

Review article

Home allergen monitoring and control – improving clinical practice and patient benefits

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Immunoassays for indoor allergens were first developed in the late 1980s, and the last decade has seen an explosion of research and clinical studies on the role of household allergen exposure in causing allergic disease, especially asthma. Monoclonal antibody-based enzyme immunoassays (ELISA) have become a cornerstone of laboratory assessment of exposure to mite, cat, dog, and cockroach allergens (1, 2). The panel of assays available for allergen measurements has grown steadily and includes assays for *Blomia tropicalis*, *Lepidoglyphus destructor*, and bovine and equine allergens (3–19) (Table 1). Over 300 publications using allergen immunoassays are now on MEDLINE databases, covering a wide range of scientific studies. These include the following:

- Sites and distribution of allergen accumulation within the home; seasonal variation in allergen levels.
- Case control studies and population studies designed to establish risk levels for allergen exposure leading to sensitization and to asthma symptoms.
- Analysis of the aerodynamic properties of indoor allergens.
- Standardization of allergenic products used for diagnosis and treatment.
- Design and monitoring of allergen avoidance studies and assessment of the efficacy of allergen control products, devices, chemicals and proce-

dures (e.g., mattress encasings, air filters, and vacuum cleaners). This allows manufacturers to design products that are of proven efficacy by using objective methods to demonstrate their effects on allergens.

As a result of these studies, the evidence that exposure to indoor allergens is an important risk factor for asthma has become stronger, and for some allergens, particularly dust mite, there is convincing evidence for a dose-response relationship between sensitization and exposure (2, 20).

Expert panel reports and position statements from the European Union (EU), the US National Heart, Lung, and Blood Institute (NHLBI), and the American Academy of Allergy, Asthma, and Immunology (AAAAI) have recommended allergen avoidance as an integral part of asthma management (2, 21–23). However, until recently, measuring allergen exposure in homes has largely been a procedure carried out by research laboratories. Over the past 2 years, commercial reference laboratories in Europe and in the USA have been providing allergen analysis services, and patient-based allergen-detection tests and personal monitoring systems are being introduced. This review focuses on recent advances in developing these systems and how measurements of allergen exposure can be used to improve clinical practice and provide benefits for allergic patients.

Immunoassays for household allergens

Monoclonal antibody (mAb)-based ELISA techniques have become established as the reference standard for indoor allergen analysis. The advantages of ELISA are high throughput, accurate quantitation (ng/g or µg/g allergen protein), and defined specificity, by using mAbs to allergens of known molecular structure and allergenic importance (Table 1). Successful strategies for developing these assays, including selection of mAbs and assessment of assay variability and performance, have recently been reviewed (24). A number of assays are available for assessing exposure to the most common dust-mite species, as well as animal allergens and cockroach allergens. The gaps in the repertoire are for assays for American cockroach allergen and fungal allergens. Although an assay for *Per a 3* of American cockroach has been described, the assay has not yet been validated for environmental measurements (15). Recently, two assays for the *Alternaria* allergen *Alt a 1* have been described and used for comparing *Alt a 1* levels in allergen extracts (18, 19, 25). The problem with these and other assays for fungal allergens (e.g., *Asp f 1*) has been in validating the assays for environmental exposure measurements. *Asp f 1* is not expressed in spores, which are the most common form of *Aspergillus* in house dust (16, 17). Similarly, it has proved difficult to measure *Alt a 1* in house-dust samples, and this may reflect the fact that extensive fungal contamination is required to produce allergen that can be detected in the assays. *Alt a 1* can be eluted from *Alternaria* spores; however, the spore count has to be very high (> 100 000 spores/ml) for allergen to be detectable, and it seems unlikely that such high spore concentrations will routinely be found in domestic environments (18).

Producing and maintaining allergen standards is critical to the reproducibility and accuracy of allergen assays. In the past, standards have been established by comparing the allergen content of a reference preparation (e.g., mite or cat extract) relative to a purified sample of a given allergen (*Der p 1* or *Fel d 1*). It is important to realize that until recently all allergen standards were simply extracts that had been calibrated to a known concentration: they were not purified allergens. Standards have been established by researchers, regulatory agencies, or manufacturers and biotechnology companies for "in house" or commercial use (reviewed in Refs. 24, 26–28). However, currently, there are no international standards for purified allergens. Such standards would be of great value in comparing allergen measurements in epidemiologic studies and for standardization of allergenic products used for diagnosis and immunotherapy. A new initiative to develop recombinant allergen standards is being organized by the WHO/IUIS Allergen Standardization Committee. The aim is to develop recombinant allergen standards for mite (groups 1 and 2), birch (*Bet v 1*), grass pollen (*Phl p 1* and *Phl p 5*),

and olive pollen (*Ole e 1*) allergens. The program will involve comparison of both natural and recombinant allergens, and criteria will be established for protein measurements and for assessing allergenic activity. Currently, bacterially expressed *rBlo t 5* and *rAlt a 1* are being used as standards in ELISA, and most of the allergens listed in Table 1 have been expressed as recombinants with immunoreactivity comparable to the natural allergen (29, 30). The WHO/IUIS Allergen Standardization program is being funded by the EU and will involve collaborations between academic researchers, allergen manufacturers, and biotechnology companies. The aim is to produce the purified allergens that will serve as primary standards for immunoassays. For example, mite-allergen *Der p 2* has been expressed at high level in *E. coli*. Recombinant *Der p 2* is highly immunoreactive and has been used in NMR and x-ray crystallographic studies to determine the tertiary structure of the allergen and the location of mAb-binding epitopes (31–33). Thus, it will become possible to establish a primary standard using *rDer p 2* that can be stored in WHO-approved repositories, and this would be the international standard for *Der p 2* measurements (analogous to current IgE standards).

Patient-based allergen detection systems

The limitations of ELISA are that dust extraction, sample preparation, and the assays themselves are time-consuming, and their use is confined to well-equipped research or clinical laboratories. The level of public awareness of the role of indoor allergens in asthma has grown dramatically over the past 10 years and has spawned the development of simple qualitative or semiquantitative tests that enable patients themselves to assess mite-allergen levels in their homes. The first of these tests was the chemical test for guanine (the *Acarex* test), a surrogate test for mites (the major producers of guanine in houses dust) (34). This test correlates reasonably well with levels of mite allergen and, although it has not been widely used, is still marketed in Europe. The production of allergen-specific mAbs made it possible to develop innovative tests for specific mite (and other) allergens, including DUSTSCREEN, the ACLOTES, and, most recently, rapid lateral flow tests which enable allergen to be detected in 5–10 min (35–37). These tests use specific mAbs or polyclonal antibodies bound to membranes in simple dipstick or cassette formats. DUSTSCREEN is a nitrocellulose-based strip test which detects multiple allergens in a single test with one dust sample. The nitrocellulose strip has six capture mAb "spots" for different allergens, which are detected by a cocktail of enzyme-labeled mAb. This test can be quantified with a strip reader and shows good correlation with ELISA (35). However, DUSTSCREEN takes several hours to perform, and it is best suited for

Table 1. ELISA for indoor allergens

Allergen*	Capture** mAb	Second ⁺ antibody	Allergen standards	Reference
Mite				
Der p 1*	5H8	4C1 ^B	N1BSC 82/518, UVA 93/03	3
	10B9	5H8 ^B	NIBSC 82/518, UVA 93/03	3
	PIA03	P1A01 ^B	92-Dp	4
Der f 1	6A8	4C1 ^B	UVA 93/02	3
	F1B01	F1A05	92-Df	4
Group 2*	1D8	7A1 ^B	UVA 97/01	5
Group 7	WH9	HD19 ^B	n.a.	6
Blo t 5	4G9	4D9 ^B	rBlo t 5	7
Lep d 2*	Le5B5	RaαLep d 2	rLep d 2	8
Mammalian				
Cat, Fel d 1	6F9	3E4 ^B	CBER Cat E3, UVA 94/01	9
Dog, Can f 1*	6E9	RaαCan f 1	NIBSC 84/685, UVA 98/01	10, 11
Rat, Rat n 1*	RUP-6	RUP-1 ^B	Affinity purified Rat n 1	12
Cow, Bos d 2*	mAb ³	mAb1 ^B	nBos d 2	13
Horse, Equ c 4	103	14G4 ^B	n.a.	—
Cockroach				
Bla g 1	10A6	RaαBla g 1	UVA 97/02	14
Bla g 2*	8F4	RaαBla g 2	UVA 97/02	14
Per a 3	A-2	E-4 ^{AP}	Purified Per a 3	15
Fungi				
Asp f 1	4A6	RaαAsp f 1	Affinity purified Asp f 1	16, 17
Alt a 1	121G	121G ^B	rAlt a 1	18
	Mab-1	Mab-2	Affinity purified nAlt a 1	19

* Allergens for which the tertiary structure has been established by x-ray crystallography, nuclear magnetic resonance spectroscopy, or molecular modeling. ** mAb used to coat ELISA microtiter plates. ⁺ mAb or polyclonal rabbit antibody used for allergen detection. B: biotinylated; AP: alkaline phosphatase conjugate; n.a.: not available.

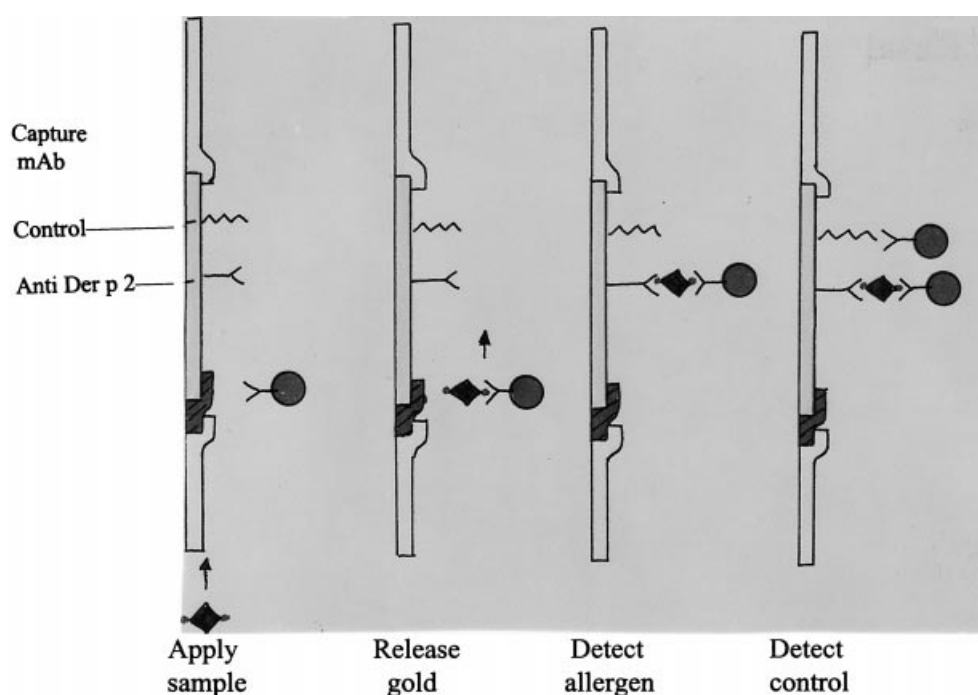


Figure 1. Rapid lateral flow tests for allergen detection by gold-labeled mAb. Capture anti-Der p 2 mAb is “striped” onto the membrane, and gold-labeled secondary mAb is impregnated in a pad with an absorbent wick at one end of the membrane. When dust extract is applied to the wick, allergen diffuses into the pad and binds to the gold-labeled mAb. This complex flows further along the membrane until it meets the line of capture mAb, where the complex binds and forms a visible red line. The intensity of color development is proportional to the allergen concentration in the sample.

pharmacy, clinic, or office use where allergen levels on dust samples can be obtained the same day. ACLOTES, a dipstick test for mite, uses polyclonal rabbit antibodies conjugated to colloidal dye (Samaron Pink) for detection and takes 30–60 min to develop (36). Results are graded according to the intensity of the pink color that develops and correlated with ELISA.

The most recent advance is the development of true rapid tests for mite allergen which use lateral flow technology and gold-labeled mAb for detection (Fig. 1). The lateral flow test has been developed for mite group 2 allergen and has the advantages that it detects both *Dermatophagoides pteronyssinus* and *D. farinae*, is quite sensitive (detection limit ~100 pg), and gives results in 10 min (37). The rapid test uses technology similar to that of pregnancy tests and is designed for home use as part of a kit which includes a simple, disposable, plastic dust sampling and extraction device (the MITEST dust collector) (38). The MITEST collector samples per unit area (0.25 m²) and allows dust to be collected and extracted within 2 min. Prototype rapid tests have also been developed for mite group 1 allergen and Fel d 1. In principle, lateral flow technology can be applied to other allergens, such as those of cockroach, rodent urine, foods, and latex, thus providing simple tests of exposure for a variety of environmental allergens.

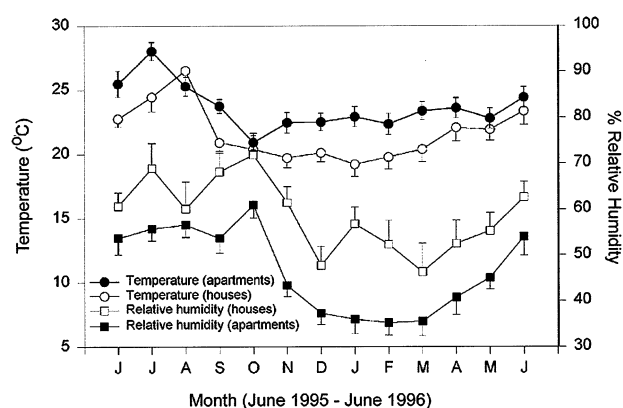
Dust analyses provide a useful, but indirect measure of personal allergen exposure, and the shortcomings of dust analysis have prompted attempts to monitor airborne allergen levels. Airborne measurements of animal allergens can often be made by conventional ELISA under undisturbed conditions (11, 39–42). The sensitivity of such measurements has recently been increased by 5–10-fold by commercial ELISA amplification systems, which use either catalyzed reporter deposition or polymeric streptavidin to amplify the signal, and which have detection limits in the low pg range (12, 43–45). However, even with amplification systems, detection of mite and cockroach allergens in the air has proved difficult (2, 39, 46). Tovey and colleagues have developed a novel personal sampling device that enables inhaled particulate allergen to be directly visualized and measured. The HALOGEN system uses silicone intranasal samplers which can be worn by the patient for 4–8 h during normal domestic activities. Particles that are inhaled during respiration are deposited onto small plastic slides coated with allergen-specific mAb and can be immunostained to form an allergen “halo”, or directly assayed for allergen by amplified ELISA (reviewed in Ref. 47). The HALOGEN system has been successfully used to detect inhaled particles bearing Der p 1, Fel d 1, pollen allergens, and fungal spores (47–50).

Monitoring allergen exposure in clinical practice

Allergen avoidance has been recognized as an integral

part of the management of patients with asthma, together with antiasthma drugs and immunotherapy. This recognition is based on the extensive epidemiologic studies on sensitization and exposure to indoor allergens that have been carried out worldwide, in which immunoassays for measuring exposure have played a major role. Currently, several prospective studies are underway to investigate the effects of early childhood exposure on asthma prevalence, including controlled trials of avoidance in infancy to determine whether effective reductions of allergen exposure at home decrease the prevalence of the disease (20, 51–53). The outcomes of these studies could have an enormous impact on the significance of indoor allergens from a public health perspective. The AAAAI position statement on environmental allergens emphasizes the fact that patient adherence to allergen avoidance recom-

A



B

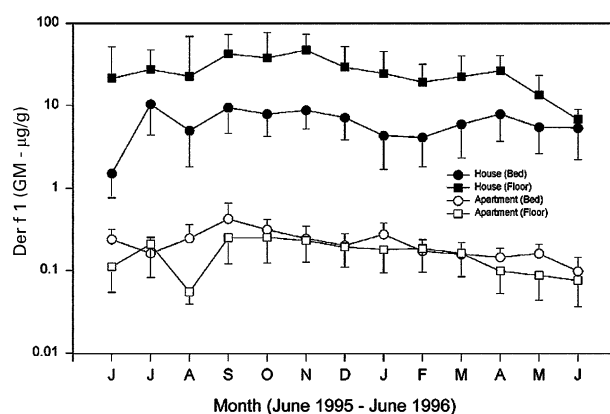


Figure 2. Year-round comparison of temperature and relative humidity (RH) (A) and mite-allergen levels (B) in houses and apartments in Boston, MA. The apartments had a common heating system which maintains high temperature and low RH from November to June. In contrast, single-family homes had lower temperatures, RH >50% year-round, and ~100-fold higher allergen levels. Reproduced courtesy of Dr Ginger Chew (Columbia University) and with the permission of the publishers (Allergy 1999;54:1058–1066).

mendations is often low, at 20–50% in clinical trials and probably lower in clinical practice (23). This underscores the need for better patient education and care to ensure that avoidance procedures are properly implemented.

Monitoring allergen exposure can play a role in demonstrating whether patients are exposed to significant concentrations of indoor allergens and in encouraging compliance with avoidance procedures. Curiously, the NHLBI expert panel report suggested that patients' exposure could be assumed on evidence of allergen sensitization (skin tests or *in vitro* IgE tests) and clinical history (22). However, patient history may not be a good guide to mite or cockroach sensitization, or to exposure to animal allergens if the patient does not keep furred pets. Even if sensitization can be demonstrated, patients may not be, or may not believe themselves to be, significantly exposed at home (54). Climatic and housing conditions vary widely in Europe and across the USA, making it unwise to make assumptions about allergen exposure. Studies in the USA have shown that allergen exposure in Boston (MA) varies according to housing type: centrally heated apartments which have low relative humidity (<45% relative humidity [RH]) for 6 months had extremely low levels of mite allergen (<0.5 µg/g dust), whereas single family homes with >50% RH year-round had 10–100-fold higher allergen levels (Fig. 2) (55). Other studies show that mite allergens can occur in apparently dry arid regions in homes that use evaporative cooling systems (56). Animal allergens are found in significant quantities in homes that do not contain pets, in schools, and in other public places, and cockroach allergens are found in about 20% of homes in the USA that have no visible evidence of cockroach infestation (40, 54, 57–59).

These observations suggest that assessments of allergen exposure should not be assumed. Over the past 2 years more than a dozen commercial reference laboratories in the USA and in Europe have begun to provide allergen-analysis services. Interestingly, in the USA, with the exception of contract research studies, these services are most often used by indoor air quality (IAQ) specialists and environmental companies, not allergists! Although making house visits to collect samples for allergen analysis is time-consuming, and not reimbursed by health authorities, a new study carried out by DeBlay et al. in Strasbourg (France) shows that use of an "indoor environmental technician" (IET) to visit homes resulted in greater compliance with avoidance measures and significantly greater reductions in allergen levels (60). This multicenter study involved around 380 rhinitis/asthma patients divided into two groups, those who received avoidance advice from their allergist alone, and those who received it from their allergist and from the IET during a home visit. The problem with allergen

avoidance has always been that even if avoidance reduces allergen exposure by 80–90%, reservoir levels may remain higher than proposed threshold levels for sensitization, e.g., 2 µg/g mite allergen, in homes with very high allergen levels (>10 µg/g). This is a potential problem for patient-based tests, such as lateral flow tests, which may give positive reactions even when substantive allergen reduction is achieved. At present, such tests should be used as screening tests to demonstrate exposure, while ELISA is the preferred technique for following avoidance procedures.

Allergists should consider indoor allergen exposure when making recommendations about immunotherapy and about allergen avoidance. Precedents from grass pollen and ragweed hay fever studies suggest that immunotherapy is most effective when given out of season, when allergen exposure is negligible. An earlier report suggested that monitoring allergen exposure is beneficial in evaluating mite immunotherapy among asthma patients (61). Demonstrating that the patient is sensitized and exposed to relevant allergen could help to reinforce advice about immunotherapy or about the selection of appropriate avoidance procedures. Several allergen control devices and procedures have been systematically tested for their effects on allergens. These include mattress encasings, vacuum cleaners, acaricides, protein denaturants, air cleaners, air ducts, and procedures that reduce ambient humidity (62, 63). Allergists can provide patients with clear information about the efficacy of these procedures and make appropriate practical recommendations. The greatest benefits are to improve patient knowledge of the relationship between allergen exposure and allergic symptoms, so that patients can make informed choices about controlling allergen exposure in the home (63). Patient-based tests and personal sampling systems should encourage compliance with avoidance procedures. The use of environmental technicians, allied health personnel, or IAQ specialists may help with implementation and encourage changes in lifestyles to reduce allergen exposure.

The net result is that both allergists and patients benefit from objective information about allergen exposure. It has been estimated that a twofold reduction in allergen exposure could reduce the risk of developing asthma and asthma severity (64–66). While this effect may be optimistic for a relatively modest reduction in allergen exposure, it suggests that reducing allergen levels of key reservoirs (in bedrooms, living rooms, and basements) by more than 50% may reduce asthma morbidity. Over the next decade, we can look forward to further applications and advances in immunoassay technology that should provide better understanding of the role of allergen exposure in asthma and lead to the development of effective intervention strategies.

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Potential conflict of interest

Dr Chapman is founder of the INDOOR biotechnologies companies (Charlottesville, VA, and Manchester, UK), which are involved in the production of allergen detection systems and provide reference laboratory services.

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