic allergen nomenclature has been developed by the International Union of Immunological Societies' (IUIS) Allergen Nomenclature Subcommittee: the first three letters of the source genus followed by a single letter for the species and a number denoting the chronologic order of allergen identification. Thus the abbreviated nomenclature for *Dermatophagoides pteronyssinus* allergen 1 is Der p 1 (see <http://www.allergen.org>). To be included in the IUIS nomenclature, the allergen must have been purified to homogeneity and/or cloned, and the prevalence of IgE antibody (ab) must have been established in an appropriate allergic population by skin testing or in vitro IgE ab assays.¹⁶ Molecular cloning has determined the primary amino acid sequences of more than 500 allergens and most common allergens can be manufactured as recombinant proteins. There are over 50 three-dimensional structures of allergens in the Protein Database (PDB) and allergens are found in ≈180 protein families in the Pfam protein family database (<http://www.sanger.ac.uk/software/Pfam>) (Figure 25-1).^{16–19} It has been argued that this is a small number of protein families, given that there are over 10 000 protein families in Pfam, and that this implies that only a limited group of proteins (with certain structural features) have the potential to become allergens.^{17,20} However, detailed structural analyses have not revealed any common features or motifs that are associated with the induction of IgE responses. Recent studies have resolved the crystal structure of Bla g 2/mAb complexes. Mutagenesis of surface residues is being used to identify IgE epitopes and generate hypoallergenic variants for vaccine development.¹⁸

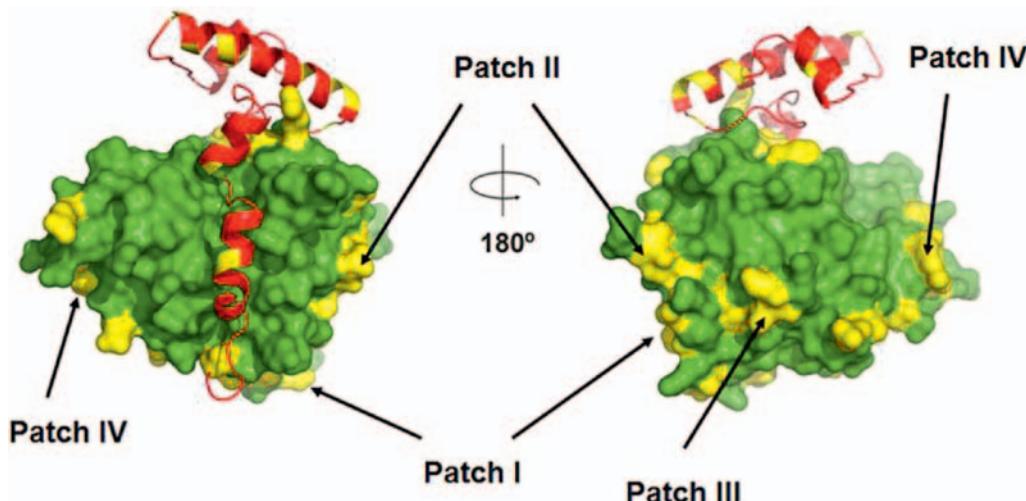


Figure 25-1 X-ray crystal structures of the mite cysteine protease allergens, Der p 1 and Der f 1. Residues that differ between the two allergens are shown in yellow and labeled as patches I, II, III, and IV. The conserved Cys35 active site residue is shown in orange. (From Chruszcz M, Chapman M, Vailes L et al. J Mol Biol 2009; 386:520–530.)

BOX 25-1 Key concepts

Indoor Allergens: Structure and Function

- Allergens are soluble proteins or glycoproteins of molecular weights of 10 to 50 kDa.
- More than 500 allergen sequences are deposited in protein databases (GenBank, PDB), and about 50 tertiary structures have been resolved by X-ray crystallography.
- Allergens have diverse biologic functions and may be enzymes, enzyme inhibitors, lipid-binding proteins, lipocalins, or regulatory or structural proteins.
- Allergens promote T cells to differentiate along the Th2 pathway to produce IL-4 and IL-13 and to initiate iso-type switching to IgE.
- Biologic functions of allergens, such as proteolytic enzyme activity or other adjuvant-like effects, can enhance IgE responses, damage lung epithelium and cause allergic inflammation.

Allergens belong to protein families with diverse biologic functions: they may be enzymes, enzyme inhibitors, lipid-binding proteins, ligand-binding proteins, structural or regulatory proteins (Box 25-1, Figure 25-2).¹⁶ Some dust mite allergens are digestive enzymes excreted with the feces, such as Der p 1 (cysteine protease), Der p 3 (serine protease), and Der p 6 (chymotrypsin). Enzymatic activity of mite allergens promotes IgE synthesis and local inflammatory responses via cleavage of CD23 and CD25 receptors on B cells and by causing the release of proinflammatory cytokines (interleukin [IL]-8, IL-6, monocyte chemotactic protein-1 [MCP-1], and granulocyte-monocyte colony-stimulating factor [GM-CSF]) from bronchial epithelial cells.²¹ Mite protease allergens cause detachment of bronchial epithelial cells in vitro and disrupt intercellular tight junctions. Activation of mite proteases could damage lung epithelia and allow access of other nonenzymatic allergens, such as Der p 2, to antigen-presenting cells. Der p 2 has structural homology to MD-2, the lipopolysaccharide (LPS) binding component of the Toll-like receptor 4 (TLR4) complex. Recent studies have shown that Der p 2 can drive signaling of the TLR4 complex and may enhance the

expression of TLR4 on the airway epithelium and have intrinsic adjuvant activity.²² Mite feces contain other elements, including endotoxin, bacterial DNA, mite DNA, and chitin that could also influence IgE responses and inflammation.^{23,24}

With the exception of cat allergen Fel d 1, most animal allergens are ligand-binding proteins (lipocalins) or albumins. Lipocalins are 20- to 25-kDa proteins with a conserved, eight-stranded, antiparallel β -barrel structure that bind and transport small hydrophobic chemicals. In contrast, Fel d 1 is a calcium-binding, steroid-inducible, uteroglobin-like molecule – a tetrameric 35-kDa glycoprotein, comprising two subunits which are heterodimers of two chains comprising eight α -helices.²⁵ Fel d 1 has two amphipathic water-filled cavities which may bind biologically important ligands. Rat and mouse urinary allergens are pheromone- or odorant-binding proteins. The CR allergen Bla g 4 is a lipocalin that is produced in utricles and conglobate glands of male CRs and may have a reproductive function. Other important CR allergens include: Bla g 1, a gut-associated allergen; Bla g 2, an inactive aspartic proteinase; Bla g 5 (glutathione transferase family); and the Group 7 tropomyosin allergens (Figure 25-2).²⁶ Fungal allergens have been cloned from *Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium*, and *Trichophyton* spp., and they include proteolytic enzymes, heat shock proteins, or ribonucleases.

Evaluation of Allergen Exposure

Environmental Assessments

Counting Critters

Biologists and pest management companies have counted dust mites in dust samples and trapped CRs to assess infestation and allergen exposure. These methods are useful in studying population dynamics, seasonal variation, and the effect of physical and chemical methods for reducing mite and CR populations. However, they are time-consuming and unsuitable for routine measurements of allergen exposure. Allergen levels may remain high when mite or CR levels have been reduced, and simply enumerating mites/CRs may not be a reliable indicator of allergen exposure. Similarly, several epidemiologic studies on cat allergen exposure have relied on questionnaires and direct

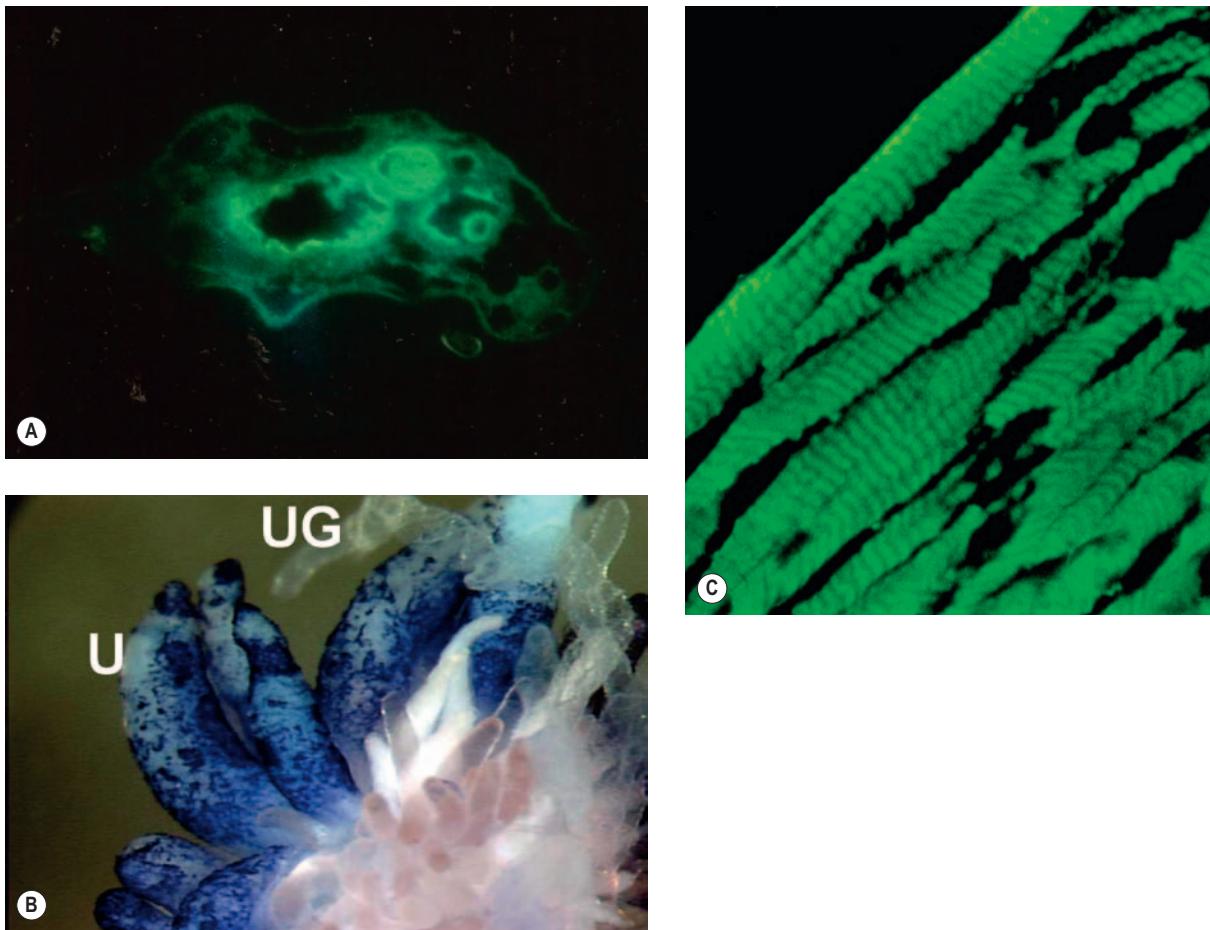


Figure 25-2 Biologic functions of indoor allergens. **(A)** Localization of Der p 1 in the mite digestive tract by immunofluorescence (courtesy of Dr. Euan Tovey, University of Sydney, Australia.). **(B)** In situ hybridization showing Bla g 4 in the uricose gland (UG) and utricles (U) of male cockroach (from Fan Y, Gore C, Redding K et al. *Insect Mol Biol* 2005;14:45–53). **(C)** Immunofluorescence of tropomyosin (Per a 7) in cockroach muscle tissue (from Arruda LK, Vailes L, Ferriani V et al. *J Allergy Clin Immunol* 2001;107:419–428.)

observations of the numbers of cats in children's homes as a measure of exposure. The amount of cat allergen that accumulates in homes is dependent on furnishings (especially carpets) and air exchange rates, so the number of animals is not a sufficient measure of exposure.

Enzyme-Linked Immunosorbent Assays (ELISA) for Major Allergens

Since the mid-1980s, quantitative assessments of allergen exposure have been made by measuring major allergens in reservoir dust samples (bed, carpet, soft furnishings) using monoclonal antibody (mAb)-based ELISA. ELISA methods have defined specificity, high sensitivity (≈ 1 ng/mL), and provide accurate and reproducible measurements.^{6,27} The ELISA use either pairs of mAbs directed against nonoverlapping epitopes on the allergen molecule or capture mAb and polyclonal rabbit antibody for detection. Robust ELISA tests require high-affinity mAb of defined specificity and standards with known allergen content. ELISA has been the gold standard for indoor allergen exposure assessment for 25 years. A growing number of academic and commercial laboratories in the USA and in Europe offer ELISA testing services. While ELISA provides reliable quantitative exposure assessment, it does require a separate test for each allergen. The associated time and cost involved is an impediment for large studies of exposure assessment and especially for studies involving multiple allergens.

Multiplex Array for Indoor Allergens (MARIA)

Recently, innovative fluorescent multiplex array technology has been developed that allows the most common indoor allergens to be detected at once in a single test.²⁸ The multiplex array for indoor allergens (MARIA) uses mAb that are covalently bound to polystyrene beads containing different ratios of orange-red fluorescent dyes. Up to 100 dye combinations are available to create different bead sets. Beads coupled with mAb directed against different allergens are incubated with the dust samples and bound allergen is detected using a cocktail of biotinylated detector mAb and streptavidin phycoerythrin. Fluorescent intensity is measured using a two channel laser flow cytometer: a red laser identifies beads by their internal color as bearing a specific allergen; a green laser quantifies the intensity of the bound streptavidin-conjugated fluorophore, and measures the amount of allergen bound. In most cases, the same combinations of mAb used in ELISA can be used in MARIA and there is an excellent quantitative correlation between the results for MARIA and ELISA (Table 25-1).²⁸ The multiplex test occurs within a single microtiter well and the assay conditions are the same for each allergen, resulting in improved standardization and reproducibility. Other advantages of MARIA compared to ELISA are the time savings achieved by analyzing multiple allergens at once, as well as improved sensitivity, accuracy and greater inter-laboratory reproducibility. For allergen exposure assessment, nine indoor allergens can be measured by MARIA: Der p 1, Der f 1,

Table 25-1 Antibody Combinations and xMAP Bead Sets Used in MARIA*

Allergen	Capture Monoclonal Antibody	Biotinylated Antibody	xMAP Bead Set
Der p 1	10B9	5H8	33
Der f 1	6A8	4C1	51
Mite Group 2	1D8	7A1	53
Fel d 1	6F9	3E4	58
Can f 1	10D4	6E9	20
Rat n 1	RUP-6	RUP-1	69
Mus m 1*	Rabbit anti-Mus m 1	Ra anti-Mus m 1	62
Bla g 2	1F3	4C3	47
Alt a 1	121G	121G	28

*The Mus m 1 bead set uses polyclonal antibodies.

mite group 2, Fel d 1, Can f 1, Mus m 1, Rat n 1, Bla g 2, and Alt a 1 (Table 25-1).

Allergen standards are an integral component for calibration of both ELISA and MARIA and enable allergen measurements made by different laboratories to be directly compared.^{29,30} In the past, ELISA standards were allergen extracts (not purified allergens) that were calibrated to contain a known amount of allergen by reference to national or international standards, where available. For example, Der p 1 measurements were standardized using the WHO/IUIS international *D. pteronyssinus* reference (NIBSC 82/518) which was estimated to contain 12.5 µg Der p 1 per ampoule.⁶ In 2000, the WHO/IUIS Allergen Standardization Committee initiated a project to produce international standards of purified allergens with verifiable allergen content. The project was funded through the European Union as the Certified Reference Materials for Allergenic Products (CREATE) study. The aim was to develop recombinant allergen standards for mite group 1 and group 2 allergens, as well as birch, rye grass, and olive pollen allergens. Purified natural and recombinant allergens were rigorously compared for protein content, structure, allergenic activity and ability to serve as primary standards for immunoassays.³¹ Two of the allergens developed in CREATE, Bet v 1 and Phl p 5, are currently being evaluated by the European Directorate for the Quality of Medicines as biological reference materials for inclusion in the European Pharmacopoeia.^{31,32} It is anticipated that other allergen standards will be developed through a similar mechanism. The principles of CREATE were used to formulate a single standard of purified natural allergens that could be used for calibration of both ELISA and MARIA.^{28,32} The single 'universal' allergen standard contained eight purified allergens whose protein content was determined by amino acid analysis. The standard was compared with previous ELISA standards and conversion factors were developed to enable previous ELISA results to be compared with the current single standard.³²

'Point-of-Care' Tests

Simple qualitative or semiquantitative tests that can be used in allergy clinics or physicians' offices or by consumers have been developed. The aim of these 'point of care' tests is to provide patients with tests that can be used to monitor allergen levels in their homes and to reinforce education about the role of allergens in causing asthma. The first such test was Acarex, a dipstick that

measures guanine in house dust (a surrogate for dust mites). Lateral flow technology has been used to develop rapid tests that can measure specific allergens in 10 minutes. These tests are analogous to pregnancy or drug tests and are designed for use by patients and other consumers. The mite allergen test uses the same mAb as the mite group 2 ELISA and can detect both *D. pteronyssinus* and *D. farinae*. The test includes a simple dust collection and extraction device that allows dust to be collected and extracted within 2 minutes. The rapid test has indicator lines that provide patients with estimates of high, medium, and low allergen levels and which broadly correlate with group 2 levels determined by ELISA.³³

Allergen Sampling in Dust and Air

Allergens are typically measured on dust samples that are collected by vacuuming an area of 1 m² for 2 minutes and extracting 100 mg of fine dust in 2 mL of buffer. Samples are usually collected from three or four sites in the home, including mattresses, bedding, bedroom or living room carpet, soft furnishings, or kitchen floors. The results are expressed as nanograms or micrograms of allergen per gram of dust. Measurements of group 1 allergens in bedding provide the best index of mite exposure and show a good correlation between results expressed as micrograms of allergen per gram of dust or per unit area (µg/m²).³⁴ Cat and dog allergens are widely distributed throughout the house and accumulate at clinically significant levels in houses that do not contain pets. Not surprisingly, the highest concentrations of CR allergens are usually found in kitchens, although in heavily infested homes allergen accumulates on flooring and in bedding.

Measurement of allergen levels in dust provides a valid index of exposure but cannot be used to monitor personal exposure. The aerodynamic properties of mite, cat, dog, and CR allergens have been studied using particle sizing devices such as the Cascade impactor and Andersen sampler.^{9,35,36} Mite and CR allergens occur on large particles of 10 to 40 µm in diameter and cannot be detected in rooms under undisturbed conditions. After a disturbance, such as using a vacuum cleaner without a filter, these particles remain airborne for about 20 to 40 minutes. In contrast, cat and dog allergens can be easily detected in air samples under undisturbed conditions and persist in the air for several hours.³⁷ Animal dander particles (skin flakes) are less dense than mite feces, and approximately 25% of animal allergen occurs on smaller particles, 5 µm in diameter, that remain airborne.^{9,37}

Clinical Significance of Indoor Allergens

Measurement of indoor allergen levels in reservoir dust and air samples has played a key role in determining risk levels for allergen exposure. Previous International Workshop reports recommended that allergen exposure be expressed as µg allergen/gram dust (or ng/m³ for air samples).⁶ Exposure data collected in epidemiologic studies, population surveys and birth cohort studies has strengthened the association between indoor allergen exposure and allergic respiratory diseases. Prominent studies include the National Inner-City Asthma Studies (ICAS)^{13,14} and the National Survey of Lead and Allergens in Housing (NSLAH) in the USA;^{38,39} the European Community Respiratory Health Survey (ECRHS);^{40,41} and a series of birth cohort studies in the USA, Europe, Australia and New Zealand.⁴²⁻⁴⁶ Childhood asthma is more closely linked to allergic sensitization and allergen

exposure than adult asthma. Studies in both inner-city and suburban children with asthma indicated that >80% of school-age children with asthma are sensitized to at least one indoor allergen and that allergic sensitization is a strong predictor of disease persistence in later life.^{44,47,48} In the ICAS, 94% of the study population of severe asthmatics was sensitized to at least one allergen and the number of sensitivities correlated with asthma severity.¹⁴ Equally compelling is the recently confirmed observation in the German MAAS cohort that high-level allergen exposure in early life is associated with chronic asthma in children.^{44,48}

Epidemiologic studies have allowed risks for allergic sensitization to be attributed to certain levels of allergen exposure among different populations of atopic individuals (Table 25-2). Mite allergen levels at high altitude or in 'allergen-free' rooms are generally <0.3 µg/g and <10% of atopic individuals are likely to become sensitized at this low level of mite exposure. Persistent exposure of atopic individuals to ≈2 µg of mite allergen is likely to result in sensitization in a majority of atopic individuals and will increase as mite allergen levels exceed 2 µg/g. Adjusted odds ratios (ORs) for sensitization and exposure to 2 µg/g mite group 1 allergen range from 3 to 6, and in many parts of the world sensitization to mites is the strongest independent risk factor for asthma. A survey of 1054 middle school children in Virginia showed that dust mite sensitization was independently associated with asthma (OR 6.6, $P < 0.0001$) and that dust from 81% of homes contained more than 2 µg/g mite group 1 allergen.⁴⁹ A prospective study of 939 German schoolchildren, which followed them up to the age of 7 years, showed a 7-fold difference in sensitization to mites between children exposed to less than 0.03 µg/g mite group 1 (first quartile) compared to those exposed to 1 to 240 µg/g (fourth quartile).⁵⁰ This data is consistent with a dose response relationship between exposure and sensitization for mite allergens. Mite allergen exposure levels above 10 µg/g are considered high risk for sensitization and results of NSLAH indicate that these levels are found in ≈23% of US homes (22 million housing units).³⁹

Data on cat and dog allergen exposure in relation to sensitization are more difficult to interpret. Exposure to Fel d 1 of <0.5 µg/g is considered to be low and is a low risk for sensitization (Table 25-2).¹⁵ Paradoxically, the prevalence of sensitization can be reduced among atopic individuals who keep cats from birth and are continuously exposed to Fel d 1 levels of >20 µg/g.⁵¹⁻⁵³ This level of exposure appears to reduce the prevalence of sensitization by ≈50%. High exposure to Fel d 1 (>20 µg/g) gives rise to a modified Th2 response – a form of tolerance that results in a lower prevalence of IgE antibody responses. In contrast, low-dose exposure to Fel d 1 (1 to 8 µg/g) is most strongly associated with the development of IgE antibody. The dose-response studies may explain why, in population

surveys, sensitization to cats is often lower than that to dust mites. In countries such as New Zealand, where 78% of the population owns cats and high levels of allergen occur in houses, the prevalence of sensitization to cat is only 10% and cat is not as important a cause of asthma as dust mites.⁴⁶

Most houses that contain cats or dogs have Fel d 1 or Can f 1 levels of greater than 10 µg/g, whereas homes that do not contain these pets may contain 1 to 10 µg/g animal allergen.⁸⁻¹⁰ What distinguishes animal allergen exposure from other indoor allergens is the wide range of exposure levels (from <0.5 to >3000 µg/g) and the ubiquitous allergen distribution. Cat and dog allergens occur in schools, offices, workplaces, and public buildings, where they are passively transported by their owners, and they can cause both sensitization and symptoms in these environments. An atopic child who lives at home without a cat can become sensitized by visiting homes or attending schools where cat allergen is present. A Swedish study showed a 9-fold increased risk of asthma exacerbations at school among 6- to 12-year-old children who attended classes with other children who kept cats compared with those in classes with fewer than 18% cat owners.⁵⁴ Thus passive exposure of schoolchildren to animal allergens can exacerbate asthma, even among children who are being treated with asthma medications.

CR allergen exposure has been assessed by measuring Bla g 1 and Bla g 2, which cause sensitization in 30% and 60% of CR-allergic patients, respectively.⁵⁵ Most dust samples from CR-infested homes contain both allergens, although there is only a modest quantitative correlation between levels of the two allergens. Analysis of Bla g 1 and Bla g 2 levels in the homes of asthma patients admitted to the emergency departments in Atlanta, Georgia, and Wilmington, Delaware, showed that homes with visible evidence of CRs contained more than 8 U/g Bla g 1 and more than 2 U/g (approximately 0.1 µg/g) Bla g 2.⁵⁶ In inner-city Baltimore, the proportion of asthmatic children (aged 4 to 9 years) with positive skin tests to CR increased from 32% among children exposed to 1 to 2 U/g Bla g 1 to 45% among children exposed to more than 4 U/g.⁴⁷ Multicenter case-control studies carried out among 12- to 13-year-old schoolchildren in Charlottesville, Virginia, and Los Alamos, New Mexico, showed that a 4-fold increase in Bla g 2 exposure (from 0.08 to 0.33 µg/g) was associated with highly significant increases in wheal size of CR skin tests.¹⁵ These studies provide evidence for a dose-response relationship between CR allergen exposure and sensitization. The reported CR allergen levels are several-fold lower than those for either mite or animal allergens, suggesting that CR may be more potent in stimulating IgE responses. The National Cooperative Inner City Asthma Study (NCICAS) showed that sensitization and exposure to CRs (>8 U/g Bla g 1) was associated with increased asthma morbidity. Among inner-city children from

Table 25-2 Allergen Exposure Thresholds for Sensitization

Risk for Sensitization*	Allergen Level in Dust Sample				
	Mite Group 1 (µg/g)	Fel d 1 (µg/g)	Can f 1 (µg/g)	Bla g 1 (U/g)	Bla g 2 (µg/g)
High	>10	1-8	1-8	>8	>1
Medium	2-10	8-20	8-20	1-8	0.08-0.4
Low	<0.3 [†]	<0.5	<0.5	<0.6	<<0.08
		>20	>20?		

*For atopic children.

[†]Levels found in 'allergen-free' hospital rooms or in houses/apartments maintained for at least 6 months are less than 45% relative humidity.

eight US cities enrolled in the study, 37% were allergic to CRs, and hospitalizations, unscheduled medical visits, and days lost from school due to wheezing or asthma were strongly associated with CR allergen exposure.^{13,47} These data have been confirmed in the ICAS study which showed similar correlations between sensitization, CR exposure and asthma morbidity in Bronx, New York and in Dallas.¹⁴ In the USA, high CR allergen levels are associated with lower socioeconomic status, living in inner cities, and race (African-American or Hispanic). Cockroach allergy is not an entirely urban problem. Suburban and rural homes, including trailer homes, that harbor high levels of CRs, cause sensitization and respiratory disease in these populations.

Monitoring Allergen Exposure as Part of Asthma Management

The most recent National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) significantly strengthened guidelines recommending allergen avoidance as an important goal of asthma management (Box 25-2). Targeted interventions in the homes of allergic individuals can significantly improve health and should be part of the management of children with asthma. Studies of inner-city asthma demonstrated that reduction of indoor allergen exposure leads to improvement of asthma symptoms, associated with a reduced use of medication and also a reduction in lost work or school time due to asthma.⁵⁷ The guidelines recommend using patient histories and allergic sensitization as evidence of allergen exposure but do not include any environmental assessment. There are several flaws with this approach. Allergen levels in homes vary widely across the USA, depending on climate, geographic location, housing type and condition, and socioeconomic status. The NSLAH publications illustrate that high indoor allergen levels are a potential problem in many homes.^{39,58} Conversely, many US homes have low or undetectable allergen levels. For example, Der f 1 levels in Boston, Massachusetts, were 10-fold to 100-fold higher in single-family homes than in centrally heated apartments.⁵⁹ Thus marked variations in allergen exposure were demonstrated in a single US city and are related to changes in relative humidity.^{59–61} Other observations show that inner-city homes located on the East Coast have lower mite allergen levels than those reported in the urban South.^{47,62} Clinically relevant levels of cat allergen are found in homes that do not contain cats and in some schools.

BOX 25-2 Therapeutic principles

Control of Environmental Factors that Affect Asthma (NAEPP EPR-3)

- For patients who have persistent asthma, the clinician should evaluate the potential role of indoor allergens.
- Use the patient's medical history, skin testing or in vitro testing to identify allergen exposures that may worsen the patient's asthma.
- Patients who have asthma at any level of severity should reduce, if possible, exposure to allergens to which the patient is sensitized and exposed.
- Know that effective allergen avoidance requires a multifaceted, comprehensive approach.
- Consider allergen immunotherapy when there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive.

Finally, CR allergen is found in about 20% of homes that have no visible evidence of CR infestation.⁵⁶ The significance of these studies is that allergen exposure should not be assumed and that knowledge of allergen levels in the home is needed to provide objective advice about exposure and avoidance.

Allergen measurements have been used to validate the efficacy of a variety of physical and chemical control procedures and devices, including mattress encasings, vacuum cleaner filters, acaricides, protein denaturants, detergents and carpet cleaners, steam cleaning, humidity control and air filtration systems.⁶³ It is important that products and devices be tested for their effects on specific allergens so that allergists can verify claims made by manufacturers and make evidence-based recommendations.

Despite over 20 years of study supporting a role for allergen avoidance in the treatment of asthma, a recent review from the Nordic Cochrane Centre concluded that extensive US and EU expert panel reports on allergen avoidance were misleading and that reducing dust mite allergen levels was 'ineffective' as a treatment strategy.⁶⁴ Earlier meta-analyses by the Cochrane Center were criticized because they included studies that used avoidance protocols that did not result in reduction of allergen levels. In a rebuttal of the most recent Cochrane review, Platts-Mills argued that meta-analysis was compromised in avoidance studies because of the variability in the studies that have been performed and because the Cochrane review was selective about which studies were included in the meta-analysis.⁶⁵ Successive Cochrane reviews have failed to take into account that patients are rarely sensitized only to dust mite allergens and one of the most clinically effective avoidance studies involved tailored approaches to allergen control together with comprehensive patient education.⁵⁷

The availability of point-of-care tests for indoor allergens will educate patients about the role of allergens in causing allergic disease. The importance of educating patients so that they can play a leading role in controlling their disease has been emphasized.⁶³ The objectives of making exposure measurements are to show that in addition to having IgE reactivity to an allergen, the patient may be exposed to the relevant allergen at home. This information is expected to reinforce the link among allergen sensitization, exposure, and disease activity; enable informed decisions to be made about treatment options, and encourage implementation and compliance with intervention procedures.

Conclusions

Indoor allergens are a risk factor for the development of asthma as well as other allergic diseases. The most important indoor allergens have been cloned, sequenced and expressed and over 50 three-dimensional structures of allergens have been resolved. Indoor allergens have diverse biologic functions and may be enzymes, lipid-binding proteins, ligand-binding proteins, structural or regulatory proteins. The biologic function of allergens may enhance IgE responses and play a direct role in causing allergic inflammation. The level of environmental exposure to allergen as well as the atopic predisposition of the individual also influences the development of IgE responses and Th2 responses. Measurement of allergen in reservoir dust samples provides the best index of allergen exposure and can be accurately measured by ELISA for major allergens. A new generation of tests (MARIA) uses fluorescent multiplex array technology and enables multiple allergens to be tested simultaneously in dust or air samples. The MARIA technology is especially suited to large population studies or cohort studies and for routine allergen exposure assessment. The NAEPP-EPR 3 guidelines for the management

of asthma recommend that for any patient with persistent asthma, the clinician should (1) identify allergen exposures; (2) use skin testing or in vitro testing to assess specific sensitivities to indoor allergens; and (3) implement environmental controls to reduce exposure to relevant allergens. Avoidance procedures that can help to reduce exposure to indoor allergens have been developed and can reduce symptoms and medication requirements. The combination of improved allergen-monitoring techniques and validated allergen-avoidance procedures should improve asthma management and reduce the public health problems associated with sensitization to indoor allergens.

Acknowledgements

This chapter is dedicated to the memory of Dr Richard Sporik, pediatric allergist and friend, whose premature death in 2008 was a great loss. Richard's seminal studies of the role of indoor allergens in the etiology of childhood asthma are a lasting legacy.

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