8. Allergy and epidemiology

Say what the use, were finer optics given,
To inspect a mite not comprehend the heaven?
Or touch, if trembling alive all o'er,
To smart and agonise at every pore.

Alexander Pope, 1733,
An Essay on Man.

8.1 Introduction

This chapter deals with the allergic disorders associated with dust mite allergens, principally allergic asthma, atopic eczema and allergic perennial rhinitis. The main theme is the natural history of allergen exposure, concentrating on allergen levels and mite population densities in relation to temporal and spatial variation in the prevalence of these disorders, particularly atopic asthma. I do not review epidemiology of asthma or allergy more generally. This topic has been investigated in two large, long-term, international studies of asthma and allergies in adults and children respectively: the European Community Respiratory Health Survey (ECRHS; Burney *et al.,* 1994; European Community Respiratory Health Survey, 1996; Janson *et al.,* 2001; Sunyer *et al.,* 2004; www.ecrhs.org) and the International Study of Asthma and Allergies in Childhood (ISAAC; International Study of Asthma and Allergies in Childhood Steering Committee, 1998; Asher *et al.,* 2006; Pearce *et al.,* 2007; Ait-Khaled *et al.,* 2007; http://isaac.auckland.ac.nz). Several 'environmental' factors have been examined in these studies, including effects of climate (Verlato *et al.,* 2002; Weiland *et al.,* 2004), economic status (Stewart *et al.,* 2001), diet (Ellwood *et al.,* 2001) and mite allergen exposure (Zock *et al.,* 2006). Although there were differences in absolute prevalence values between the two studies, in general the patterns of prevalence were similar: low in Eastern Europe and higher in Western Europe with a strong northwest-southeast gradient, and highest in English-speaking countries (Pearce *et al.,* 2000).

The story of the relationship between dust mites, allergy and asthma is complicated by the fact that atopy, the genetic predisposition to make IgE antibodies to common allergens, may or may not be associated with the presence of disease, and that asthma, eczema and rhinitis can be provoked by agents other than allergens and may not be associated with atopy. Therefore, the disease states of relevance to this chapter are those combining allergen-specific IgE antibodies and/or a positive skin-prick test to dust mite and other common airborne allergens; where there is a family history of atopy; and where patients have active asthma, eczema and rhinoconjunctivitis. Nomenclature of allergy and allergic diseases was revised by Johansson *et al.* (2001) and Figure 8.1 indicates the overlap between atopy and allergic disease

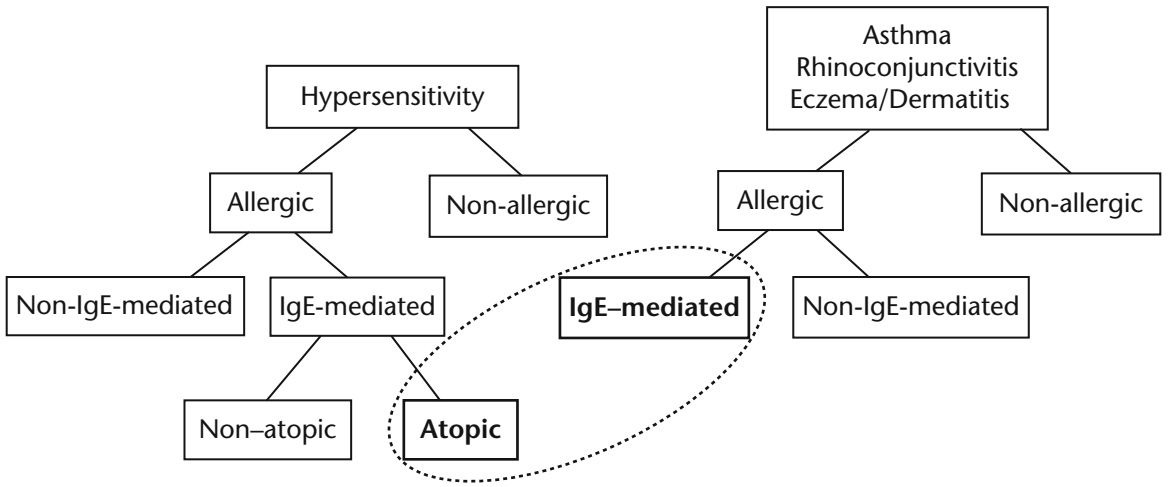

Figure 8.1 Interaction between categories of hypersensitivity and immune response (left) and disease (right) in relation to allergy, IgE antibody isotype and atopy. Dotted line: interface between atopy and disease relevant to mite allergens. Modified from Johansson *et al.* (2001).

based on this classification. For practical purposes in epidemiological studies, atopy has been defined by a positive skin-prick test to common airborne allergens such as those of dust mites, cats, dogs, pollens, cockroaches and various moulds. If the proportion of people with asthma who have specific IgE or positive skin-prick tests is known, the population attributable fraction of asthma due to atopy can be calculated (Pearce *et al.*, 1999, 2000; Sunyer *et al.*, 2004; Weinmayr *et al.*, 2007).

8.2 Diseases associated with dust mites

Over the years, dust mites have been implicated in several diseases and disorders, mostly with an allergic basis. The evidence for the associations ranges from very high to possible for most of the allergic conditions, and low to non-existent for the non-allergic ones.

8.2.1 Allergic diseases

a Allergic asthma

Asthma is probably not a single disease. It is hard to characterise unambiguously, but it involves wheeze, shortness of breath, airway narrowing and inflammation. However, the wide variety of provoking agents and the variable time course of symptoms in childhood and adulthood point towards the existence of different types of asthma – so-called phenotypes. The recognition and classification of different phenotypes has been around for many years, and non-allergic asthma and allergic asthma is one of the better known broad classifications. But it is not clearly understood whether these phenotypes represent clinical manifestations of different underlying diseases or whether they are different stages in the progression of the pathology of a single disease – inflammation of the airways – that presents differently in different people according to their susceptibility to different provoking agents. Classifications of asthma phenotypes are starting to emerge, with improved characterisation derived from large-scale epidemiological studies and clinical trials of patients with particular phenotypes (Wenzel, 2006).

A large proportion of spending on healthcare is devoted to asthma and it accounts for massive loss of time from school and work, with associated productivity losses (Weiss *et al.*, 1992). Asthma has been the subject of billions of dollars worth of research funding involving thousands of researchers, and yet we still have no clear understanding about how to prevent it, despite many developments in our knowledge, despite it being the subject of tens of thousands of research papers and several major textbooks (e.g. Barnes *et al.*, 1997; Naspitz *et al.*, 2001; Gershwin and Albertson, 2001; the British Library Catalogue has over 1500 records of books with the word 'asthma' in the title). What has happened is that we have realised that it is complex, challenging, elusive, and that many of the concepts that were received wisdom 10 years ago have since been discarded or are being re-evaluated.

Asthma is among the most common chronic diseases of childhood, particularly in urbanised, English speaking countries with a high standard of living. While treatable, asthma has increased in prevalence

since the 1960s, though some studies indicate a levelling off in the last few years (Asher *et al.,* 2006; Anderson *et al.,* 2007). In the ISAAC study, 4–32% of 6–7-year-olds (mean 14%) and 2–37% of 13–14-year-olds (mean 12%) had wheeze in the previous 12 months. Prevalence was above 20% for 13–14-year-olds in Australia, New Zealand, the UK, Ireland, the USA, Canada, Peru, Costa Rica and Brazil, and below 6% in India, China, Taiwan, Indonesia, Albania, Georgia, Romania, Russia and Greece (International Study of Asthma and Allergies in Childhood Steering Committee, 1998). In a subset of centres, the population attributable fraction of wheeze due to atopic sensitisation was 41% in countries with high annual per-capita gross national income (GNI; range 13–60%) and 20% in countries with low GNI (range 0–94%; Weinmayr *et al.,* 2007). In the ECRHS study, for those countries common to the ISAAC study, adult asthma (diagnosed) also had a higher prevalence in Australia, New Zealand, the UK and the USA (7–12%), and lower prevalence in India and Greece (~3%; European Community Respiratory Health Survey, 1996). The mean population attributable fraction of adult asthma due to atopic sensitisation was 30%, and 18% for sensitisation to dust mites (Sunyer *et al.,* 2004).

b Rhinitis, rhinoconjunctivitis, keratoconjuntivitis and otitis media

Allergic rhinitis means sneezing, runny, blocked or itchy nose. Allergic rhinoconjunctivitis means these symptoms plus watery, inflamed or itchy eyes. Allergic rhinitis has been classified as seasonal, provoked by pollens (what most people would call hay fever) and perennial, triggered by indoor allergens (mites, pets, moulds, cockroaches). More recently it has been classified as intermittent or persistent, and by severity (see Mösges and Klimek, 2007). Allergic rhinitis affects 5–30% of the population, with children aged 6–14 being most affected (Bousquet *et al.,* 2001; Asher *et al.,* 2006). Effects of rhinitis can include sleep impairment and hence poor cognitive function and impaired quality of life (Meltzer, 2007).

Keratoconjunctivitis

This is a rare, chronic severe inflammation of the conjunctiva affecting mostly young boys. It is considered to be an IgE mediated disorder associated with atopy (Frankland and Easty, 1971; Johansson *et al.,* 2001), although not invariably so. Evidence for an association with dust mites is slight, and includes mite-specific IgE in tears and sera of patients (Sompolinsky *et al.,* 1984) and a seasonal peak in symptom severity corresponding with maximum mite population density in patients' homes (Mumcuoglu *et al.,* 1988).

Secretory otitis media (glue ear)

It has been reported that 20–90% of children with glue ear are sensitised to common inhalent allergens. Nasal allergy is considered to have some causal involvement (Pelikan, 2007). The association between allergens and glue ear was reviewed by Bisgaard and Mygind (1987).

c Atopic eczema and papular urticaria

Atopic eczema (or atopic dermatitis) is a chronic inflammatory skin disease, particularly common in infancy (10–20% prevalence; Sehra *et al.,* 2008). Prevalence of eczema in general in the ISAAC study was 1–20% and increasing (Asher *et al.,* 2006). In the ECRHS study, a mean of 7.1% of adults had eczema in the previous 12 months and 2.4% had eczema attributable to atopy (Harrop *et al.,* 2007). Prevalence of eczema, like asthma, shows marked geographic variation, tending to be high in Western Europe, Australia and New Zealand and low in Eastern Europe, the Mediterranean and South-East Asia (Asher *et al.,* 2006; Harrop *et al.,* 2007). Positive skin-prick tests, elevated levels of serum IgE to at least one airborne allergen, as well as allergen-specific cellular responses, are common findings among patients with atopic eczema (Mitchell *et al.,* 1982; Chapman *et al.,* 1983; Rawle *et al.,* 1984; Reitamo *et al.,* 1986; Tanaka *et al.,* 1989).

Papular urticaria (also known as nettle-rash: the common stinging nettle is *Urtica dioica*) is an itchy eruption consisting of localised non-pigmented papules. Alexander (1972) reported positive intradermal tests using *Dermatophagoides* spp. extract and high densities of dust mites in homes of a third of a group of children with papular urticaria but not in a control group, suggesting that some cases of urticaria may be due to dust mite allergens. Dixit (1973) reported three cases of people with urticaria who were positive by skin-prick test to dust mites and whose condition seemed to be associated with exposure to dust mites.

d Anaphylaxis

Anaphylaxis is a rapid-onset, severe, systemic allergic reaction. Symptoms include respiratory

and cardiac failure. This condition can be fatal. Edston and van Hage-Hamsten (2003) report a case of a 47-year-old farmer who was allergic to dust mites and who died of anaphylactic shock. Serum tryptase activity of post-mortem blood was substantially elevated, indicating massive release of this enzyme from mast cells, a characteristic marker of anaphylaxis. Serum anti-*D. pteronyssinus* and *D. farinae*-specific IgE was also elevated, as were levels of house dust mite allergen in the patient's bed. Dutau (2002) reviewed cases of anaphylaxis due to ingestion of food contaminated with mites (see below). Wen *et al.* (2005) ascribed a case of anaphylaxis to consumption of a pancake contaminated with *Blomia freemani*. A similar case was described by Erben *et al.* (1993) involving pancake mix contaminated with *Dermatophagoides farinae*. In a Venezuelan study of several cases of anaphylaxis that occurred after eating flour and wheat products, high levels of mite contamination were found in 25/30 cases, (Sánchez-Borges *et al.,* 1997, 2001). Oral, mite-induced anaphylaxis was reviewed by Sánchez-Borges *et al.* (2005).

Sudden Infant Death Syndrome (SIDS)

A role for anaphylaxis in SIDS caused by mite allergens was proposed by Mulvey (1972), having observed anaphylactic-type reactions among several patients inadvertently given high doses of mite allergen preparations during immunotherapy. Turner *et al.* (1975) considered anaphylaxis induced by allergy to dust mites may be one causative factor in SIDS deaths in Western Australia. Surveys in homes of SIDS patients (Mulvey, 1972) and in nursery bedding (Tovey *et al.*, 1975; Ingham and Ingham, 1976) indicated that infants received exposure to high population densities of mites. Post-mortem levels of serum beta-tryptase (a marker for anaphylaxis) in infants who died from SIDS, compared with children who died from known non-anaphylactic causes, was elevated in one study (Buckley *et al.,* 2001) but no different from the control group in another (Hagan *et al.,* 1998). The role, if any, for mite-mediated anaphylaxis in SIDS remains unclear.

e Gastrointestinal allergy

There are a few reports of ingestion of pyroglyphid mites causing symptoms of gastrointestinal allergy. Scala (1995) described a case of a 5-year-old girl, skin-test positive to dust mites, who had suffered persistent vomiting but no respiratory symptoms. Her bedroom was indicative of high dust mite exposure and her symptoms abated after allergen avoidance. Subsequent nasal challenge with *Dermatophagoides* extract induced vomiting. It was suggested that sensitisation of the gut to dust mites, following allergen inhalation and transfer to the gut by saliva deglutition and oesophageal peristalsis, may have resulted in gastroenteric symptoms. Specific IgE to inhalent allergens has been found in intestinal washings of children with atopic eczema, and the enteric mucosa may sometimes be the first tissue to receive exposure to inhalent allergens (Marcucci *et al.*, 1985).

There are several well-documented cases due to ingestion of relatively large quantities of stored products mites in foodstuffs (Matsumoto *et al.,* 1996), and many foods can become contaminated with mites, especially grain and flour, dried meat and fish, and even beer (mites can contaminate malted barley). In parts of the world where flour and dried goods are still sold retail as loose commodities, mite contamination and consumption is common. Cheeses become infested by mites of the genera *Tyrophagus* and *Tyrolichus* (Robertson, 1952) and some have mites introduced onto them intentionally, including Altenburger (colonised by *Tyrolichus casei*), and Cantal from the Auvergne region of France. The mites colonise as the cheeses are maturing and a layer of dead mites develops on the rind, giving the cheeses a distinctive, slightly salty taste. Barber *et al.* (1996) and Sánchez-Monge *et al.* (1996) in their studies on the interactions of *Dermatophagoides* spp. allergens with inhibitors derived from various cereals, assert that infestation of flour with *Dermatophagoides pteronyssinus* is a common event, but although *D. farinae* was first described from samples of flour (Hughes, 1961), *Dermatophagoides* spp. are not considered to be major pests of flour compared with acaroid and glycyphagoid mites.

The oral administration of allergen can induce specific immune tolerance (Cox *et al.*, 2006), and this occurs naturally in the gut as a result of exposure to the many allergens contained in foods. It seems not unreasonable that immune tolerance in the gut may be induced by allergens associated with inhalent particles.

8.2.2 Non-allergic disorders associated with dust mites

a Acariasis

This is a condition in which live mites are deemed to be living in the lungs, gut or the urinogenital system. Usually mites are found during pathological examination of samples of sputum, faeces or urine (Sasa, 1950, 1951; Chen and Fu, 1992; Li *et al.,* 2003). With pulmonary acariasis, mites may have been accidentally inhaled following high occupational exposure involving stored products, whereas intestinal acariasis is likely due to ingestion of contaminated food.

b Kawasaki disease

Kawasaki disease (KD) is a systemic vasculitis of unknown aetiology, involving skin rash and fever, first recognised in the 1960s, and mainly affecting children <5 years old (Tanaka *et al.,* 1976). The role of mites is now all but discounted, and I mention KD for historical interest because of the fuss and flurry it created at the time. *Rickettsia*-like organisms, assumed to be vectored by dust mites, were found in biopsies (Hamashima *et al.,* 1973, 1982; Carter *et al.,* 1976). Some patients had raised IgE antibody (Kusakawa and Heiner, 1976; Furusho *et al.,* 1981; Fumimoto *et al.,* 1982) and prior respiratory disease (Bell *et al.,* 1981), while others did not (Klein *et al.,* 1986). Onset of KD was claimed to be associated with domestic cleaning and mite exposure (Patriarca *et al.,* 1982; Ohga *et al.,* 1983), prompting mite surveys in homes of patients (Ishii *et al.,* 1983; Klein *et al.,* 1986). A new twist emerged when a strain of *Proprionibacterium acnes* was isolated from blood of patients, and mites from their homes. Since mites ingest skin scales and the bacterium causes acne, the finding is unremarkable. But H. Kato *et al.* (1983) found *P. acnes* caused cardiopathology similar to KD in experimental animals and suggested mites were vectors of *P. acnes*. The theory of microbial aetiology persisted, with *Pseudomonas* spp. (Keren and Wolman, 1984), *Coxiella burnetti* (Lambert *et al.*, 1985) and retroviruses (Shulman and Rowley, 1986) as candidates. So what does cause Kawasaki disease? It is almost certainly not dust mites. Much of the speculation was fuelled by studies published as short letters without peer-review. Those mite researchers involved reported neutral findings (Ishii *et al.,* 1983) or cast doubt upon the role of dust mites (Jordan *et al.*, 1983; Murray *et al.,* 1984).

c Delusions of parasitosis

Delusions of parasitosis is a psychological disorder in which the patient believes that small parasites, insects, mites or worms are living in the skin or in the bodily orifices (Alexander, 1984). It is a very distressing condition of chronic duration, but it is not caused by allergy dust mites, even though some patients may claim otherwise (Woodford, 1980).

d Sick building syndrome

Sick building syndrome is an occupational disease associated with air quality in modern buildings (Apter *et al.,* 1994). There is no general definition, but there is a complex of non-specific symptoms including dizziness, rhinoconjunctivitis, sore throat, headache, fatigue, chest tightness, wheeze, skin dryness and gastrointestinal symptoms. It has been attributed to electromagnetic radiation from office equipment, organic chemicals in cleaning and construction materials, indoor air of low humidity, pollen, and microorganisms in the air-conditioning system. A role for dust mites in sick building syndrome has been suggested because some of the symptoms were assumed to have an allergic basis and because dust mites and their allergens can be detected in carpets and office furniture (Janko *et al.,* 1995). There are no hard data to indicate that dust mites play any role in sick building syndrome.

8.3 Sensitisation and the development of allergy and allergic disorders

8.3.1 Birth cohorts

Early infancy has been identified as the critical period for sensitisation to allergens (e.g. Holt *et al.*, 1990). Several studies have charted the unfolding relationship between allergen exposure, the development of allergy and the expression of allergic disease from birth through childhood. These birth cohort studies involve newborn infants at high risk of development of allergy because of a family history of atopy. In a birth cohort of 67 children with a family history of allergic diseases, Sporik *et al.* (1990) found all but one of the children with active asthma at age 10 had more than 10 μg g^{-1} of Der p 1 in their beds and carpets at age one. The higher the Der p 1 concentration, the earlier was the onset of the first episode of wheeze. In a cohort of over 900 children followed up to age seven, Lau *et al.* (2000) found a linear relationship between the concentrations of Der 1 (Der p 1 + Der f 1) in

homes and the proportion of children who developed allergies to mites. By age three, there was a higher proportion of mite-sensitised children who had developed asthma than children who were not sensitised (ca. 30% v. 10%).

More recently, several studies of infants and children have not found linear dose-response relationships between concentrations of allergens and development of allergy or asthma. The Childhood Asthma Prevention Study (CAPS) involved about 600 children in Sydney, Australia, between 1997 and 2004. Half the children received allergen avoidance measures and the other half were a control group (Mihrshahi *et al.,* 2003). Results were analysed at ages five and eight. There were no differences in numbers of children with asthma, eczema or allergy by age eight. Also, children with low or high mite allergen levels in their beds had lower prevalence of asthma, eczema or allergy than those with medium levels of exposure, i.e. the relationship between allergen exposure, sensitisation and disease was a bell-shaped curve (Almqvist *et al.,* 2007; Tovey *et al.*, 2008; Figure 8.2 below). One explanation for this result is that reducing allergen exposure in homes with high levels of mite allergens also reduces exposure to something in house dust that may be beneficial or protective against the development of allergy.

The Manchester Asthma and Allergy Study (MAAS; Custovic *et al.,* 2002) was based on 251 newborn children with a family history of atopy, randomised to receive stringent allergen avoidance or a control group. The allergen avoidance group had a *greater* prevalence of children with allergy to dust mites at age three, although they had better lung function than children in the control group (Woodcock *et al.,* 2004). Again, this suggests allergen control reduces exposure to some sort of component that is protective against the development of allergy.

A non-linear dose-response between allergen exposure (to cat but not mite) was found by Torrent *et al.* (2007) in a birth cohort study of 1500 children in Spain and the UK (the Asthma Multicentre Infant Cohort Study). They suggested a minimum level of exposure was required to induce sensitisation in an all-or-nothing manner, and above this threshold there was no obvious dose-response.

The PARSIFAL study (Prevention of allergy – risk factors for sensitisation in children related to farming

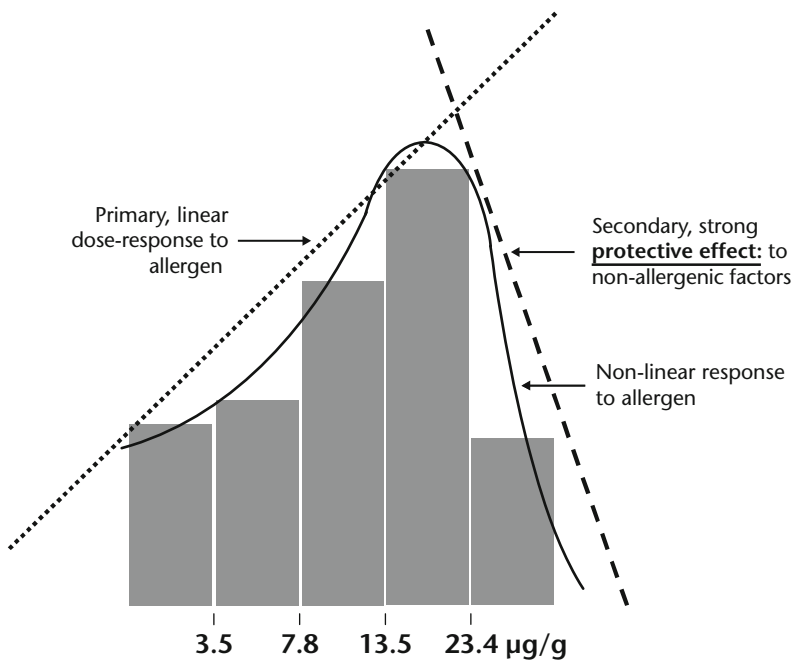

Figure 8.2 Non-linear dose-response between exposure and sensitisation to dust mite allergens. (Figure courtesy of Euan Tovey.) Columns represent relative prevalence of sensitisation to dust mites among 516 children at age five in the CAPS study. Figures on the *x* axis are quintiles of time-weighted average Der p 1 levels (micrograms per gram of dust) in the mattresses of the children. Mattress dust was sampled when children were aged three, six, nine and 12 months, then six-monthly until age five (cf. Almqvist *et al.,* 2007).

and anthroposophic lifestyle) involved 400 children from five European countries and aimed to identify lifestyle factors associated with farming and anthroposophy (the teachings of Rudolph Steiner) that predispose towards lower prevalence of atopy. Farming families have high exposure to bacteria and fungi through contact with soil, crops and animals, and anthroposophists tend to avoid the use of antibiotics and have a diet that includes fermented vegetables containing live lactobacilli (Alm *et al.,* 1999). PARSIFAL was not a birth cohort study, but found, like the CAPS study, a bell-shaped dose-response curve between mite allergen concentrations in mattress dust and prevalence of sensitisation to dust mites (Schram-Bijkerk *et al.,* 2006). The authors suggested that the protective effect at high allergen concentrations was due to exposure to immune modulators such as endotoxins from bacteria as well as soluble beta-glucans and other polysaccharides from fungi.

These studies add to the evidence of a causal relationship between exposure to domestic allergens and development of sensitivity and asthma. They also indicate that the relationship between allergen exposure and disease is not straightforward. The finding in the CAPS and PARSIFAL studies of a non-linear (bell-shaped) relationship between levels of allergen in beds of children and the prevalence of asthma and allergy indicates a primary dose-response and a secondary, seemingly protective effect at high exposure. The data suggest a scenario whereby the development of large populations of dust mites and allergen concentrations is associated with the development of large microbial communities. The removal of dust mite allergens, deemed to be beneficial within a linear dose-response paradigm, appears also to remove some useful compounds derived from microorganisms that modulate the immune system and help prevent the development of allergies and allergic asthma.

There is quite a lot known about bacterial endotoxins and their protective effect on the immune system, including early reports of 'tolerance' following repeated injections of endotoxin in children with asthma (Peterson *et al.,* 1964) and some studies have found a protective effect of endotoxin against sensitisation to allergens (Braun-Farlander *et al.,* 2002; Gehring *et al.,* 2004). But we know almost nothing about the interactions between bacteria, fungi and mites, and the extent to which large mite populations are associated with the development of diverse and abundant microbial communities in house dust. Some basic elements of the interaction between mites and microorganisms were examined in Chapter 2 (Figures 2.7, 2.18). As a general ecological principle, the more diverse and abundant a community in terms of species-richness, functional groups and numbers of individuals present, the greater the prospects for the development of complex interactions between the component organisms. This principle is the basis of research on community and food web ecology (Chapter 4). It is plausible that diverse and abundant communities of mites, fungi and bacteria have far greater levels of complexity than we have considered hitherto, with consequences for our understanding of the interaction between allergen exposure and disease.

8.3.2 The hygiene hypothesis and the microbiota hypothesis

In affluent societies, we have become obsessed with attempting to eradicate 'germs'. Because people tend to be unaware that most microorganisms are not pathogenic, and that they have an immune system designed to give them efficient protection against the ones that are, we spend absurd amounts of money on antibacterial cleaning products, soaps, wipes, swabs and sprays. Dirt and germs have become a collective phobia. Our lack of basic biological knowledge has been exploited and we have been sold the idea that *all* bacteria are harmful. If we do not rigorously attempt to remove them from our kitchen surfaces and bathrooms, according to the advertising messages, then we must be neglectful and slovenly and place our families at risk of gastroenteritis or worse, even though frequent use of cleaning sprays has been associated with an elevated risk of asthma (Zock *et al.,* 2007). In our ignorance, daily we flush thousands of gigalitres of water laden with cleaning chemicals down our sinks and lavatories with virtually no thought to the environmental impact.

Most bacteria are beneficial. Without them, we would not be here, because they drive all the major biogeochemical cycles on the planet. Decomposition and nutrient cycling of nitrogen, phosphorous, carbon and sulphur are essential to plant growth, biodiversity and food production. It has been known for a very long time that consuming certain bacteria stimulates the so-called innate immune system.

The hygiene hypothesis, simply stated, is that allergic diseases can be prevented by infection in early

childhood. Declining family size and higher standards of hygiene and cleanliness in recent years have reduced opportunities for cross-infection and resulted in more widespread clinical expression of atopic disease (Strachan, 1989, 2000; see also Rook and Stanford, 1998; Hamilton, 1998). Exposure to a range of viruses, bacteria and fungi – including *Mycobacterium* spp., found in soil and water; lactobacilli in probiotic foods – can confer protection against the development of allergies through exposure to microbial endotoxins, beta-glucans and polysaccharides. The elicitation of cellular immune mechanisms involve two sets of T-cell helper (Th) phenotypes, Th1 associated with diseases caused by infectious agents and Th2, with allergic responses. The theory for the role of infection in early childhood revolves around the notion that a reduction in infections due to increased standards of healthcare and hygiene has led to a failure to elicit Th1-type responses, thus leaving the immune system open to challenge from allergen exposure and Th2-type responses, resulting in greater prevalence of allergy (reviewed by Holt *et al.,* 1999).

Wold (1998) proposed a variation of the hygiene hypothesis called the 'microbiota hypothesis', whereby altered bacterial colonisation of the infant gut resulting in failed induction of immune tolerance is responsible for increased prevalence in allergic sensitisation. The microbiota hypothesis is based on the premise that exposure to lactobacilli, bifidobacteria and mycobacteria skew immune responses to immunoregulation rather than inflammatory responses, and lack of exposure to such bacteria in industrialised societies may be responsible for the increase in allergy. There are strong lines of evidence that link gut microbiota with atopic sensitisation and disease (reviewed by Noverr and Huffnagle, 2005; Penders *et al.,* 2007) and the role of the gut, and the gut-associated lymphoid tissue as an immune organ of relevance to allergy is now starting to be investigated.

8.4 Allergen exposure

Mite allergens are only one of several groups of allergens found within homes, the others being those derived from mammalian pets, fungi and insect pests. In addition there are microorganisms, pollutants such as cigarette smoke, gases from cookers and heaters, volatiles from certain building materials and cleaning products and a host of other compounds capable of affecting the human immune system. The evidence for the causal relationship between exposure to house dust mite allergens and asthma has been steadily amassed since the work of the Leiden group in the 1960s. Voorhorst *et al.* (1964, 1967, 1969) showed that the prevalence of positive skin-prick test reactions to extracts of *Dermatophagoides pteronyssinus* correlated well with atopy and the density of dust mites in homes (which also correlated with the degree of dampness of the homes). Independently, Miyamoto and coworkers (Miyamoto *et al.,* 1968, 1969, 1970; Oshima, 1967) concluded that house dust mites were the most important allergenic component of house dust and showed that the allergenic potency of dust related to the population density of the mites it contained.

Some reviews of the epidemiology of mite-allergic asthma (Sporik and Platts-Mills, 1992; Peat, 1995) have taken the approach of assessing the eight criteria of Bradford Hill (1965) relating to causal associations between disease and environmental factors. These include the strength, consistency, specificity, timing and biological plausibility of the association between disease and risk factor; whether there is a 'dose-response' relationship between factor and disease; whether a cause-and-effect interpretation concords with the known biology of the disease and whether the association can be demonstrated experimentally. All these criteria have been addressed for dust mites and allergic asthma, to a greater or lesser extent, though the dose-response relationship has been the topic of debate (Peat, 1995; Marks *et al.,* 1995b; Platts-Mills *et al.,* 1995; see below).

8.4.1 Mite allergen concentrations as risk factors for allergy and asthma

The First International Workshop on House-Dust Mite Allergy, held in 1987 (Platts-Mills *et al.,* 1989b), established preliminary guidelines for levels of mite allergens in houses that represented a risk factor for allergic disease. The guidelines, based on the very few epidemiological studies available at the time (e.g. Korsgaard, 1982, 1983b), were that 2 μg of *Dermatophagoides* group 1 allergen per gram of reservoir dust from mattresses and carpets (deemed equivalent to 100 mites per gram) be regarded as a risk factor for sensitisation and the development of asthma, and that 10 μg of Der 1 g^{-1} (500 mites per gram) be regarded as a major risk factor for the development of acute asthma in mite-allergic individuals. At the Second International Workshop (Platts-Mills *et al.,* 1992), these threshold levels were regarded as relevant to the development of asthma, based on studies of mite

allergen exposure and risk, published after the First International Workshop (Lau *et al.,* 1989; Charpin *et al.,* 1991; Peat *et al.,* 1987, 1993; Sporik *et al.,* 1990; Arruda *et al.,* 1991). The paper by Sporik *et al.* (1990) details a longitudinal birth cohort (and represents a key study linking allergen exposure during infancy to development of asthma), whereas the others were cross-sectional studies of mostly school-age children. The threshold levels have been widely adopted as a reference framework for allergen 'exposure', evidenced by the many publications that present data in terms of frequencies of dust samples in exposure classes (typically, <2, 2–10 and >10 μg g^{-1}), rather than more informative statistics such as a geometric mean or median and a measurement of variation.

The concept of 2 μg and 10 μg Der 1 as exposure risks includes the assumptions that:

- there is a positive dose-response (be it linear, or log.-linear or sigmoidal; Platts-Mills *et al.,* 1995) between exposure, sensitisation and disease;
- mite allergens are a primary risk factor for allergic sensitisation and disease;
- allergen measurement in reservoir dust is an accurate and clinically meaningful measure of exposure;
- a fixed level of exposure is globally applicable; and
- there is equivalence between exposure measured as mite population density and allergen concentrations.

So what is the evidence for these assumptions? We have seen examples of large birth cohort studies where there is a non-linear relationship, or no relationship, between allergen exposure, sensitisation and disease (Woodcock *et al.,* 2004; Schram-Bijkerk *et al.,* 2006; Almqvist *et al.,* 2007; Torrent *et al.,* 2007; Tovey *et al.*, 2008). There is now more evidence from longitudinal studies that the relationship between exposure, sensitisation and disease is complex and multifactorial, involving microorganisms, the gut as well as the lungs as an immune organ, diet, lifestyle, exposure to infectious agents, allergens other than dust mites, including the apparently protective effect of exposure to pets early in life (reviewed by Pearce *et al.,* 2000), as well as other factors (cold air, stress) that can trigger asthma. Little of this was known in 1987, partly because large birth cohort studies had not yet been done.

Most allergens have been measured in settled, or reservoir dust. For risk factor values of allergens in reservoir dust to be relevant to sensitisation and disease, we have to assume that the quantity of allergens released into the air and inhaled is proportional to the amount in settled dust. The problem is that there is no obvious, predictable relationship between allergen concentrations in reservoir dust and the amount of allergen inhaled (O'Meara and Tovey, 2000; see below). There may well be a scaling effect in that reservoir levels in *large* long-term studies represent an *indicator* (i.e. an indirect measure) of airborne exposure, but the indicator signal is not apparent in smaller studies of shorter duration.

Literature records of Der 1 allergen levels in beds indicate the geometric mean concentration of Der 1 is >2 μg at two-thirds of localities around the world and >10 μg at a third (see section 8.7 below and Figure 8.12 therein). In other words, the risk factors of Der 1 exposure for sensitisation and disease fall well within the range of bed Der 1 in most homes in most parts of the world surveyed to date. Levels of 2 μg Der 1 g^{-1} in beds would be considered low compared with those in Sydney, Strasbourg and Seattle, but very high in Tokelau, Tartu and Turin. Of the studies used to support the 2 μg and 10 μg risk factors, only that by Lau *et al.* (1989) was at a low allergen location (Berlin). The locations of the other studies fall within the top 20 most heavily Der 1-polluted places in the world (Charpin *et al.,* 1991 – Marseilles; Peat *et al.,* 1987 – Sydney; Sporik *et al.,* 1990 – Poole; Arruda *et al.,* 1991 – Sao Paulo). In a case-control study of 74 children, Marks *et al.* (1995b) found homes in Sydney all exceeded the risk levels for allergens and there was no dose-response relationship between exposure and sensitisation or asthma. There was no difference in allergen exposure between children with atopy and non atopics. Children with asthma and house dust mite allergy had slightly but significantly *lower* allergen exposure than those with no asthma or who were not sensitised to dust mites.

One might expect lower thresholds at places where exposure is low. Of studies done at such locations (Southampton, Stockholm, Berlin respectively), Price *et al.* (1990) proposed a sensitisation threshold of 0.5 μg Der 1 g^{-1} in carpet dust, Wickman *et al.* (1991) found Der 1 in beds of mite-sensitised children was 106 ng g^{-1} (geometric means calculated from their Figure 1) compared with 34 ng g^{-1} for atopic children not sensitised and 44 ng g^{-1} from non-atopic controls, and Wahn *et al.* (1997) found children who were sensitised to dust mite by age three had a median of 0.9 μg

Der 1 g^{-1} in carpet dust compared with 0.2 μg g^{-1} for children who were not sensitised. Peat *et al.* (1995a, b) found where levels of dust mite allergens were low (central Australia), children became sensitised to other, more abundant allergens like *Alternaria* or rye grass. Similarly, Sporik *et al.* (1995) at Los Alamos, New Mexico, found that where mite allergen levels were low, sensitisation was mainly to high levels of cat allergen.

Significant positive correlations have been demonstrated between Der p 1 concentrations and mite density (Tovey *et al.,* 1981; Lind, 1986b; Colloff *et al.,* 1991; Warner *et al.,* 1998; Mumcuoglu *et al.,* 1999; Terra *et al.,* 2004; see section 8.7.1 below), though showing some variation in equivalence to 2 μg of Der 1 g^{-1} = 100 mites g^{-1} and 10 μg of Der 1 g^{-1} = 500 mites g^{-1}. Other studies found no statistical relationship between Der 1 and mite numbers (Wen and Wang, 1988).

In a systematic review of the epidemiological data available up to about 1999 on allergen exposure as a risk factor for asthma, Pearce *et al.* (2000) emphasised the limitations of the cross-sectional population-based studies on asthma prevalence in relation to allergen exposure. Because prevalence is a product of incidence (i.e. the number of new cases per unit time) *and* duration (i.e. how long the disease persists in individuals), a factor such as allergen exposure might prolong duration, thus translating into higher prevalence in the population, even though it might have little or no effect on incidence. Longitudinal studies (if they last long enough) can separate the contributions of a factor to both incidence and duration. Pearce *et al.* (2000) considered the proportion of cases attributable to exposure to mite allergens (the 'population attributable risk'), and found 'allergen exposure is at most a minor risk factor for development of asthma in children'. However, in adults there are positive associations of current mite allergen exposure with current asthma (Gelber *et al.,* 1993; Björnsson *et al.,* 1995; van der Heide *et al.,* 1997c).

In summary, there is some evidence (though it is not consistent) that the level of exposure is linked to the risk of developing sensitisation to dust mites in childhood (though not necessarily other allergens), and that the relevant level of exposure associated with sensitisation is likely to vary geographically. Exposure to dust mite allergens varies enormously in different parts of the world. Where mite allergen levels are high, prevalence of atopic sensitisation to mites tends to be high (e.g. Peat *et al.,* 1996), but the prevalence of asthma and atopic sensitisation *in general* are not closely or consistently linked with house dust mite exposure in infants and children. Trials of allergen avoidance aimed at primary prevention of childhood asthma have generally been disappointing (van Schayck *et al.,* 2007; Chapter 9). However, levels of allergen exposure are associated with asthma in atopic adults who are sensitised to dust mites.

8.4.2 Allergen levels in homes in relation to disease status

We have already seen that there is no consistent evidence that high allergen exposure is related to prevalence of sensitisation to dust mites. It has been assumed that people who have developed mite-allergic asthma have more mites or higher levels of allergens in their homes than the general population (e.g. Sidenius *et al.,* 2002a), but is it true or just another house dust mite myth? Of those surveys involving comparisons of dust mite populations in homes of patients with asthma with healthy control subjects at the same location, no significant difference was found in six examples (Sesay and Dobson, 1972; Ishii *et al.,* 1979; Htut *et al.,* 1991; Hart and Whitehead, 1990; Mumcuoglu *et al.,* 1994; Sun and Lue, 2000); significantly more mites in homes of mite-sensitised asthmatics were found in two (Korsgaard, 1983b; Saha *et al.,* 1994); and significantly more mites in homes of controls in one (Colloff, 1987c). For mite allergens, there was no difference in seven surveys (Call *et al.,* 1992; Pauli *et al.,* 1993; Konishi and Uehara, 1995; van Strien *et al.,* 1995; Wang and Wen, 1997; Sopelete *et al.,* 2000; Scrivener *et al.,* 2001) and significantly higher concentrations in homes of asthmatics in one (Addo-Yobbo *et al.,* 2001). By way of contrast, homes of patients with atopic dermatitis had consistently higher mite populations or allergen concentrations than other homes (Beck and Korsgaard, 1989; Harving *et al.,* 1990; Colloff, 1992c; Holm *et al.,* 1999).

8.4.3 Sampling and measurement of allergens in reservoir dust

The main methods for sampling reservoir dust are brushing or vacuum cleaning, although vacuuming is the method of choice. The consensus view is that important sampling sites are the mattress and bedding because most people are in contact with them for about eight hours per day, but bedroom carpets, living room carpets and upholstered furniture are also important, especially for infants who may spend as

much or more time per day in contact with these items than with bedding. Brushing results in markedly lower estimates of mite population density than vacuum cleaning (Abbott *et al.,* 1981), though a higher diversity of species may be collected (Stenius and Cunnington, 1972). It is clear that it is not valid to compare amounts of mites or allergens collected by brushing with those collected by vacuum cleaning (Chapter 6). The power and airflow rate of vacuum cleaners vary considerably and may influence amounts of mite and allergen collected, although there is no consistent evidence that this introduces a systematic bias during monitoring. A turbo head fitted to a vacuum cleaner removed considerably higher quantities of house dust from carpets, but not house dust mites, than did a plain suction nozzle (Wassenaar, 1988b). The type of surface being sampled may influence sampling efficiency. Mulla *et al.* (1975) found 35% of total mites present were removed by the first of three vacuum samplings of a carpet, whereas 80% were removed from a bare floor. Similarly, air samples above synthetic carpets yielded relatively smaller amounts of allergens than above natural ones, possibly due to differences in static electric charge (Price *et al.,* 1990).

There is an issue regarding whether mite allergen concentration should be expressed by unit weight of dust or by unit area sampled. Most researchers have used the former, and most of the available data is expressed this way. That expressed by unit area cannot be compared with anything else in a meaningful way unless both units are used (which is becoming more common), or a conversion factor is given. Custovic *et al.* (1995) showed a high statistical correlation for the two measures with mattress dust (with a conversion factor of approximately $y = x - 1$, i.e. $10\ \mu g\ g^{-1} = 9\ \mu g$ per m^2). Doull *et al.* (1997) found the weight of sampled dust and its Der p 1 content were significantly correlated in samples taken from both planar surfaces (mattresses) and non-planar surfaces (mixed lounge room furniture/carpet samples). Unit weight tends to be easier to standardise than unit area especially when sampling non-planar surfaces like upholstered furniture, but unit weight may be biased by the origin and differential density of the dust (Abbott *et al.,* 1981). Dust from carpets tends to contain a larger proportion of dense particles of sand and grit than dust from mattresses which consists almost entirely of low-density skin scales. Sieving may help to equalise density but is not always guaranteed to remove dense particles (van Leeuwen and Aalberse, 1991). Also, interpretation of trials of allergen avoidance is difficult when unit weight has been used because the size of the dust reservoir may be depleted by intensive vacuum sampling used to remove allergens, potentially leading to artifactual changes in allergen concentration.

The most common method for quantifying domestic allergens is enzyme-linked immunosorbent assay (ELISA), and for group I allergens of *Dermatophagoides* spp. two ELISA systems dominate: one developed in Denmark (Lind, 1986), one in the USA (Luczynska *et al.,* 1989). Both systems yield very similar results with the same samples (see, for example, Brunekreef *et al.,* 2005). The assay involves adsorbing group I-specific monoclonal antibody to wells of a microtitre plate, followed by successive incubations with an extract of the dust specimen and biotinylated group I-specific monoclonal antibody. The reaction is visualised colorimetrically using streptavidin-labelled horseradish peroxidase. Amplified ELISA methods can increase sensitivity of conventional ELISA by around 15-fold (Custovic *et al.,* 1999). Sampling and assay of indoor allergens was reviewed by-Luczynska (1997).

Guanine assay is a semi-quantitative proxy measurement of allergen in house dust (Bischoff *et al.,* 1985; van Bronswijk, 1986). Guanine is the major excretory product of arachnids, so is an indicator of the abundance of dust mite faecal pellets and Der 1 concentration. There is some evidence that use of the semi-quantitative version of this test, which can be done simply in homes of patients in about two minutes, may increase patient compliance with allergen avoidance (Ransom *et al.,* 1991). Statistically significant positive correlations have been demonstrated between concentrations of guanine in house dust and both concentrations of allergen Der p 1 (van Bronswijk *et al.,* 1989) and density of house dust mites (van Bronswijk, 1986).

8.4.4 Monitoring airborne allergens and personal exposure

Airborne allergens and personal allergen exposure were the subjects of a review by O'Meara and Tovey (2000), their paper being essential reading on these topics. This section summarises some of its main points.

There is little or no correlation between reservoir allergen concentrations and airborne ones in most

studies, yet the relationship between reservoir allergen and the amount that becomes airborne and available for inhalation is critical to understanding the relationship between personal exposure, sensitisation and development of symptoms. Many factors are involved, including the size and shape of allergen-bearing particles, type of allergen, the amount of disturbance that reservoir dust is subject to, the nature of the reservoir source, the duration of exposure and proximity of the person to the source of the allergen. Suspension of allergen-containing particles resulting from simulated walking disturbance indicates an interaction between the mechanical disturbance and aerodynamic effects (Gomes *et al.*, 2007).

Airborne group 1 and 2 mite allergens are found on particles of >5 μm diameter, which may be flakes, fibres or spherical faeces (De Lucca *et al.,* 1999; Custovic *et al.,* 1999). Particle size is an important factor influencing the duration that allergen-bearing particles remain airborne (Swanson *et al.,* 1985; Platts-Mills *et al.,* 1986b; Luczynska *et al.,* 1990a). Reservoirs of allergen may be large, but only a small proportion becomes airborne when disturbed (Tovey *et al.,* 1981) and only a tiny portion of the airborne component is inhaled (see Figure 8.3). There is enormous variation in airborne allergen levels. Allergen is often undetectable in the air in the absence of disturbance but may increase over 1000-fold when reservoir dust is disturbed during activities such as cleaning and vacuuming, bed-making, walking across a carpeted floor or simply moving around in bed. Sakaguchi *et al.* (1992) found a mean of ca. 220 pg Der 1 per m^3 in the air around sleepers, compared with about 20 pg per m^3 in the lounge room and suggested a mean nightly exposure of approximately 0.6 ng. The addition of a mattress cover dropped the airborne level in the bedroom to about 10 pg per m^3, indicating the bed was the major source of airborne allergen for the sleeper.

Measurements of airborne allergen can be done using large Petri dishes as settling plates left exposed for up to a week (Tovey *et al.,* 1992; Karlsson *et al.,* 2002). More technically sophisticated sampling involves either static or breathing zone volumetric air samplers, but few airborne particles may be detected in the absence of disturbance of the reservoir dust. In a comparison of sampling of reservoir dust, volumetric air sampling and settling dust (using two methods), there was moderate correlation, except for reservoir dust versus settling on Petri dishes (Tovey *et al.,* 2003).

Direct personal exposure can be measured simply and accurately using intranasal samplers, consisting of a pair of soft plastic sleeves that fit snugly into the nostrils. Each sampler contains an adhesive filter strip onto which particles impact (Graham *et al.,* 2000; Figure 8.4). The device is inserted, and particles collected over 10–30 min. on the filter during normal breathing. The strips are removed and immunoassayed using a modified protein blotting and immunostaining system. Allergen-containing particles are visualised as halo-like bodies, and counted under a

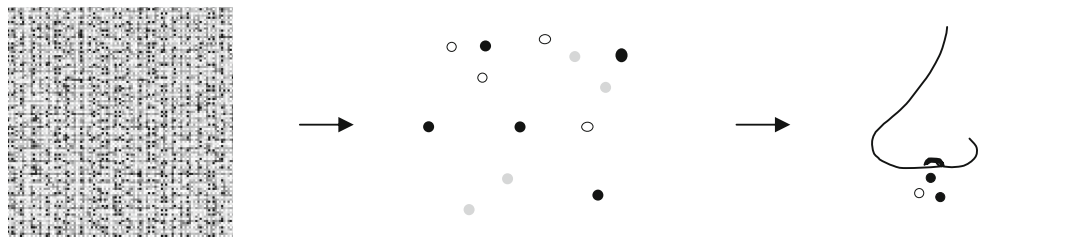

Figure 8.3 Relationship between approximate orders of magnitude in amounts of allergen in reservoir dust and amounts inhaled. Amount in reservoir dust per cubic metre based on 10–100 g of dust per square metre of carpet with a pile depth of 1 cm. Inhaled amount based on inhalation rate of 3–6 Der p 1-bearing particles hr^{-1} (Gore *et al.,* 2002) and a minute volume of 10 L.

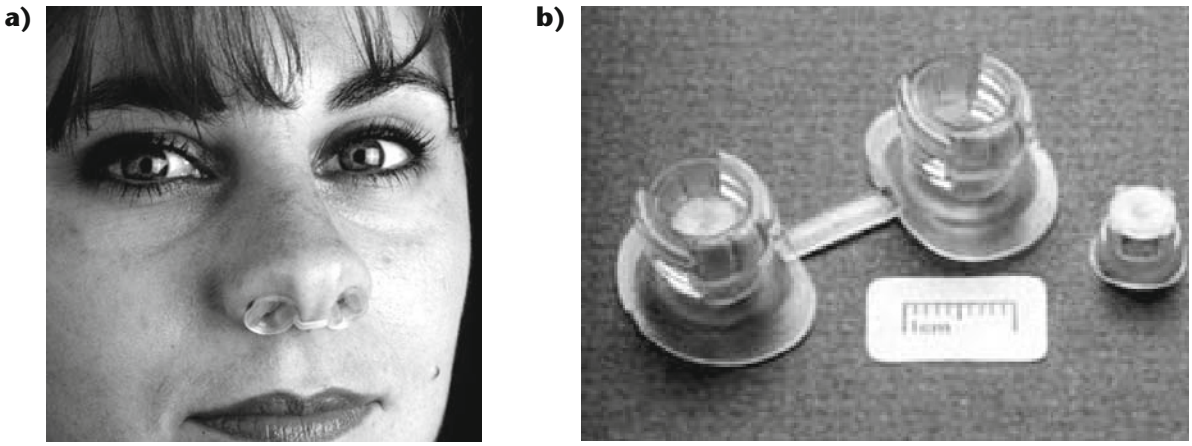

Figure 8.4 Nasal filters for monitoring of personal allergen exposure. **a)** Inserted in nostrils; **b)** showing details of filter (cf. Tovey *et al.,* 2000b for details). (Images courtesy of Euan Tovey.)

compound microscope (Tovey *et al.*, 2000b). Particles without halos are also counted. Those particles with mite allergen represent a relatively small fraction of total particles (Poulos *et al.,* 1999). The sampler collects almost all particles with an aerodynamic equivalent diameter of ≥10 μm (ca. 50% of those of ~5 μm). The immunostaining method is highly reproducible and sensitive down to single particles carrying amounts of allergen in the order of <1 pg. If serum IgE from an atopic patient with multiple sensitisation is used for immunostaining (instead of monoclonal antibody), it will detect all the particles bearing the different allergens that the patient is allergic to.

Assessment of personal exposure to mite allergen using intranasal sampling of 12 volunteers under natural conditions (in bed at home, three samples per night for six nights) found significant correlations between the median number of Der 1 and Der 2-bearing particles and the reservoir allergen levels in the beds (Gore *et al.*, 2002). The median number of allergen-bearing particles inhaled per person during a 30 min. period was three (range 0–79). Based on an estimate of 0.1 ng Der p 1 per faecal pellet (Tovey *et al.,* 1981), this provides a direct measure of nightly exposure to mite allergens of approximately 5 ng of Der p 1 during eight hours of sleep.

8.5 Spatial scales of variability in mite allergens in reservoir dust

Temporal (seasonal) variation in allergen levels and mite populations was covered in Chapter 5. The following sections deal with spatial variation in mite allergen concentrations. The same scaling effects and groupings are applicable as used in Chapter 4, namely microhabitat (variation within homes), macrohabitat (variation between homes) and variation between regions to provide a global perspective.

Apart from the well-known tendency for beds to contain higher concentrations of allergens than carpets, there is little information on variation between habitats within homes. Tovey (1995) partitioned bedroom carpets in 10 different rooms into squares of 0.25 m^2 and sampled each square. In one sample the range was 17–85 μg g^{-1} of Der p 1, with no obvious distribution pattern apart from slightly lower levels near the window. Similarly, Simpson *et al.* (1998) found no consistent pattern of allergen distribution and coefficients of variation around 80–90% for within- and between-room Der p 1 concentrations in carpets. Loan *et al.* (1998) found a mean coefficient of variation around 50% in living rooms and suggested that for large-scale epidemiological studies a single site from the centre of the room, in front of a couch or chair or from a corner, is representative of the whole room. In replicated samples taken at a two-week interval, Marks *et al.* (1995a) found the range for a single sample from beds and floors was accurate to 3.1-fold and 3.5-fold respectively.

8.6 Variability in allergen concentration between homes

When researchers identify factors for increased risk of allergen exposure they usually mean factors associated with differences in allergen concentrations in reservoir dust. Since there is no clear relationship between the amount of allergen in reservoir dust and the risk of exposure, or for that matter between mite populations and allergen production, it is probably

best to think of these factors in a more restricted sense as simply indicators of high or low reservoir allergen levels.

Some of these factors were covered in Chapter 4 for mite population densities (including age of homes, socio-economic status of occupants, housekeeping, crowding and height of homes above ground level). Here they are considered in relation to allergen concentrations. The two sections could have been combined, but the rather scant data on mite population densities are mostly from small-scale ecological studies involving only a few factors. Those on allergen concentrations are mostly from much larger population-based epidemiological studies with high statistical power, where many factors were examined simultaneously using multivariate statistical techniques. One of the aims of many of these studies is to attempt to explain the high variation in allergen concentrations between homes (Simpson *et al.,* 2001).

Although risk factors associated with housing are sometimes referred to as determinants, there are few examples of direct causal associations with elevated allergen concentrations. Risk factors are often surrogates for immediate influences on mite population size. For example, presence of visible mould on walls and ceilings is an indicator of elevated humidity which favours mite population growth. The classification herein attempts to make some sort of sense of risk factors and how they may help explain differences in reservoir allergen concentrations between homes. Factors are divided into those associated with:

- housing characteristics, including condition, construction and design;
- human behaviour, social and economic status; and
- the immediate external environment.

In order to obtain estimates of the relative magnitude of allergen concentrations associated with various risk factors, I have focused on epidemiological studies with data from discrete geographic localities, rather than pooled data from several localities where climate influences, even over small distances, may have confounding effects (Kuehr *et al.,* 1994a; Basagaña *et al.,* 2002). For the studies in Table 8.1, statistically significant differences in allergen concentrations are given as geometric means or medians of Der 1 (mostly Der p 1) in $\mu g\ g^{-1}$ from floors or beds, based on initial, univariate models. The reason for presenting these data is to contrast the between-study variation in unadjusted means. For the sake of clarity at the expense of completeness, I have not included in the table those studies that give odds ratios in the absence of means or, for the most part, separate models of Der p 1 and Der f 1. Risk factors for the two allergens are not consistent (Kuehr *et al.,* 1994b; Hirsch *et al.,* 1998; Gross *et al.,* 2000; Zock *et al.,* 2006; Fig. 8.5), reflecting different physiological and environmental requirements of *Dermatophagoides farinae* and *D. pteronyssinus*. Most of the information presented in Table 8.1 relates to Der p 1 from discrete geographic localities, whereas much of that for Der p 1 and Der f 1 is pooled from several localities.

Most authors also conducted multivariate linear regression. Factors that might be significant with univariate analyses may not be so following multivariate analyses (i.e. after adjusting for all other factors) and vice-versa. Adjusted, independent risk factors from multivariate analyses are listed in Table 8.2.

8.6.1 Housing characteristics

a Type of home

Apartments or flats tend to have lower Der 1 concentrations than detached or semi-detached houses, but the size of the effect is relatively small (average for statistically significant studies 1.8-fold for floors) and inconsistent (2/6 studies of floors showed statistical significance). This factor is likely to be co-dependent with the age of the home, construction (Mihrshahi *et al.,* 2002) and its elevation above ground (Dharmage *et al.,* 1999), because apartments may tend to be newer and/or higher up and made of brick or concrete rather than timber.

b Age of home and state of repair

Older homes had higher Der 1 concentrations and the effect was greater and more frequent for beds than floors (average 2.1-fold for carpets, 4/9 studies statistically significant; 3-fold for beds, 4/5 studies statistically significant). Varekamp and Voorhorst (1960) found high inter-home variability in the allergenicity of dust samples they used to make extracts for skin-prick testing. Damp homes contained dust that was more allergenic. Older homes in Leiden, the Netherlands, tended to be damper and in poorer repair than newer homes, with 72% of pre-1918 homes having dry rot, compared with only 11% of post-1918 homes. Julge *et al.* (1998) made the point that older apartments in Tartu, Estonia, had damp

Table 8.1 Residential and domestic factors associated with (mainly) elevated exposure to mite allergens, based on univariate analyses. NS = not statistically significant

Factor	Floor				Bed				Reference
	1st value	2nd value	Fold-difference	Value of P	1st value	2nd value	Fold-difference	Value of *P*	
Type of home									
Apartment v. house	0.26	0.38	1.46	NS					Julge *et al.*, 1998
Apartment v. house	8.70	9.30	1.07	NS					Plácido *et al.*, 1996
Apartment v. detached	9.92	13.10	1.32	NS					Mihrshahi *et al.*, 2002
Non-detached v. detached	12.40	19.10	1.54	<0.05	17.2	21.2	1.2	<0.05	Dharmage *et al.*, 1999
Apartment v. detached	0.83	1.77	2.13	0.04	1.4	1.9	1.4	NS	Chan-Yeung *et al.*, 1995
Apartment v. detached	0.40	0.79	1.98	NS	0.9	0.6	0.7	NS	Chan-Yeung *et al.*, 1995
Age of home									
=10 yr v. >10 yr	1.30	1.40	1.08	NS					Atkinson *et al.*, 1999
<16 yr v. 17–36 yr	2.30	3.80	1.65	NS					Luczynska *et al.*, 1998
<16 yr v. >16 yr	28.20	43.60	1.55	NS					Wickens *et al.*, 2001
<20 yr v. >20 yr	6.40	14.50	2.27	<0.05					Plácido *et al.*, 1996
<25 yr v. =25 yr	0.21	0.44	2.10	<0.001					Julge *et al.*, 1998
=10 yr v. >10 yr	9.41	15.31	1.63	0.001	9.3	18.8	2.0	<0.0001	Mihrshahi *et al.*, 2002
<20 yr v. >20 yr	0.85	1.99	2.34	0.04	0.9	2.5	2.8	0.01	Chan-Yeung *et al.*, 1995
<20 yr v. >20 yr	0.66	0.78	1.18	NS	0.5	0.8	1.4	NS	Chan-Yeung *et al.*, 1995
<16 yr v. >36 yr	13.90	19.10	1.37	NS	8.0	23.5	2.9	<0.05	Dharmage *et al.*, 1999
<15 yr v. >55 yr					0.4	1.6	4.5	<0.001	Simpson *et al.*, 2002
Size of home									
>2 rooms v. =2 rooms	5.10	5.30	1.04	NS					Plácido *et al.*, 1996
Housing construction									
Concrete v. timber	0.22	0.55	2.50	<0.05					Julge *et al.*, 1998
Brick v. weatherboard	1.60	3.02	1.89	NS					Couper *et al.*, 1998
Brick v. weatherboard	12.28	12.39	1.01	NS	12.6	20.7	1.6	<0.0001	Mihrshahi *et al.*, 2002
Other v. brick cladding	10.50	21.70	2.07	<0.01	19.4	28.6	1.5	<0.01	Garrett *et al.*, 1998
Foundation/flooring									
Concrete v. timber	0.82	2.37	2.89	NS					Couper *et al.*, 1998
No sub-floor space v. space	15.40	19.10	1.24	NS	15.4	21.2	1.4	<0.05	Dharmage *et al.*, 1999
Concrete v. timber	9.80	15.80	1.61	0.001	10.2	19.6	1.9	<0.0001	Mihrshahi *et al.*, 2002
Timber v. concrete	12.20	23.30	1.91	<0.01	24.5	23.6	1.0	NS	Garrett *et al.*, 1998
Floor not wood v. wood on stumps					11.2	23.8	2.1	<0.05	Dharmage *et al.*, 1999
Not concrete v. concrete					3.5	7.4	2.1	0.007	Luczynska *et al.*, 1998

continued

Table 8.1 Continued

Factor	Floor				Bed				Reference
	1st value	2nd value	Fold-difference	Value of P	1st value	2nd value	Fold-difference	Value of *P*	
Presence of damp									
No damp v. damp	0.23	0.51	2.22	<0.05					Julge *et al.*, 1998
No damp v. damp in living room	1.30	4.30	3.31	0.002					Atkinson *et al.*, 1999
No damp v. damp	7.20	20.00	2.78	<0.001					Plácido *et al.*, 1996
No damp v. damp	15.40	23.50	1.53	<0.05	17.2	29.0	1.7	<0.05	Dharmage *et al.*, 1999
Condensation absent v. present	2.80	4.50	1.61	<0.05	3.4	4.7	1.4	NS	Luczynska *et al.*, 1998
Condensation absent v. present					40.0	49.5	1.2	0.05	Wickens *et al.*, 1997
No damp v. damp					44.8	60.0	1.3	0.04	Wickens *et al.*, 1997
No damp v. damp in bedroom					0.5	0.7	1.4	NS	Atkinson *et al.*, 1999
No window condensation v. present					0.8	1.5	2.0	0.001	Simpson *et al.*, 2002
No damp v. damp in bedroom					1.1	4.5	4.1	0.001	Simpson *et al.*, 2002
Presence of mould									
No mould v. mould	1.68	4.21	2.51	0.05					Couper *et al.*, 1998
No mould v. mould	15.40	23.50	1.53	<0.05	17.2	29.0	1.7	<0.05	Dharmage *et al.*, 1999
No mould v. mould	12.14	17.15	1.41	NS	13.7	23.2	1.7	0.01	Mihrshahi *et al.*, 2002
No/slight mould v. heavy mould	15.40	15.70	1.02	NS	20.5	29.5	1.4	<0.05	Garrett *et al.*, 1998
Indoor temperature & humidity									
<18°C v. >18°C	0.11	0.32	2.91	<0.001					Julge *et al.*, 1998
Mattress RH <51% v. >51%					41.3	52.8	1.3	0.03	Wickens *et al.*, 1997
Heating									
Central heating v. wood stove	1.42	2.11	1.49	NS					Couper *et al.*, 1998
No central heating v. with	15.40	21.20	1.38	<0.05	21.2	21.1	1.0	NS	Dharmage *et al.*, 1999
Heating unused week prior v. used	12.66	11.32	0.89	NS	14.1	20.4	1.5	NS	Mihrshahi *et al.*, 2002
Other v. forced air	0.55	2.31	4.20	0.009	1.1	2.3	2.2	NS	Chang-Yeung *et al.*, 1995a
Other v. forced air	0.53	0.75	1.42	NS	1.2	0.6	0.5	NS	Chang-Yeung *et al.*, 1995a
Central heating v. none					1.1	3.2	3.1	<0.001	Simpson *et al.*, 2002
Gas appliances									
Without gas oven v. with	3.00	3.70	1.23	NS					Luczynska *et al.*, 1998

continued

Table 8.1 Continued

Factor	Floor				Bed				Reference
	1st value	2nd value	Fold-difference	Value of P	1st value	2nd value	Fold-difference	Value of P	
Ventilation									
Kitchen extractor fan v. none	2.50	3.90	1.56	NS					Luczynska *et al.,* 1998
Without kitchen extractor fan v. with	12.50	19.30	1.54	<0.05	23.3	19.1	0.8	NS	Dharmage *et al.,* 1999
Open fireplace in lounge v. without	1.10	4.00	3.64	0.03					Luczynska *et al.,* 1998
Curtains and blinds									
Heavy curtains absent v. present	15.40	19.10	1.24	<0.05	19.1	21.2	1.1	NS	Dharmage *et al.,* 1999
Venetian blinds present v. absent	10.10	19.10	1.89	<0.05	20.3	21.2	1.0	NS	Dharmage *et al.,* 1999
Insulative properties									
Carpet =4 mm v. =5 mm	30.10	45.80	1.52	NS					Wickens *et al.,* 2001
Underlay =7 mm v. =8 mm	37.10	40.50	1.09	NS					Wickens *et al.,* 2001
Floor insulated v. not	26.10	42.90	1.64	<0.05					Wickens *et al.,* 2001
Walls insulated v. not	31.30	48.70	1.56	<0.05					Wickens *et al.,* 2001
No double glaze in lounge v. with	1.10	1.60	1.45	0.03					Atkinson *et al.,* 1999
No double glaze in bedroom v. with					0.5	0.5	1.0	NS	Atkinson *et al.,* 1999
No double glaze v. with					1.2	0.9	0.7	NS	Simpson *et al.,* 2002
Age of mattress									
<5 yr v. >5 yr					15.4	23.5	1.5	<0.05	Dharmage *et al.,* 1999
=2 yr v. >2 yr					10.3	15.5	1.5	0.003	Mihrshahi *et al.,* 2002
=1 mo v. >2 mo					0.3	0.5	1.7	<0.001	Atkinson *et al.,* 1999
<1 yr v. >5 yr					0.4	2.6	6.1	<0.001	Simpson *et al.,* 2002
<1 yr v. >1 yr					1.0	4.7	4.7	0.05	Luczynska *et al.,* 1998
Type of mattress									
Inner spring v. foam					14.2	21.4	1.5	NS	Mihrshahi *et al.,* 2002
Inner spring v. foam					50.2	39.3	0.8	NS	Wickens *et al.,* 1997
Foam v. inner spring					13.0	25.0	1.9	<0.01	Garrett *et al.,* 1998
Type of bedding									
Quilt on bed v. not					19.1	48.4	2.5	<0.05	Dharmage *et al.,* 1999
Blankets on Bed					19.1	26.1	1.4	<0.05	Dharmage *et al.,* 1999
Blankets not wool v. wool					12.9	27.2	2.1	<0.0001	Mihrshahi *et al.,* 2002
Blankets not synthetic v. yes					13.2	22.2	1.7	0.001	Mihrshahi *et al.,* 2002

continued

Table 8.1 Continued

Factor	Floor				Bed				Reference
	1st value	2nd value	Fold-difference	Value of P	1st value	2nd value	Fold-difference	Value of *P*	
No sheepskin on bed v. yes					13.8	23.0	1.7	0.03	Mihrshahi *et al.*, 2002
Synthetic pillow v. not					14.2	16.5	1.2	NS	Mihrshahi *et al.*, 2002
No feather pillow v. yes					14.0	16.2	1.2	NS	Mihrshahi *et al.*, 2002
Blankets not cotton v. yes					14.2	15.4	1.1	NS	Mihrshahi *et al.*, 2002
No synthetic quilt v. yes					13.5	14.9	1.1	NS	Mihrshahi *et al.*, 2002
Feather quilt v. not					13.5	14.7	1.1	NS	Mihrshahi *et al.*, 2002
Floor covering									
No carpet v. carpet	0.91	2.25	2.47	NS					Couper *et al.*, 1998
No carpet v. carpet	5.70	21.20	3.72	<0.05					Dharmage *et al.*, 1999
No carpet v. carpet	9.00	22.30	2.48	0.01					Plácido *et al.*, 1996
Rugs v. no rugs	10.07	12.83	1.27	NS	19.8	13.7	0.7	0.047	Mihrshahi *et al.*, 2002
No carpet v. carpet	0.60	1.40	2.33	0.03	0.5	0.5	1.0	NS	Atkinson *et al.*, 1999
Hard floor v. carpet	4.11	15.10	3.67	<0.0001	18.5	13.9	0.8	NS	Mihrshahi *et al.*, 2002
No carpet v. carpet	3.90	28.10	7.21	<0.0001	19.9	48.1	2.4	0.001	Wickens *et al.*, 1997
Type of carpet									
Other v. wool	15.40	32.10	2.08	<0.05					Dharmage *et al.*, 1999
Synthetic v. wool	9.90	15.70	1.59	<0.01					Garrett *et al.*, 1998
Synthetic v. wool	22.60	44.90	1.99	NS					Wickens *et al.*, 2001
Age of carpet									
Carpet <1 yr v. >1 yr	0.80	5.10	6.38	0.02					Luczynska *et al.*, 1998
Carpet <1 yr v. >5 yr	4.50	20.20	4.49	<0.05					Dharmage *et al.*, 1999
Carpet =1 yr v. >1 yr	19.40	29.60	1.53	NS					Wickens *et al.*, 1997
Carpet =1 yr v. >5 yr	0.25	1.79	7.16	<0.001					Simpson *et al.*, 2002
Number of occupants									
<3 v. =3 children	23.20	29.20	1.26	0.03					Wickens *et al.*, 1997
1–2 v. =3 children	33.50	51.00	1.52	0.05					Wickens *et al.*, 2001
=5 v. =6	1.71	5.29	3.09	0.03					Couper *et al.*, 1998
=4 v. >4	7.00	9.20	1.31	NS					Plácido *et al.*, 1996
<4 v. >4	0.99	1.95	1.97	0.02	1.4	2.1	1.6	NS	Chan-Yeung *et al.*, 1995
<4 v. >4	0.55	0.72	1.31	NS	0.6	0.9	1.6	NS	Chan-Yeung *et al.*, 1995
=3 v. =6	1.10	1.70	1.55	0.02	0.4	0.6	1.5	NS	Atkinson *et al.*, 1999
Income									
>£30 k v. <£10 k					0.8	2.4	3.1	<0.01	Simpson *et al.*, 2002
Smoking									
2 smokers in home v. no smokers	1.50	5.00	3.33	0.007					Luczynska *et al.*, 1998
Smokers in home v. no smokers	0.25	0.33	1.32	NS					Julge *et al.*, 1998
No maternal smoking v. smoking	1.89	2.18	1.15	NS					Couper *et al.*, 1998
Smokers in home v. no smokers	1.00	1.70	1.70	0.001	0.5	0.5	1.0	NS	Atkinson *et al.*, 1999

continued

Table 8.1 Continued

Factor	Floor				Bed				Reference
	1st value	2nd value	Fold-difference	Value of P	1st value	2nd value	Fold-difference	Value of *P*	
Cleaning									
Vacuuming =weekly v. <weekly	0.47	2.46	5.23	0.007					Couper *et al.*, 1998
Sweep bedroom ever v. never	0.30	2.09	6.97	0.02					Couper *et al.*, 1998
Type of vacuum cleaner									
New type (cylinder) v. old (soft bag)	3.30	6.30	1.91	0.005					Luczynska *et al.*, 1998
>1000 W v. =1000 W	33.50	48.00	1.43	NS					Wickens *et al.*, 2001
Vacuuming =weekly v. <weekly	38.90	82.10	2.11	NS					Wickens *et al.*, 2001
Laundry									
Dried outdoors v. indoors	1.85	8.07	4.36	0.05					Couper *et al.*, 1998
Exposure									
House in windy location v. not	1.78	2.34	1.31	NS					Couper *et al.*, 1998
Height of home off ground									
1st floor home v. ground floor	0.18	0.41	2.28	<0.001					Julge *et al.*, 1998
Lounge room on 1st floor v. ground	0.70	3.70	5.29	<0.001					Luczynska *et al.*, 1998
Lounge over garage v. on ground	25.00	46.00	1.84	<0.001					Wickens *et al.*, 2001
Bedroom on 1st floor v. ground	3.00	7.20	2.40	0.006					Luczynska *et al.*, 1998
=1st floor home v. ground floor	12.00	14.70	1.23	NS					Plácido *et al.*, 1996
Bedroom on 1st floor v. ground	13.90	17.20	1.24	NS	12.5	23.5	1.9	<0.05	Dharmage *et al.*, 1999

associated with poor construction (leakiness), which allows water ingress, but also facilitates natural ventilation. Damp in urban homes in Denmark and Sweden is likely to be associated with condensation resulting from efficient insulation and poor ventilation(Korsgaard *et al.*, 1983a, b; Wickmann *et al.*, 1991; Sundell *et al.*, 1995).

c Housing construction, foundations and flooring

Construction characteristics tend to be co-factors of type of home and age. For example, Garrett *et al.* (1998) found the higher allergen concentrations associated with older homes was no longer significant after adjusting for construction type (brick cladding) and foundation type. Homes with concrete slab ground floors have been associated with higher allergen concentrations than homes with an underfloor crawl space (Munir *et al.*, 1995; Luczynska *et al.*, 1998). Dharmage *et al.* (1999) found slab floors associated with lower concentrations of Der 1, as did Mihrshahi *et al.* (2002), but in the latter study this effect was not significant after adjusting for other factors because only 22% of older homes had concrete foundations. The type of foundations, as well as other construction factors (brick v. timber), is likely to co-vary with the age of the home, depending on local architectural styles and building codes.

d Temperature and humidity, damp, condensation and mould

High indoor humidity is among the most important risk factors for increased mite exposure-(Korsgaard, 1982; 1983a, b; Verhoeff *et al.*, 1995), and the relationship between domestic damp and asthma has long been known (Varekamp, 1925; Storm van Leeuwen, 1927). Emenius *et al.* (2000) found absence of condensation on double-glazed windows and low indoor water vapour generation (<3 g per m^3) were highly predictive of low indoor humidity, and a reasonable predictor of low allergen

Table 8.2 Independent risk factors, derived from multivariate analyses, of factors associated with high Der 1 concentrations in homes.

Factor	Wickens *et al.*, 1997, Wellington	Couper *et al.*, 1998, S. Tasmania	Garrett *et al.*, 1998, La Trobe Valley	Luczynska *et al.*, 1998, Norwich	Atkinson *et al.*, 1999, Ashford	Dharmage *et al.*, 1999, Melbourne	Wickens *et al.*, 2001, Wellington	Mihrshahi *et al.*, 2002, Sydney	Simpson *et al.*, 2002, Manchester	Basagaña *et al.*, 2002, Barcelona	Basagaña *et al.*, 2002, Menorca
Mould/damp/condensation		×	×		×	×			×		
Age of mattress				×	×	×		×	×		
Age/type of carpet	×					×	×		×		
Number of occupants	×	×			×		×				
Smokers in home (-ve association)				×	×					×	×
Indoor RH%	×	×	×								
Age of home						×	×	×	×		
Woollen blankets/underblanket	×		×					×			
Carpet v. hard floor		×			×			×			
Mattress type	×		×							×	
Height of home/room above ground				×			×				
Brick cladding			×								
Open fireplace				×							
Old vacuum cleaner				×							
Presence of sub-floor space						×					
No insulation							×				
Less ventilation/air conditioning										×	
High social class											×

concentrations, but presence of condensation was associated with only 20–30% risk of high indoor humidity. Presence of damp was a consistent predictor of high allergen concentrations; statistically significant in all studies of floors (average 2.3-fold greater) and 5/6 studies of beds (average 2.1-fold). Presence of mould was a good predictor for beds (statistically significant in all studies) but only associated with 1.6-fold greater Der 1 levels, whereas for floors only 2/4 studies showed significantly elevated allergen (2-fold). Garrett *et al.* (1998) found a positive correlation between bed allergen concentrations and mean bedroom relative humidity (though not absolute humidity) over quite a narrow humidity range (48–67% RH), whereas Dharmage *et al.* (1999) found only a weak association over a higher, broader range (mean 60% RH, range 32–80). A weak negative association between temperature and Der p 1 levels was confounded by humidity in their multiple regression. Temperature is likely to show variable effects in different parts of the world depending on season and climate.

e Heating and ventilation

The reduction of indoor humidity through the use of ventilation systems is associated with lower exposure to dust mites and allergens (Harving *et al.*, 1993, 1994; Wickman *et al.*, 1994a; Arlian *et al.*, 2001). Luczynska *et al.* (1998) found the presence of an open fireplace in the living room was associated with 3.6-fold lower concentrations of Der p 1 in the lounge room. The fireplaces were usually not used (most of the homes that had them were centrally heated), hence they represent a ventilation factor rather than a heating factor. These authors also found homes with gas cookers had higher Der p 1 concentrations in the lounge room.

Central heating was both negatively and positively associated with allergen concentrations (see Table 8.1). This may be due in part to patterns of use in different parts of the world, as well as comparisons of central heating with different types of heating. Centrally heated houses may be less ventilated because there is a tendency to keep windows closed if the heating is on (Dharmage *et al.*, 1999).

f Insulative properties

Wickens *et al.* (2001) found the absence of insulation from floors was the most important factor associated with elevated Der p 1 concentrations in floors. The authors suggested that insulation may buffer against ingress of humid outdoor air. A similar effect was found by van Strien *et al.* (1994), with a 3-fold increase of Der 1 on non-carpeted floors with rugs but no sub-floor insulation. Double glazing was not consistently associated with high Der 1 concentrations.

g Beds and bedding

Bed type

Mosbech *et al.* (1991) found no significant differences in allergen concentrations between different types of mattress, though Garrett *et al.* (1988) found almost double the concentration in inner-spring mattresses compared with foam, whereas Mihrshahi *et al.* (2002) found almost double the concentrations in foam mattresses, and Wickens *et al.* (2001) found no difference.

Bed age

Older mattresses have consistently higher allergen concentrations than newer ones, in concordance with the finding of increased mite population density with mattress age (see Chapter 4). 'Newer' in most studies was often less than a year old, though Custovic *et al.* (1996) showed significant accumulation of Der p 1 in new mattresses after only four months. The best data, showing a cumulative exponential increase in allergen with age, are those of Simpson *et al.* (2002; see Figure 8.5). Mihrshahi *et al.* (2002) found the age of the bed to be the strongest predictor of high Der p 1 concentrations in beds in Sydney. More dust tends to be extracted from older beds (Kuehr *et al.*, 1994b), indicating the accumulation of skin scales over time.

Bedding type

Mihrshahi *et al.* (2002) found the use of woollen or synthetic blankets, but not cotton ones, was associated with high allergen concentrations. This may be due to frequency of cleaning. Cotton blankets can be washed in a domestic washing machine whereas wool blankets have to be dry-cleaned. Garrett *et al.* (1988) also found

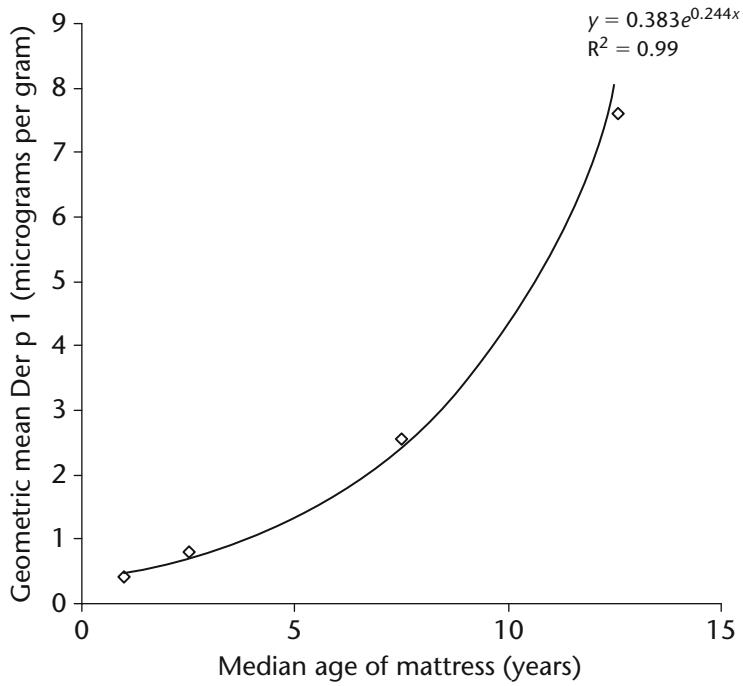

Figure 8.5 Relationship between age of mattresses and concentration of Der p 1 (data from Simpson *et al.*, 2002).

a strong positive association with woollen bedding, including underblankets, as did Kuehr *et al.* (1994b). As suggested by Mihrshahi *et al.* (2002), wool may have particular properties that create a favourable microenvironment for growth of dust mite populations.

h Carpets

Fitted carpets were consistently associated with high Der 1 levels – almost 4-fold greater than floors with no carpet. Wool carpet had higher concentrations (1.9-fold) than synthetic ones (statistically significant in 2/3 studies). Carpets more than one year old had a mean 6-fold greater allergen concentration than those less than a year old.

8.6.2 Human behaviour and social and economic factors

a Number of occupants

Homes with higher numbers of occupants tend to have higher Der 1 concentrations in floors (1.9-fold on average; 5/7 studies) but not beds. Higher density of occupancy is related to greater water use (in eastern Australia, currently around 200 L per person per day), and generation of water vapour through activities such as showering, bathing, cooking and laundry may be responsible for higher allergen levels.

b Social and economic variables

Living in the high poverty part of Boston was associated with lower Der 1 concentrations in homes (based on allergen exposure class frequencies, not geometric means) and higher cockroach allergen levels, but family income was not significantly associated with Der 1 levels after adjusting for home characteristics and ethnicity (Kitch *et al.,* 2000). But high poverty areas were dominated by apartments, which had half the frequency of high mite allergen exposure than houses. In Chapter 4, higher mite populations were found in mattresses in homes of people classified as being of lower social and economic status. This factor has no direct effect on mite populations, but it is likely to be an indicator of mattress age, because people with higher incomes are more likely to replace their beds and furnishings more frequently. Older mattresses tend to have higher allergen concentrations. Simpson *et al.* (2002) found beds of people with annual incomes under £10 000 (A$ 22 500) had 3.1-fold greater Der p 1 concentrations than people earning more than £30 000 (A$ 67 500), but income was not a significant independent variable in their multivariate analysis. Chen *et al.* (2007) found no association with income.

c Smoking

Luczynska *et al.* (1998) found a strong statistically significant negative 'dose-response' relationship with smoking and Der p 1 concentrations: no smokers in home, 5.0 μg g^{-1}; one smoker, 1.9 μg; two smokers, 1.5 μg g^{-1}. Hypotheses for this effect were denaturation of Der p 1 by nicotinic acid or a toxic effect of nicotine on dust mites. Nicotine is a potent insecticide and acaricide (Rodriguez *et al.*, 1979; Eldefrawi *et al.*, 1985). Another possibility is that Der p 1-bearing particles adhere to sticky tar condensates from cigarette smoke that are deposited onto carpets. Atkinson *et al.* (1999) found significantly higher Der p 1 on floors, but not in beds, of non-smokers. Lau *et al.* (1997) also found a significant negative association with smoking, as did Basagaña *et al.* (2002), including a 'dose-response' effect based on number of cigarettes smoked by the occupants. Julge *et al.* (1988) and Couper *et al.* (1999) found similar trends but they were not significant. Simpson *et al.* (2002) found no association and Munir *et al.* (1995) found a positive association, but with pooled data from three geographical regions.

d Domestic cleaning

Frequency of cleaning has been associated with large differences in allergen concentrations on floors (Couper *et al.*, 1998). Age and type of vacuum cleaner were predictors of Der 1 concentrations in one study where homes with older, leakier, soft-cloth bag ('upright') vacuum cleaners had higher floor allergen levels than homes with modern cylinder-type models (Luczynska *et al.,* 1998).

8.6.3 Environmental factors

a Proximity to water courses

Maunsell (1951) and Voorhorst *et al.* (1969, their Figure 27) found higher prevalences of sensitisation to dust and atopic asthma with proximity of homes to watercourses. However, in relation to Der 1 concentrations, no increased levels were found within 500 m of a lake or river (Kuehr *et al.*, 1994b; Luczynska *et al.*, 1998).

b Soil type

Voorhorst *et al.* (1969, pp. 33–35) mention a study by Tissot van Patot (1929) who found that house dust extracts taken from homes built on peaty or mixed soils in the Netherlands gave larger reactions in skin

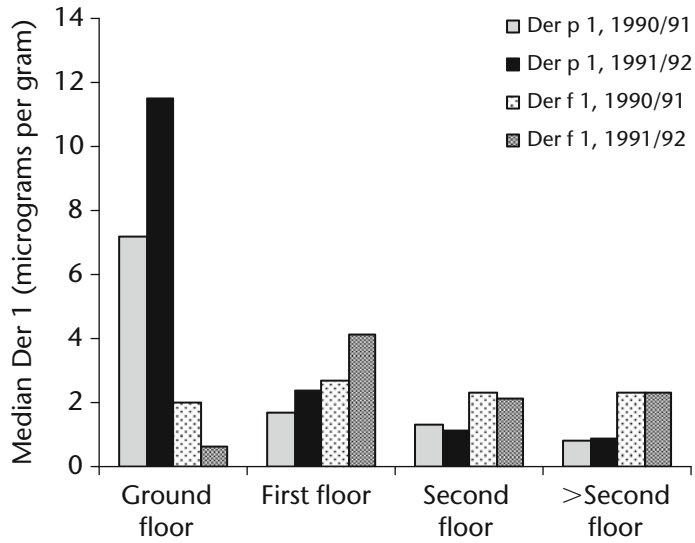

Figure 8.6 Relationship between height above ground of homes (storey level) and Der p 1 and Der f 1 concentrations in beds from two surveys, one year apart, in 1050 homes in Freiburg, Loerrach and Kehl in the Upper Rhine Valley, south-west Germany (data from Kuehr *et al.*, 1994b).

tests than those from homes built on sandy soils. This may relate to the water-holding capacity of soils and a greater likelihood of damp in homes on heavy soils than in homes that are free draining, but this factor has not been investigated further.

c Height of home above the ground

I have included this as an environmental factor because it relates to the interaction between the building and the external climate. Of those studies that show this factor to be of significance, the average magnitude of the effect is 3-fold greater Der 1 concentrations in homes at ground floor level than those at first floor level or higher. The most likely explanation for this effect is that the water vapour content of the air decreases exponentially with distance above the ground, and the drying capacity of the air via wind and turbulence increases (Geiger, 1957). Atmospheric relative humidity of 75% RH at ground level may decrease to 60% RH at 5 m above the ground. The humidity gradient is modified by diurnal fluctuations in heat exchange at the ground surface. Wickens *et al.* (2001) found significantly lower Der p 1 concentrations in lounge room floors that had a room or garage underneath them. There was no correlation between Der p 1 and relative humidity of carpets and room air, but having a room or garage below the lounge room was highly predictive of low lounge room humidity. Dharmage *et al.* (1999) found ground floor bedrooms had almost 2-fold higher bed Der p 1, but this effect was confounded by home age in their multivariate analysis. Kuehr *et al.* (1994b) found ground floor homes were more humid and had higher concentrations of Der p 1 than homes on higher floors, but that Der f 1 was not associated with the height of the home above ground (Figure 8.6).

d Exposure to wind

Couper *et al.* (1998) found a 1.3-fold lower mean Der p 1 concentration in homes situated in windy locations than homes in sheltered spots, but the difference was not statistically significant.

8.6.4 Summary – hidden sources of variation?

Factors associated with variation in mite allergen concentrations between homes fall into three general categories that are likely to show interaction and overlap. They are:

1. those that relate to processes of *colonisation and establishment* of mite populations, including habitat availability and development of habitat complexity;
2. those associated with *retention or removal* of allergens;
3. those that are associated, directly or indirectly, with variation in indoor *microclimate*, and influence the rate of growth and population density of mite populations once they become established.

The first category includes age (and possibly type) of mattresses and carpets (including their presence or absence); the second covers cleaning and the third

almost all other factors. The nature of the association between allergen concentrations and smoking is unclear and does not fit clearly into any category.

Most of the studies were based in English-speaking countries in temperate latitudes. Four were done in Australia, three in the UK and two in New Zealand. Basagaña *et al.* (2002) observed that most of the risk factors associated with the English-speaking countries lacked an equivalent association in Barcelona and Menorca and were irrelevant. Perhaps the starkest example of such differences is the finding of El Sharif *et al.* (2004) that the most significant independent factor for high allergen exposure in Ramalla, Palestine, was whether or not the home was in a refugee camp. Several studies in Table 8.2 are based on subsets of homes of parents and infants enrolled in longitudinal birth cohort studies. Selection of homes on the basis of their representative housing types might be desirable. Three studies involved random selection of homes, independent of a pre-existing study (Luczynska *et al.,* 1998; Garrett *et al.,* 1998; Simpson *et al.,* 2002). Wickens *et al.* (2001) selected houses to represent a bimodal distribution of Der p 1, based on their previous study (Wickens *et al.,* 1997).

Few authors provide an assessment of the combined effects of risk factors on Der 1 concentrations, after adjustment. Mihrshahi *et al.* (2002) found unheated brick apartments or townhouses less than 10 years old, with concrete foundations, with carpets but no rugs, with inner-spring mattresses less than two years old and bedding that did not include blankets, synthetic or feather quilts or feather pillows, but did have a synthetic pillow would have a Der p 1 concentration of 3.2 $\mu g\ g^{-1}$ (compared with a mean of 12.1 $\mu g\ g^{-1}$ for beds and floors). When only bedding factors were considered, beds would have a mean of 8.6 $\mu g\ g^{-1}$ compared with a mean of 14.3 $\mu g\ g^{-1}$. Based on the data in Tables 8.1 and 8.2, the lowest risk of high allergen concentrations would be in an uncrowded, well-ventilated newer apartment, above ground level, that had hard floors and a newer mattress without blankets.

Risk factors are basically indicators or predictors of a variable – allergen levels or mite population densities. Indicators are most useful when they are simple to assess and predictive of a more direct factor that is difficult or expensive to measure. If the direct factor is easily and accurately measured, there is no need for an indicator. A good example is indoor relative humidity, which is hard to measure in a manner that directly relates to physiological drivers of mite population growth (partly because of the co-dependent effect of temperature). Point-source or 'snapshot' measurements of humidity are of lower utility than repeated monitoring because of large seasonal and diurnal fluctuations and high spatial variation. But in regions with high precipitation, the presence of damp and mould are good indicators of high indoor humidity, while absence of condensation is a good indicator of low indoor humidity.

The remarkable feature of the allergen variation data is that most significant factors are associated with only 2- to 3-fold greater concentrations. Larger differences (4.5 to 7-fold) are associated mostly with presence of carpet or its age. The significant factors explain only a small amount of the between-home variation which is typically 2–4 orders of magnitude (for variation in larger, repeat-sampling datasets, see Marks *et al.,* 1995a, their Figure 1; Kuehr *et al.,* 1994b, their Figure 1; Crisafulli *et al.,* 2007, their Figure 2).

A source of possible additional variation, currently unexplored, is the spatial distribution of survey homes within a town or city and the effect of urban microclimatic variation (Bridgman *et al.,* 1995). Urban heat islands (UHI) are volumes of air over cities that are significantly warmer and dryer than over surrounding rural areas (Oke, 1982; Collier, 2006). The largest temperature difference is at night, during summer, and in still air. A UHI is caused partly by the emission of heat through human activities but is mainly due to the surfaces of buildings, roads and roofs warming up during the day and releasing heat at night. Materials like brick, concrete and asphalt absorb and radiate heat far more effectively than air, water or vegetation. Urban areas have lower rates of evaporation and heat loss is reduced because of low turbulence and the shading effects of buildings (Sánchez and Alvarez, 2004). Within a metropolitan area, there can be quite large differences in temperature and humidity between the central business district, high-density inner-city housing, parks and gardens, commercial districts, medium-density suburban housing, low-density outer suburbs and the rural hinterland (e.g. Coutts *et al.,* 2007). Generally, the larger the city, the larger the UHI effect (Oke, 1982). Major modifying factors on urban climate include distance from the coast, sea-breeze circulations and surrounding mountains (Ohashi and Kida, 2004). Studies have yet to be done on the geographic variation in dust mite populations or allergen concentrations within cities in relation to urban climate factors.

8.7 Regional and global variation in dust mite abundance and allergen concentrations

8.7.1 Datasets

Repeated measurements of mite allergens within the same homes over periods ranging from weeks to years have shown a reasonable degree of consistency (Kuehr *et al.,* 1994b; Marks *et al.,* 1995a; Matheson *et al.,* 2003; Antens *et al.,* 2006) though Topp *et al.* (2003), over six years, found low consistency for a group of homes containing low levels of mite allergens. Crisafulli *et al.* (2007) found remarkably consistent fluctuations over a 2- to 3-fold range in a 7-year study of over 1000 homes. In other words, mite allergen levels in homes are sufficiently stable and consistent over periods of several years to use single-measurement samples in epidemiological studies with a reasonable degree of confidence (Antens *et al.,* 2006). The same kind of studies have not been done for dust mite populations, but population growth, based on stable age theory (Chapter 5), predicts that population densities will tend to stabilise and fluctuate around a particular level, constrained by the range of temperature and humidity they are exposed to. At the regional scale, macroclimate, elevation and continentality have major effects on dust mite population densities (Chapter 4). These arguments suggest that allergen concentrations and mite population densities may be characteristic of localities that share similar climatic and geographic features.

In order to examine regional and global-scale variation in mite populations and allergens in homes, I compiled datasets from published records of the abundance of total mites, plus abundance, frequency of occurrence and percentage dominance of the top four species (see Chapter 4, Appendix 2): *Dermatophagoides farinae*, *D. pteronyssinus*, *Euroglyphus maynei* and *Blomia tropicalis* (Appendix 3), as well as concentrations of *Dermatophagoides* group 1 allergens in dust from beds and floors (Appendix 4). There was insufficient data to compare some of the other allergenic species of interest, notably *Lepidoglyphus destructor*, *Glycyphagus domesticus*, *Acarus siro* and *Tyrophagus putrescentiae*. Most of these species are represented by less than 30 records of abundance or dominance or frequency. This does not imply they are not insignificant, but rather they are often reported lumped together in their family categories of Glycyphagidae and Acaridae.

The dataset on mites is based on almost 23 500 samples from over 9000 homes. That on allergens is based on over 34 000 samples from nearly 28 000 homes. Data were included where a latitude and longitude could be matched to a record. Data pooled from multiple localities were excluded from any analyses (but not from the dataset). Means are given as geometric means wherever possible. Where arithmetic means were presented in the original publications, I have converted them to geometric means using graphs or tables where such data were available, and included 'negative' samples in the calculation. Mite abundance and allergen concentrations were excluded if semi-quantitative, based on 'exposure classes', because it is not possible to accurately calculate a measurement of central tendency from these. Values repeated in multiple publications were not replicated in the dataset. Where abundances or concentrations were presented per unit area they were excluded. The vast majority of data are expressed per unit weight and there is no reliable way of converting or comparing area data. Data from places other than homes (offices, hospitals, nursing homes and public facilities) are not included, nor are those based on samples taken by sweeping rather than vacuuming.

On the principle of *habeas corpus*, I have not attempted any integration of mite abundance and allergen concentration data regarding the mapping of distributions. The physical presence of mite bodies, identified to species, is better evidence that populations persist at a particular locality than the presence of a particular allergen. This does not mean the presence of allergen is not a good indicator of presence of mites. It is, but it is only an indicator and can tell us a lot less about structure, growth or persistence of mite populations. For now, because these data have not been collated previously, it is best the mite abundance data and allergen data be presented separately.

8.7.2 Population densities of mites

The global distribution pattern of total mite abundance (i.e. all species) in beds, floors and mixed samples is shown in Figures 8.7 and 8.8 (see also Appendix 3). Abundance data were presented as classes based on threshold equivalents (100 mites roughly equivalent to 2 $\mu g\ g^{-1}$ and 500 equivalent to 10 $\mu g\ g^{-1}$). The reason for doing so is mainly because these thresholds have been widely used and represent a familiar benchmark for many researchers. Data from 'mixed samples' (i.e. dust samples that included material from both beds and floors, or mean abundances calculated from both floor

and dust samples) were mapped together with data from floors (with which they had a similar median and range) in order to increase geographic coverage. About 75 locations were represented by mixed samples only.

Localities with the highest total mite populations in the tropics were Central and South America and the Caribbean (Colombia – Caracas, Tolú; Ecuador – Guayaquil; Barbados, Costa Rica), South-East Asia (Singapore, Kuala Lumpur, Bangkok), Africa (Nairobi, Lagos). In temperate regions, the highest numbers of mites were recorded at Iranian cities on the Caspian Sea, Algerian coastal cities, New Zealand (Wairoa, Wellington), Australia (Melbourne) and Japan (Naha, Wakayama, Osaka, Sendai, Tokyo). Lowest mite populations were at inland places in Australia (Wagga Wagga, Alice Springs), desert oases in Algeria (Biskra, Touggourt, El-Oued, Arris, Batna, Ain-Touta), central Iran (Shiraz, Karaj, Isfahan), far southern Chile (Punta Arenas, Valdivia), alpine Switzerland (Zermatt, Davos, St Moritz), continental northern Europe and Scandinavia (Katowice, Copenhagen, Umeå, Sør-Varanger), central and south-eastern Turkey, and montane continental USA (Denver).

The global pattern of abundance classes in Figures 8.7 and 8.8 shows a high proportion of large dots (>500 mites per gram) in tropical and subtropical latitudes, corresponding with the zone of highest mean annual rainfall and lowest mean fluctuation in temperature, but also at coastal localities (including inland seas like the Caspian), on islands and at places that receive high annual precipitation due to maritime climatic influences such as New Zealand and Japan. Contrastingly, Chile and coastal Peru receive low annual precipitation due to the effects of cold northerly ocean current systems (as does the west coast of southern Africa), and mite abundance is correspondingly low. Smaller dots (=100 mites per gram) tend to be in continental interiors or above 55°N.

The range of abundances based on the distribution curves (see Figure 8.9) indicates for beds 112/167 localities (67%) had more than 100 mites g^{-1}, and 59 (35%) had more than 500 mites g^{-1}. For floors, the figures were 36/115 (31%) and 17 (15%). Median abundance for beds was 243 mites g^{-1} (interquartile range, IQR 62–835) and for floors 14 mites g^{-1} (IQR 2–54, see Table 8.3). Mixed sample data were not included. Globally, *Dermatophagoides pteronyssinus* was by far the most widespread, abundant, frequently occurring and dominant species (dominance being the percentage of *D. pteronyssinus* individuals in the total mite population) in both beds and floors (Table 8.3). Beds had consistently higher densities of mites than floors. The highest recorded mean population density of *D. pteronyssinus* was from Caracas (nearly 13 000 per gram; Hurtado and Parini, 1987). *Dermatophagoides farinae* was the next most abundant and frequently occurring species, but not that much greater than *Blomia tropicalis* and *Euroglyphus maynei*. *D. farinae* was more frequent (though not as abundant) on floors, where it is more likely to be the dominant species than in beds. *Blomia tropicalis* was almost as frequent and abundant as *D. farinae*, and appears to show no marked preference for beds over floors. In tropical South-East Asia (Malaysia, Singapore) and Latin America, this species was either the dominant species or co-dominant with *D. pteronyssinus*, and it had the highest recorded mean population density of any dust mite species on floors: 8250 per gram in Singapore (Chew *et al.*, 1999a). *Euroglyphus maynei* was more abundant and occurred slightly more frequently in beds than on floors. Highest densities (>1000 g^{-1}) were all recorded from the tropics (Nairobi, Kenya; Guayaquil, Ecuador and Caracas, Venezuela) and the highest frequencies of occurrence (>50%) were at coastal localities with warm moist or temperate moist climates.

Mite population densities in beds and on floors were exponentially negatively correlated with latitude (see Figure 8.10). Ordman's (1971) records for floors from South African localities were excluded from Figure 8.10b because they were artificially low; probably due to the use of an early and inefficient extraction technique. As stated, tropical and subtropical localities tend to have the highest numbers of mites. Population densities within 30° of the equator were 2- to 11-fold greater than at 50°N. For beds, based on the regression equation, with every 10-degree increase in latitude from the equator, there was a 1.6-fold decrease in mean population density. For floors, the decrease was 1.5-fold. The significance of this relationship lies not so much with the higher rainfall zones of the tropics, for rainfall may be highly seasonal and many of the world's great deserts lie between the tropics of Capricorn and Cancer. Rather, it is due to the lower amplitude of diurnal and seasonal variation in temperature, especially at tropical coastal localities. A glance at the climate graphs for major cities in the *Times Atlas of the World* shows hardly any seasonal variation in mean monthly temperature for Singapore, Caracas or Bangkok, but at least 3- to 4-fold variation for places at temperate latitudes or inland ones in the

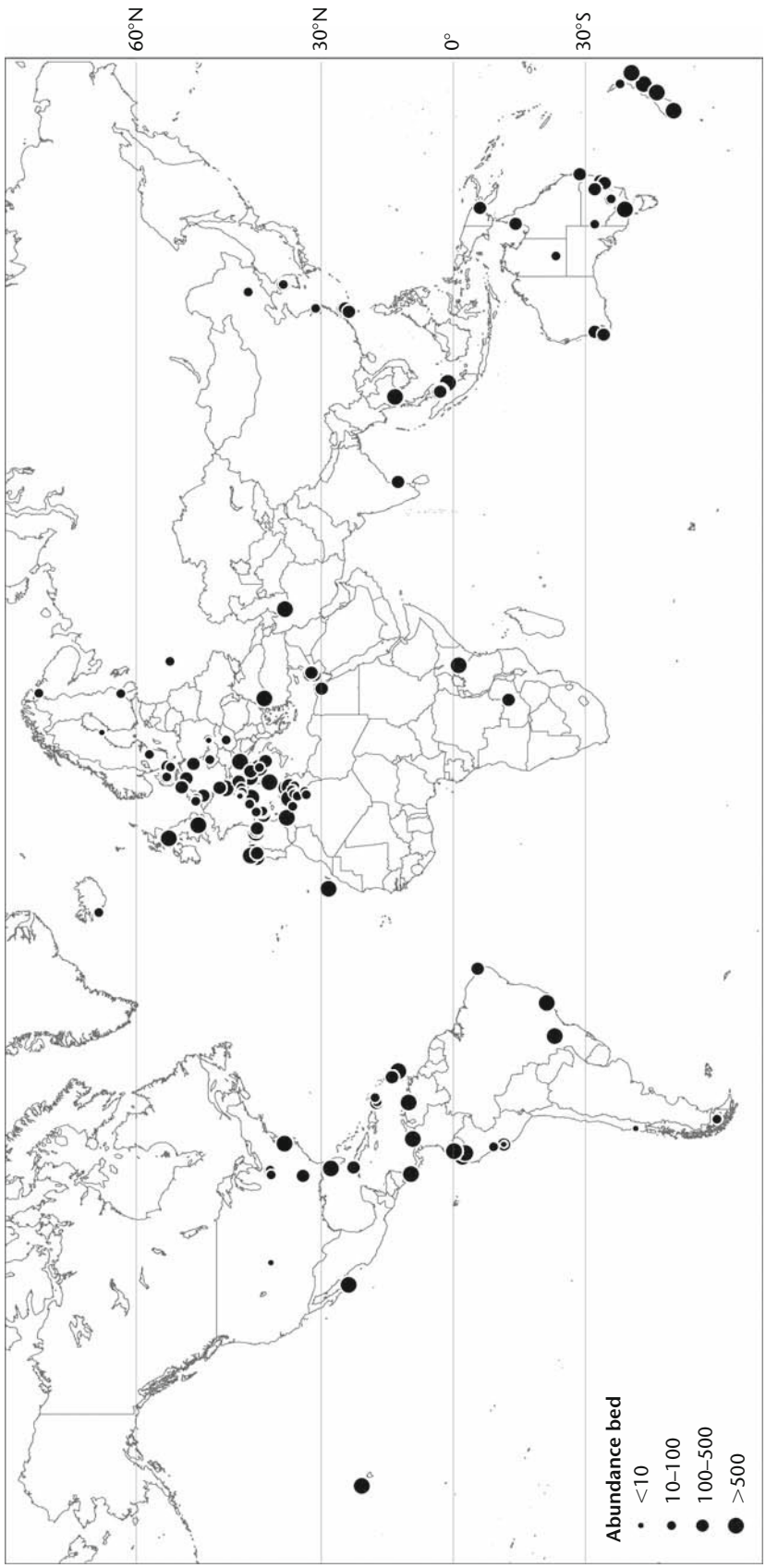

Figure 8.7 Global pattern of abundance (number per gram) of total mites (all spp.) in beds, based on published surveys (Appendix 3).

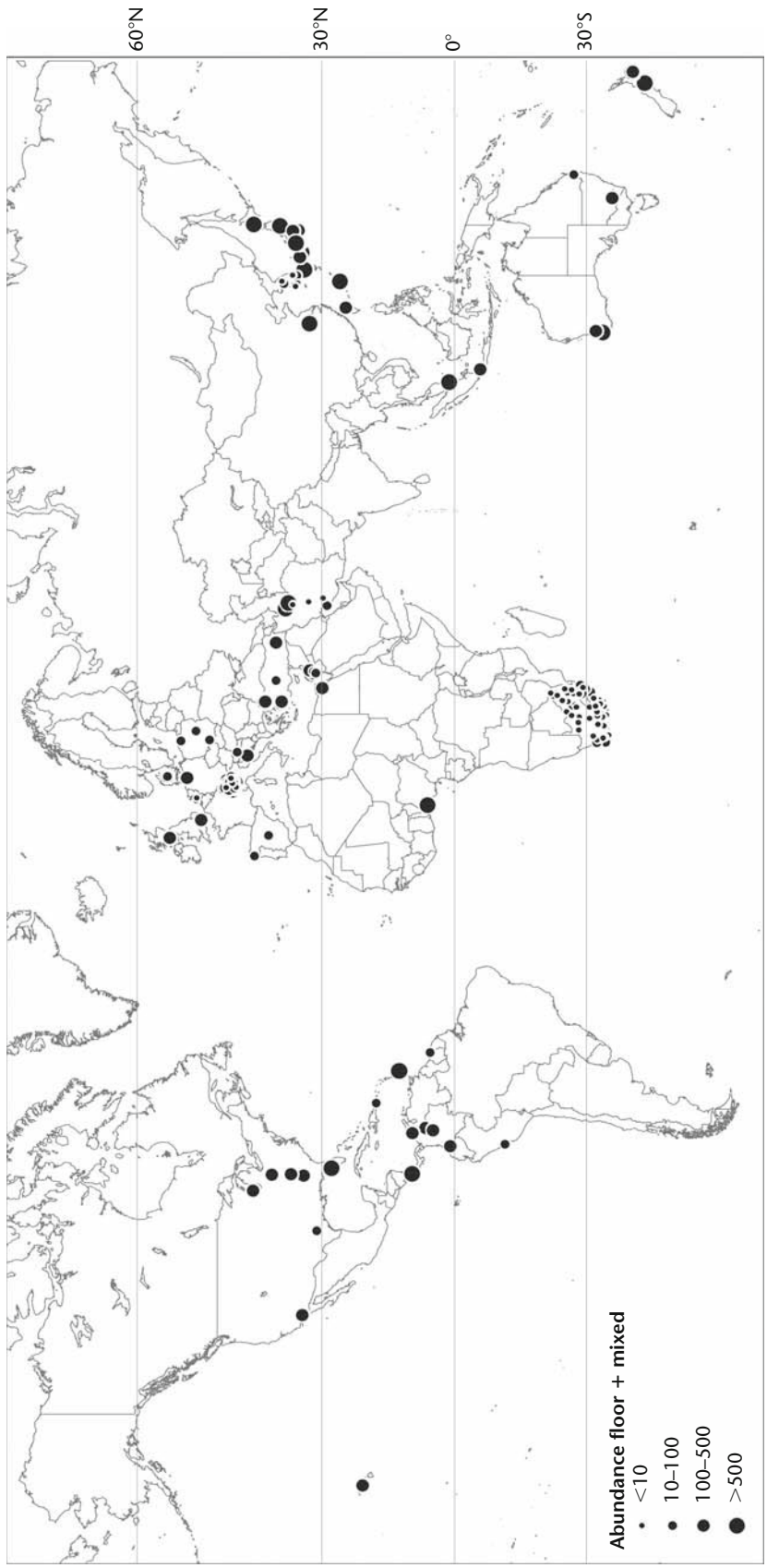

Figure 8.8 Global pattern of abundance (number per gram) of total mites (all spp.) in floors and mixed samples, based on published surveys (Appendix 3).

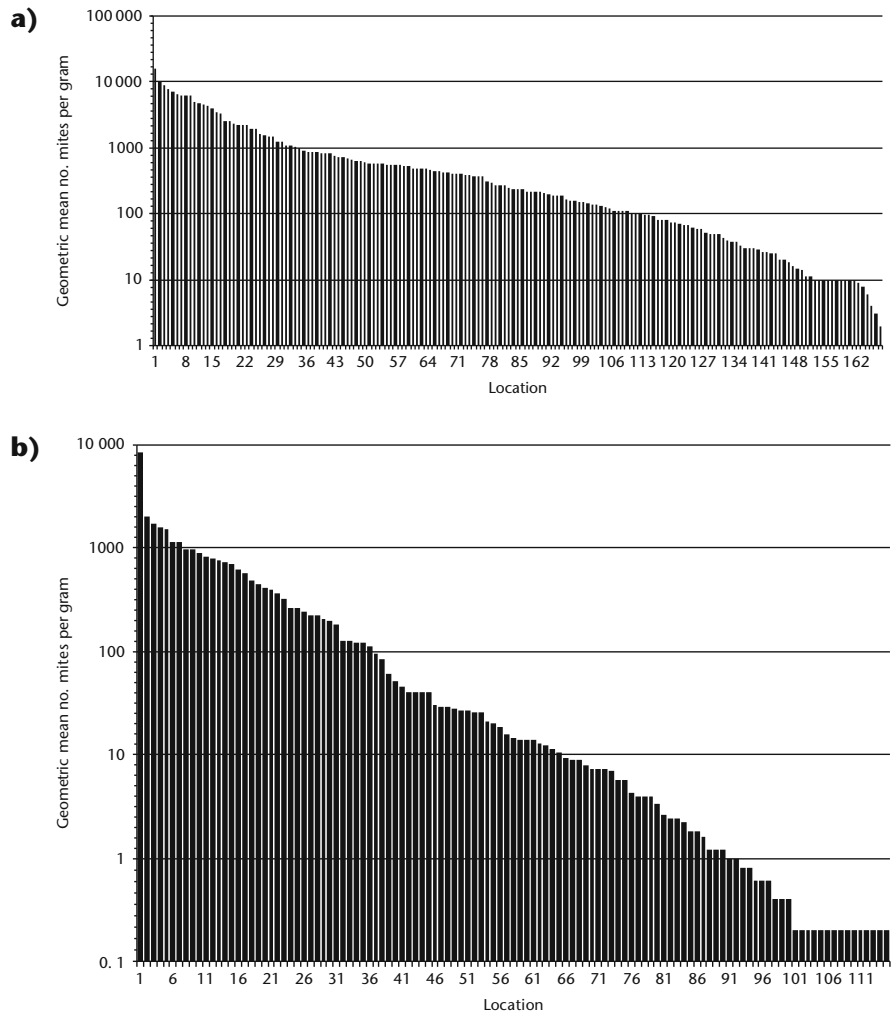

Figure 8.9 Distribution curves of ranked mean total mite abundance. **a)** In beds; **b)** on floors; with localities ordered according to abundance, based on published surveys (Appendix 3).

sub-tropics. The annual temperature range at 40–50°N is in the order of 30–40°C (maximum v. minimum recorded temperatures). More uniform seasonal temperature in the equatorial belt is accompanied by consistent day length and little difference between daytime and night-time temperatures, whereas at 50°N, mid-winter day length may be half that of mid-summer, and outdoor temperature at midday 10°C higher than at midnight. It should come as no surprise that individual global climate variables based on annual means have relatively low explanatory power in relation to mite populations. For example, monthly mean minimum temperature (expressed as an annual mean) is a significant factor (Figure 8.11a), but only part of the story.

Although highly statistically significant, the relationship with latitude explains only a small proportion of the variation in population density. An additional amount of variation can be accounted for according to whether a location is on the coast or inland. Coastal locations had five times the median number of mites in beds and eight times the number in floors than localities that were inland (see Table 8.4). Although precise distances from coasts were not calculated, the pattern on the maps (Figures 8.7, 8.8) suggests there is a tendency for localities that are strongly continental to have lower mite populations. There was no relationship between either elevation of localities above sea level or mean annual rainfall and mite population densities in beds or carpets at the global scale, although with rainfall there appears to be a cut-off point around 270 mm, below which mite populations are uniformly low.

Table 8.3 Median (and interquartile range, IQR) abundance (number per gram), percentage frequency of occurrence and percentage dominance of dust mites in beds and floors, based on published surveys (Appendix 3).

Total mites	Abundance	IQR	n	% frequency	IQR	n	% dominance	IQR	n
Beds	243	62–835	164	99	70–100	109			
Floors	14	2–54	156	100	90–100	31			
D. pteronyssinus									
Beds	191	33–585	104	87	60–98	104	67	35–83	106
Floors	83	4–337	31	100	60–100	14	34	12–69	30
D. farinae									
Beds	33	5–185	73	34	9–69	77	6	2–24	80
Floors	14	3–79	27	50	20–67	9	16	4–70	24
E. maynei									
Beds	18	2–125	68	22	8–43	56	3	1–16	68
Floors	12	4–38	11	17	13–54	10	4	1–13	13
B. tropicalis									
Beds	23	3–115	32	33	19–50	43	8	1–27	38
Floors	17	8–1100	9	95	78–100	6	41	6–73	11

The distribution and abundance of dust mites are dependent on a favourable microclimate in which they can live and reproduce. The mite population density influences allergen levels, human exposure and, to a certain extent, the prevalence and severity of disease. Microclimate within homes is influenced, for at least part of the year, by outdoor climate, even in well-sealed homes. The influence of macroclimate on dust mite populations appears, at the regional and global scales, to override the effects of indoor microclimate. In summary, some of the major lines of evidence for macroclimate effects on dust mite populations are:

- low density mite populations at high altitude in temperate latitudes, but very high densities at high altitude localities in the tropics (Caracas, Bogota, Nairobi) due to seasonally high rainfall and outdoor humidity (mean monthly RH is >81% for Caracas);
- a dust mite fauna dominated numerically by *Dermatophagoides farinae*, with its lower critical equilibrium activity, in the drier parts of Europe and North America, but by *D. pteronyssinus* in the more humid regions;
- highest dust mite population densities recorded from coastal cities with high rainfall and moderate-to-warm outdoor temperature regimes (e.g. Melbourne, Sydney, Singapore, Tokyo), but low mite population densities from cities with dry climates, e.g. those in continental interiors or high latitudes (e.g. Helsinki, Wagga Wagga, Katowice, Briançon and Denver);
- seasonal fluctuations in outdoor humidity are followed by corresponding fluctuations in dust mite population density and allergen concentrations; and
- where outdoor climate is unfavourable for part of the year (e.g. cold and dry, as in Scandinavia), the frequency of occurrence of dust mites in homes is considerably less than 100% (e.g. Copenhagen, 60%; Uukuniem and Ilomantsi, 32.4%; Oslo, 23.5%; Reykjavik, 10%).

In homes where outdoor climate is favourable for most of the year (e.g. warm-temperate and moist, as in coastal Australia and New Zealand), just about all homes contain dust mites.

8.7.3 Concentrations of allergens

There was a strongly significant correlation between mite population densities and allergen concentrations in beds at the 32 localities where both were measured

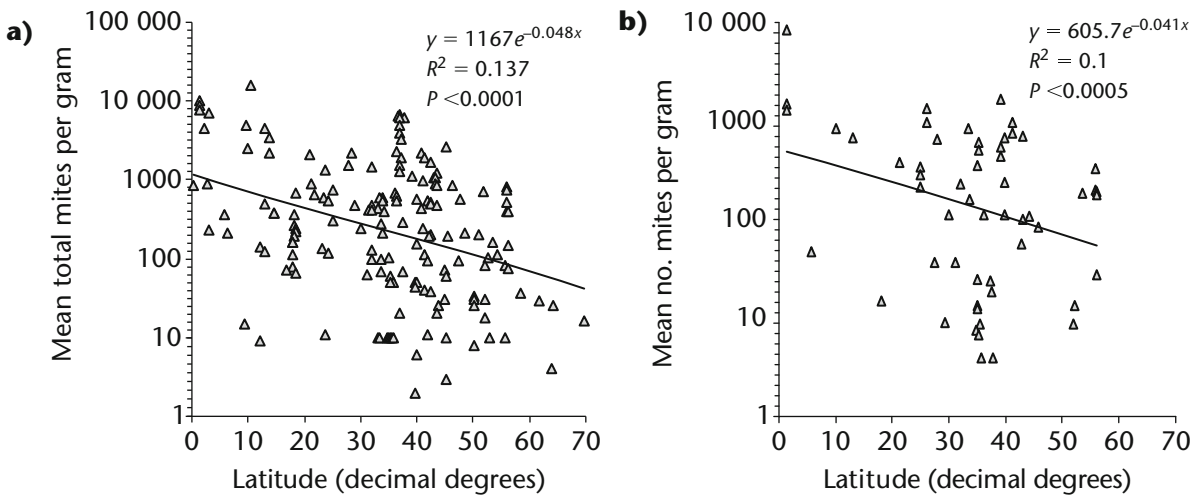

Figure 8.10 Relationship between population density of mites and latitude. **a)** In beds; **b)** on floors; with South African localities of Ordman (1971) excluded. Southern Hemisphere localities were corrected to positive latitudes.

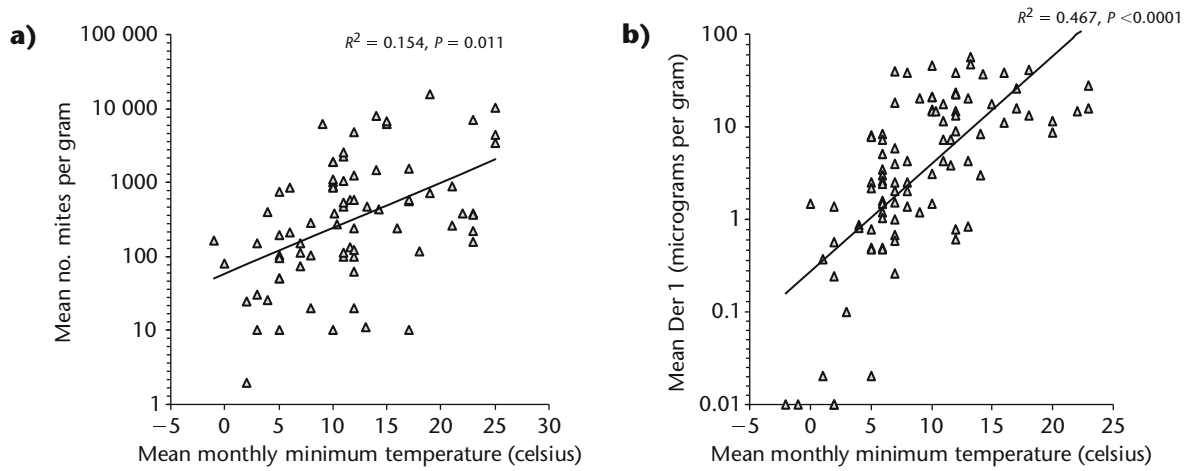

Figure 8.11 Relationship between **a)** population density of mites; and **b)** concentrations of Der 1 in beds and mean monthly minimum temperature, averaged annually.

(see Figure 8.12). There was no significant difference between mites and allergens measured as part of the same study (14 locations) and in different studies (and in different years), lending weight to the hypothesis that mite populations and allergen concentrations are relatively stable at localities with shared climatic and geographic features. Der 1 concentrations of 2 and 10 μg g^{-1} were equivalent to 150 and 450 mites g^{-1} respectively, quite close to the 100 and 500 mites g^{-1} equivalents proposed by Platts-Mills *et al.* (1989b). There were not enough data to compare mites and allergens on floors.

The geometric mean concentration of Der 1 in beds at 128 localities worldwide was >2 μg at 66% of localities and >10 μg at 35% (Figure 8.13a). Floors had >2 μg at 49% of localities and >10 μg at 19% (Figure 8.12b). The median value of Der 1 for beds was 4.4 μg g^{-1} (IQR 1.2–14.8) and for floors 1.9 μg g^{-1} (IQR 0.7–7.6; Table 8.5).

The global distribution of Der 1 concentrations in Figures 8.14 and 8.15 shows a similar pattern as for mite abundance. Like the abundance maps, data were presented as classes based on threshold concentration (2 μg g^{-1} and 10 μg g^{-1}). Again, there is a high proportion of large dots (>10 μg Der 1 g^{-1}) in tropical and subtropical latitudes and at coastal localities, and smallest dots (<0.2 μg Der 1 g^{-1}) tend to be in continental interiors or above 55°N. Exceptions are the high level of Der 1 in beds at Moscow (based on paired

Table 8.4 Median (and interquartile range) *Dermatophagoides* group 1 allergen concentrations (micrograms per gram) and total mite population density in coastal and inland localities, based on published surveys (Appendices 3 and 4). For mite population densities in floors, Ordman's (1971) South African records were excluded.

		Median	25th percentile	75th percentile	n
Total mites per gram					
Beds	Coast	546	189	1527	75
	Inland	107	30	428	92
Floors	Coast	383	182	807	32
	Inland	50	13	202	24
Der 1 µg per gram					
Beds	Coast	7.4	1.9	18.9	60
	Inland	3.1	0.8	11.6	68
Floors	Coast	4.4	1.8	13.9	29
	Inland	1.1	0.3	2.5	36

mothers' and children's beds in a small sample of apartments) and Fyn/Viborg in Denmark (from baseline measurements of a clinical trial of allergen avoidance).

The dense cluster of high allergen localities (>10 µg g^{-1}) for beds in northern Spain (Figure 8.14) represent some of the highest Der 1 concentrations recorded in Europe. This has been ascribed to an interaction of indoor risk factors with high humidity and warmer temperatures during winter at coastal localities (Echepichía *et al.,* 1995; Boquete *et al.,* 2006; Zock *et al.,* 2006), reflecting the temperate high-rainfall climate associated with westerly Atlantic low pressure systems. High allergen levels were also found at lower elevation sites in the montane Rioja region, which has a less favourable climate than the coast, though this was considered to be related to higher allergen concentrations in rural than urban homes (Lobera *et al.,* 2000). A group of very low allergen sites (with only 2–23% frequency of Der 1) in Saudi Arabia (Al-Frayh *et al.,* 1997; Figure 8.15) was associated with arid desert conditions in the central Arabian peninsula, but also at one central coastal location (Jeddah). Much higher allergen levels (and 70% frequency) were found at the most southerly town, Abha, which is only 70 km from the coast but almost 2300 m above sea level. Temperature is lower and humidity markedly higher here than at the coast.

As was found for dust mite populations, coastal locations globally had much higher median Der 1 concentrations than inland localities (2.4-fold for beds, 4-fold for floors; see Table 8.4). There was no relationship between allergen concentrations and either elevation of localities or mean annual rainfall. Allergen concentrations showed a highly significant decrease with distance from the equator (shown in Figure 8.16) and a highly significant positive correlation with mean monthly minimum temperature (Figure 8.11b). The relationship between allergen concentration and temperature is much stronger than for mite population density. Since Der 1 production is a function of population size and rates of feeding and digestive physiology, perhaps populations in colder climates are both smaller and egest faecal pellets at lower rates than those in warmer climates.

8.7.4 Regional and global patterns of allergen diversity and exposure

Previous compilations of records of mite populations and allergen concentrations (Woolcock *et al.,* 1991; Arlian *et al.,* 2002) have been preliminary or of limited geographic coverage because there were far fewer published records available than there are now. The datasets in Appendices 3 and 4 are certainly not complete. There are several publications I have been unable to obtain. Some of these are abstracts of conference proceedings, are published in very hard-to-find periodicals or both. I would be grateful to all readers who can supply copies of publications that have not been cited.

One of the main outcomes of mapping the abundance of dust mites and their allergens has been to highlight the information gaps, the main one being uneven geographic coverage. Quantitative data are harder and more expensive to generate than

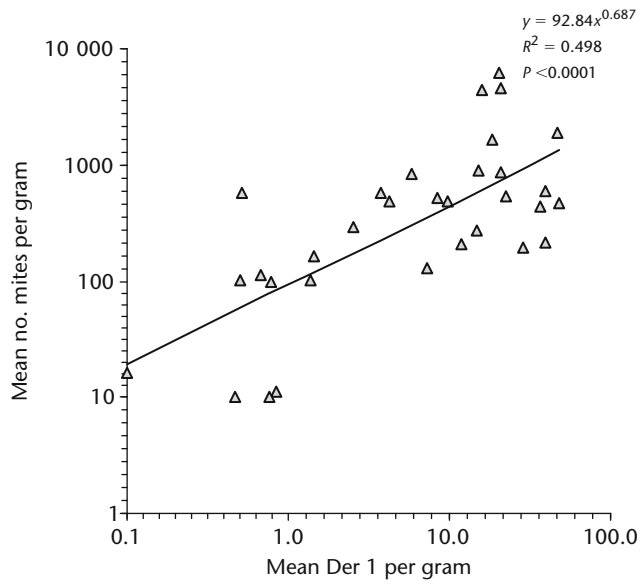

Figure 8.12 Relationship between mean Der 1 concentrations and mean total numbers of mites in beds, based on published surveys.

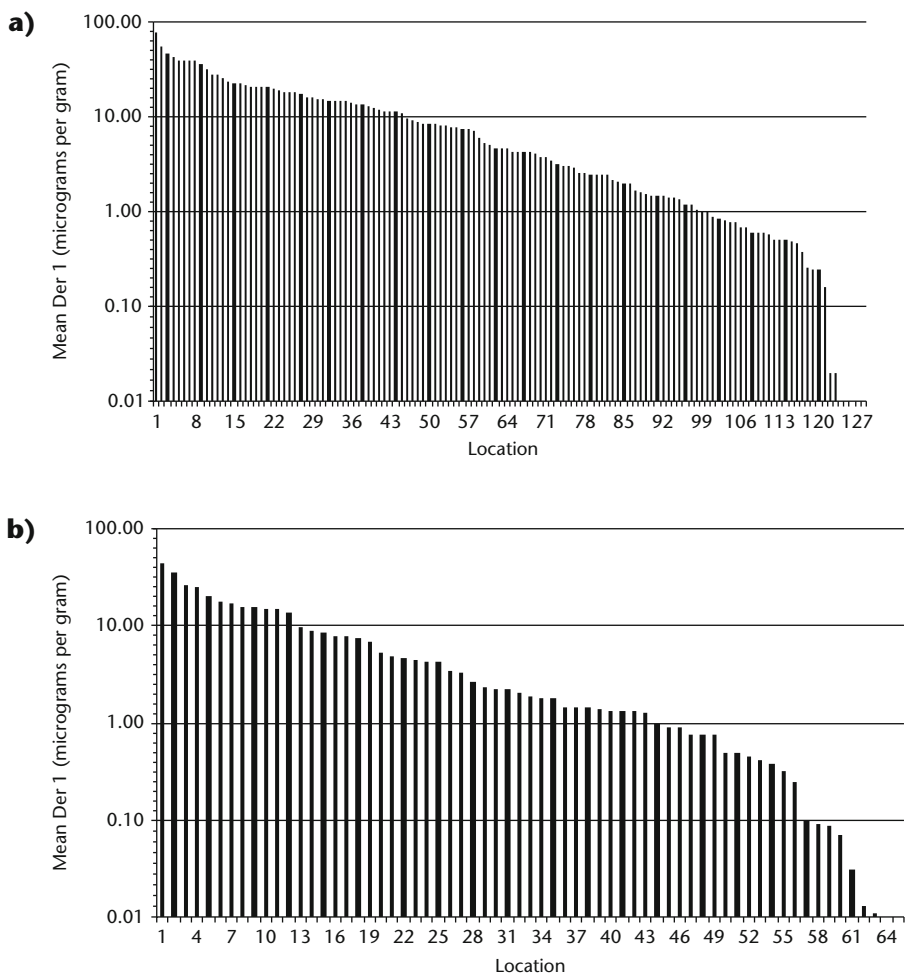

Figure 8.13 Distribution curves of ranked mean Der 1 concentrations. **a)** In beds; **b)** on floors; with localities ordered according to abundance, based on published surveys (Appendix 3).

Table 8.5 Median (and interquartile range, IQR) concentrations and percentage frequency of *Dermatophagoides* group 1 allergens (micrograms per gram), based on published surveys (Appendix 4).

		Concentration	IQR	n	% positive samples	IQR	n
Der 1							
	Beds	4.4	1.2–14.8	128	91	74–100	43
	Floors	1.9	0.7–7.6	65	86	45–100	12
Der p 1							
	Beds	2.8	0.5–13.3	113	85	45–100	53
	Floors	1.9	0.7–6.6	50	97	68–100	21
Der f 1							
	Beds	0.7	0.2–2.2	62	68	26–81	32
	Floors	0.3	0.1–0.8	25	38	15–68	13

point-source species records, and much less is available (compare map in Figures 8.14 and 8.15 with the 'all localities sampled' map in Figure 4.48). Nonetheless, many more published records could have been included in the quantitative maps had they been more geographically precise and/or expressed the data as geometric means.

The reason for compiling these records is, in part, to assist clinicians in making better-informed decisions about patterns of mite allergen exposure in their region, especially regarding appropriate diagnostic skin-prick testing and IgE antibody assays for allergies. The distribution maps in Chapter 4 show which species occur where, but the quantitative maps and appendices provide information on the relative magnitude of exposure of *Dermatophagoides* group 1 allergens and the abundance and frequency of the four most widespread and clinically important species. These species assemblages are examined in more detail below.

a Species assemblages and allergen exposure

The main regional combinations of dust mite species, based on mite community structure and relative dominance, are listed below. These species assemblages are responsible for different global patterns of allergen diversity, exposure and IgE responses.

Dermatophagoides farinae and *D. pteronyssinus* co-occur frequently in most of continental Europe, Russia, the Middle East, Asia, North America and Latin America. Mixed populations are rare in the UK, Norway, Portugal, north-western Spain, North Africa, the Caribbean, Australia and New Zealand. Zock *et al.* (2006) found much higher frequency of occurrence of Der p 1 in Western Europe and the Atlantic coast (where *Euroglyphus maynei* may also be present), whereas Der f 1 was the more frequent mite allergen on the Mediterranean coast, central and north-eastern Europe and eastern Scandinavia. Relative concentrations of the two allergens show similar distribution patterns and frequencies (frequency of occurrence of both Der f 1 and Der p 1 is strongly correlated with concentration), with Der p 1 dominating in Western and southern Europe (see Figure 8.17). Where total Der 1 concentrations are high (>10 μg g^{-1}), Der p 1 is almost always the dominant allergen. This trend persists worldwide (one exception being southern Brazil) and may be related to the capacity of *D. pteronyssinus* for more rapid population growth than *D. farinae* under optimal conditions (Arlian *et al.,* 1998a). A slightly less pronounced longitudinal trend is present in both Latin America and the USA, with Der p 1 tending to be the dominant allergen on the western sides of the continents and Der f 1 on the east (shown in Figure 8.18).

Dermatophagoides farinae, *D. pteronyssinus* and *D. microceras* co-occur mainly in Scandinavia, though group 1 allergen from *D. microceras* (Der m 1) has also been found with Der p 1 and Der f 1 in Belgium, Austria and the USA (Lind, 1986b; Schwartz *et al.,* 1987). It is likely that the abundance, frequency of occurrence and geographical range of *D. microceras* has been underestimated because it has been confused with its sibling species, *D. farinae* (Cunnington *et al.,* 1987). This finding may be of clinical significance because Lind *et al.* (1987) demonstrated *D. microceras*-specific antibody responses in some patients with atopic asthma. In Norway, where *D. farinae* is rare,

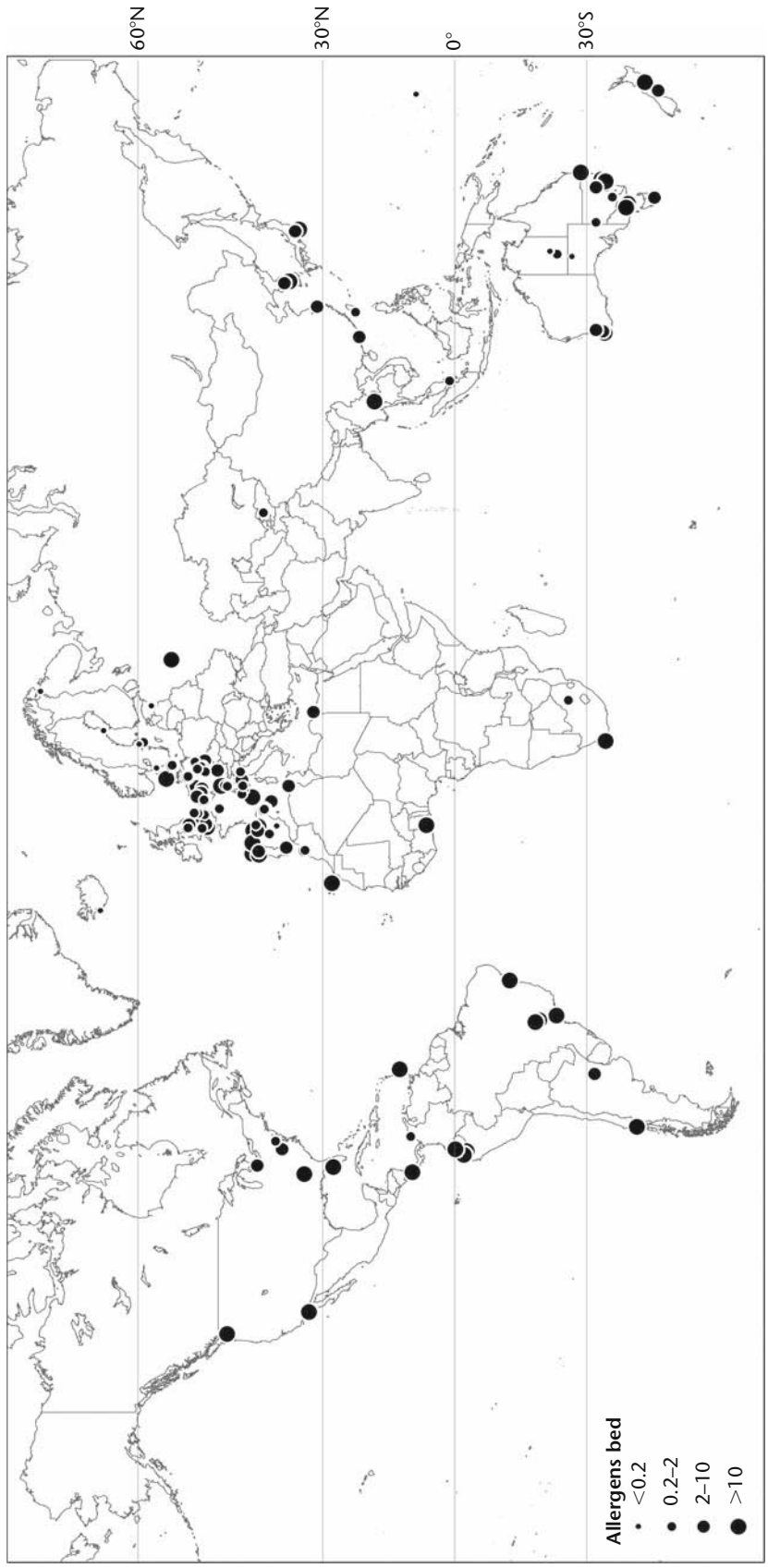

Figure 8.14 Global pattern of *Dermatophagoides* group 1 allergen concentrations (micrograms per gram) in beds, based on published surveys (Appendix 4).

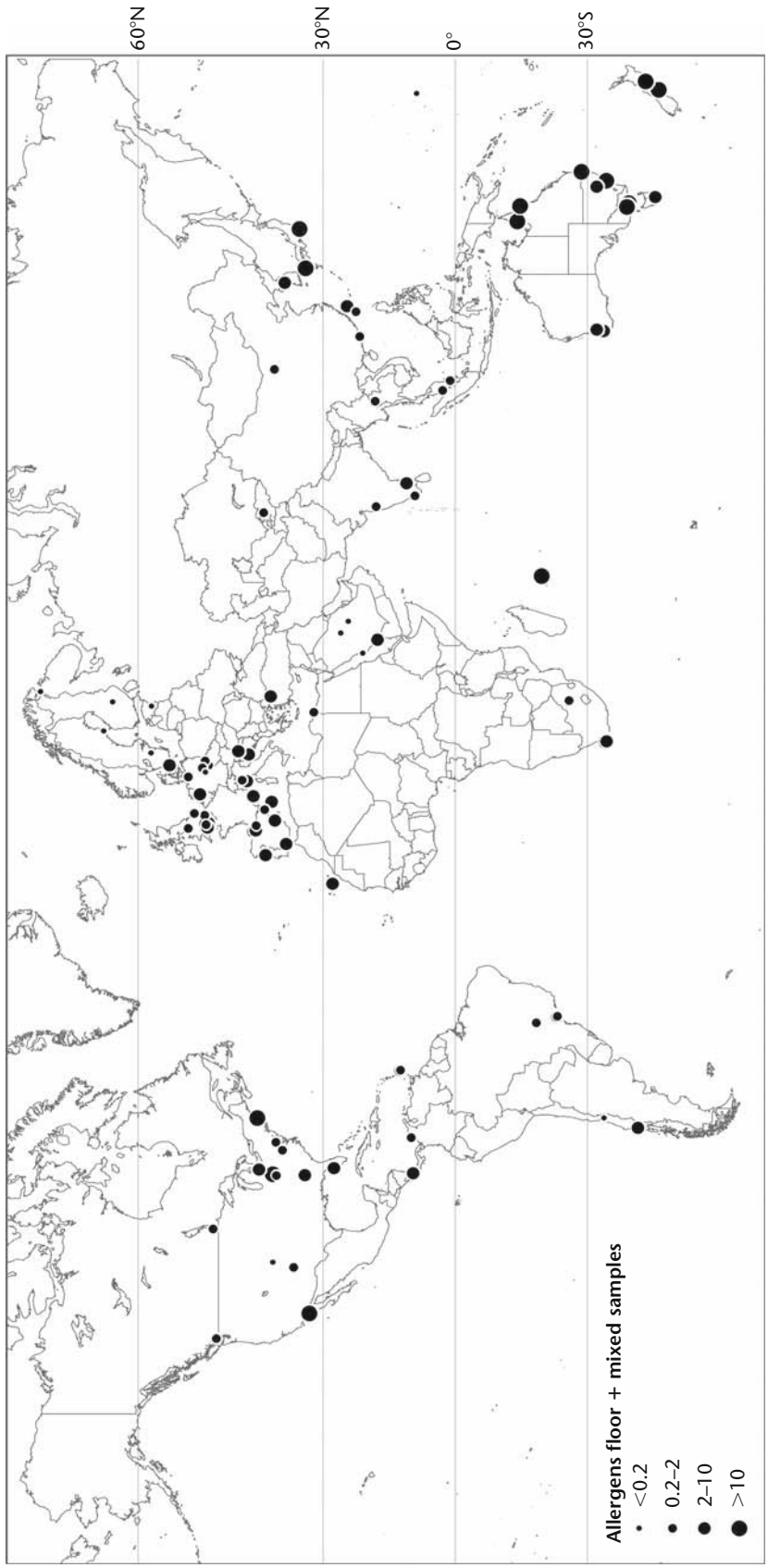

Figure 8.15 Global pattern of *Dermatophagoides* group 1 allergen concentrations (micrograms per gram) on floors, based on published surveys (Appendix 4).

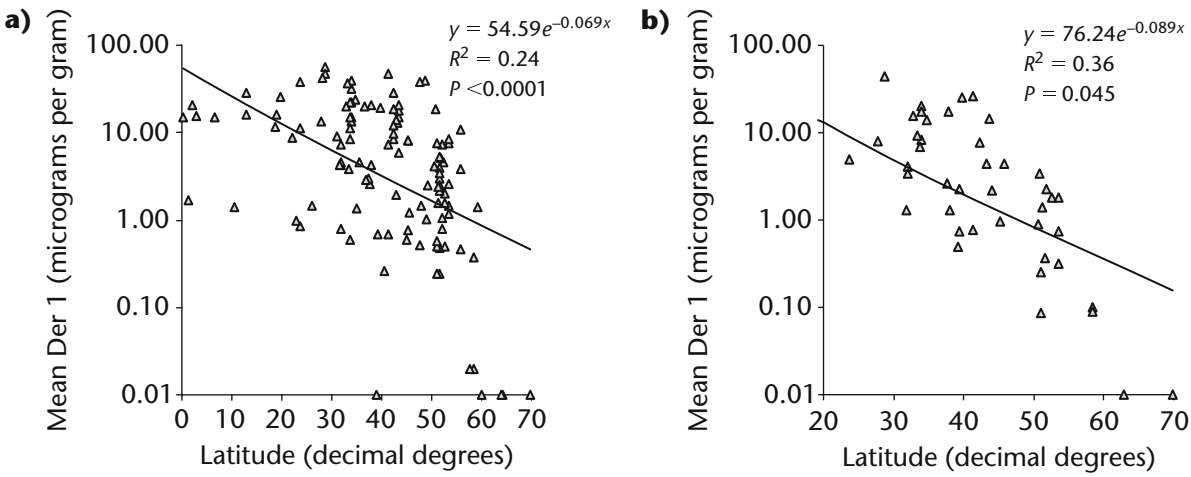

Figure 8.16 Relationship between Der 1 concentrations and latitude. **a)** In beds; **b)** on floors. For floors, tropical desert localities (Saudi Arabia) were removed. Southern Hemisphere localities were corrected to positive latitudes.

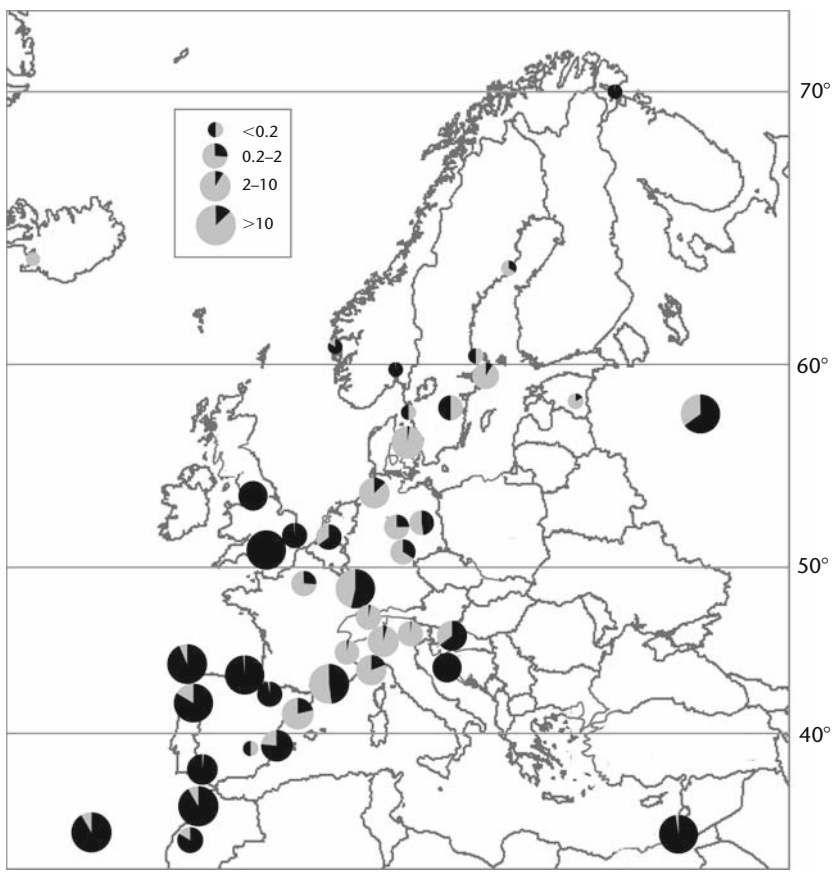

Figure 8.17 Relative concentrations (micrograms per gram) of Der p 1 (black) and Der f 1 (grey) in beds (and some mixed samples) in Europe, North Africa and the Middle East, based on records in Appendix 4.

D. microceras is the second most frequently occurring species after *D. pteronyssinus*. Of 540 homes in Oslo, *D. pteronyssinus* was present in 24% and 9% contained *D. microceras*. Only one specimen of *D. farinae* was found (Mehl, 1998). Der m 1 concentrations at three localities in Sweden ranged from 0.1–932 μg g^{-1} and represented about 30% of the total group 1 concentration, and Der m 1 was found in about half the homes where group 1 allergens were detected (Warner *et al.*, 1998).

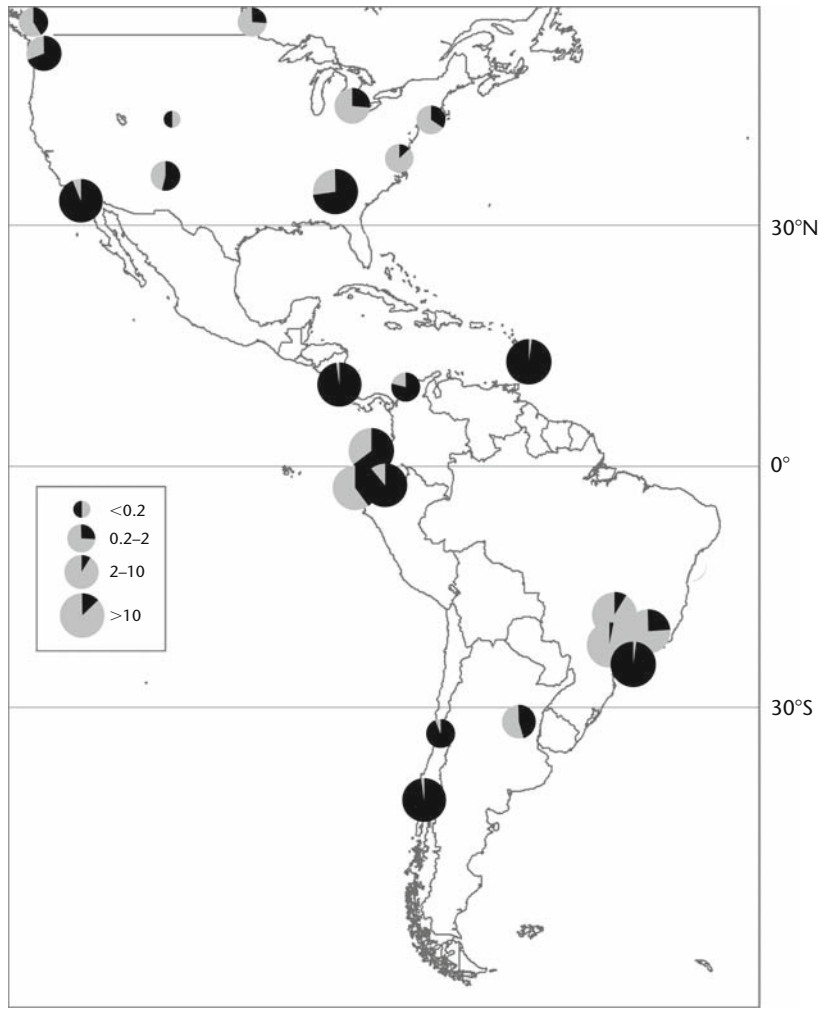

Figure 8.18 Relative concentrations (micrograms per gram) of Der p 1 (black) and Der f 1 (grey) in beds (and some mixed samples) in Latin America, the Caribbean, USA and Canada, based on records in Appendix 4.

D. pteronyssinus and *D. siboney* are found together in Cuba, where *D. siboney* occurs in over 80% of homes and represents ca. 40% of the total mite population (Dusbabek *et al.,* 1982; Cuervo *et al.,* 1983). *Blomia tropicalis* (see below) also commonly co-occurs, but *D. farinae* is rare or absent (Ferrándiz *et al.,* 1996). About 80% of patients with asthma had IgE antibodies to Der s 1 and the species is regarded as an important cause of sensitisation to dust mites in Cuba (Ferrándiz, 1997; Ferrándiz *et al.,* 1995b, 1996). The significance of *D. siboney* is that it is likely to be much more widespread in the Caribbean than just Cuba. It has been found in dust samples from homes in Kingston, Jamaica (Colloff, unpublished) and infrequently (though in substantial numbers) in mattress dust in Puerto Rico and Martinique (Montealegre *et al.,* 1997; Lafosse Marin *et al.,* 2006). It probably also occurs on mainland South and Central America also, where it may have been misidentified as *D. farinae*.

Blomia tropicalis and *D. pteronyssinus* are found together in the tropics and subtropics, particularly coastal Latin America, the Gulf of Mexico and the Caribbean, West Africa, South-East Asia and northern Australia. At localities where both species are present, rates of co-occurrence are often very high (>80% of samples). *B. tropicalis* tends to occur most frequently nearest to the equator (see Figure 8.19), often in very large numbers, and often as the numerically dominant species. Hence it is a major source of allergen exposure in the tropics, as confirmed by high concentrations of total Blo t allergens, detected by inhibition immunoassay (Puerta *et al.,* 1996b; Zhang *et al.*, 1997), and by ELISA for Blo t 5 (Yi *et al.,* 2004; Lee *et al.,* 2005)

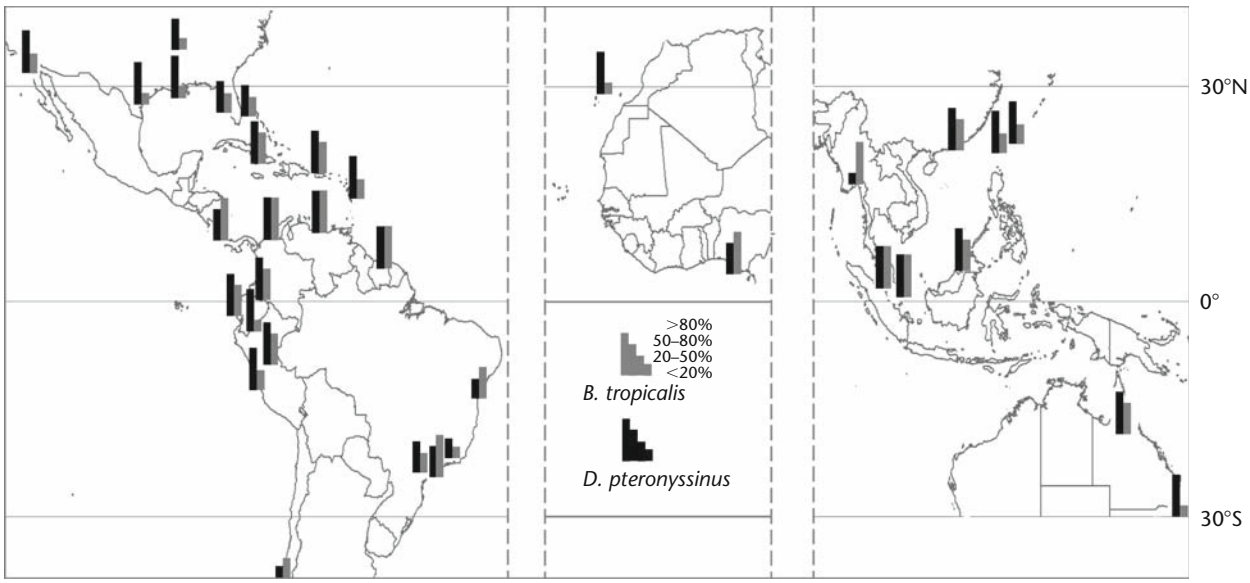

Figure 8.19 Frequency of occurrence of *Dermatophagoides pteronyssinus* and *Blomia tropicalis* at localities where both species are present, based on records in Appendix 4.

there is a high prevalence of sensitisation among atopic asthmatic patients to allergens of both *B. tropicalis* and *D. pteronyssinus* (summarised by Fernández-Caldas and Lockey, 1995, 2004). *D. farinae* and *Euroglyphus maynei* may also co-occur at localities with *B. tropicalis* and *D. pteronyssinus*, but there are insufficient data to get a clear breakdown of rates of co-occurrence within individual homes.

D. pteronyssinus and *E. maynei* are the two major species that co-occur, where *D. farinae* is rare, in the UK, Australia and New Zealand, as well as a couple of locations in Spain (Santiago de Compostella – Agratorres *et al.,* 1999; Santa Cruz, Tenerife – Sanchez-Covisa *et al.,* 1999) and coastal Algeria (Louadi and Robaux, 1992). Population growth of *E. maynei* is slower than most other domestic mites (Chapter 5) and it is rarely the numerically dominant species, usually accounting for less than 25% of the total mites (Colloff, 1991c).

D. pteronyssinus and *Lepidoglyphus destructor* are found together in rural areas and farming communities in Northern Europe. Some of the exposure to *L. destructor* allergens is occupational, relating to farming and the presence of mites in hay, straw and barns (van Hage-Hamsten *et al.,* 1985; Cuthbert *et al.,* 1984; Cuthbert, 1990; Härfast *et al.,* 1996; Radon *et al.,* 2000). In other cases, storage mites, including *L. destructor*, are associated with IgE sensitisation in urban homes (Warner *et al.,* 1999). In a random sample of 540 urban dwellers in Reykjavik, Iceland, 25% had a positive skin-prick test, and 6% had IgE-mediated allergy, to *L. destructor* (Gislason and Gislason, 1999). Over half the population had handled mite-contaminated hay or been exposed to hay dust during the short, intensive, rainy Icelandic hay harvest. For this population, *L. destructor* is possibly a more important source of allergens than *D. pteronyssinus* (Hallas *et al.,* 2004).

Currently our knowledge of regional and global scale variation in allergen concentrations is based solely on data for *Dermatophagoides* group 1 allergens. Group 2 data are available from a few studies but currently insufficient to be able to attempt a synthesis. For mites other than Pyroglyphidae, Lep d 1 and Blo t 5 assays are being used, but again there is as yet insufficient information to draw any inferences.

8.8 Epidemiological implications of variation in allergen concentrations

In regions like Scandinavia where there are relatively low population densities of dust mites, there tend to be far fewer homes that have detectable mites or allergens than in those areas where dust mite populations are high (Wickman, 1993, 1995; Wickman *et al.,* 1991, 1993). Under these circumstances, the prevalence of sensitisation will be only as high as the prevalence of homes with sensitisable levels of allergen in them, which may fall well short of the genetic potential of the population to develop sensitisation to dust mites and clinical symptoms of atopy. In regions where all homes

have house dust mites, the prevalence of sensitisation may be close to what the genetic status of the population will allow and the population potential for clinical atopy nears saturation. Two of the most contrasting examples are as follows: Dotterud *et al.* (1995) in a survey of 424 children at Sør Varanger, Northern Norway, found only 20 were sensitised to dust mite (4.7%; current asthma 2.6%) and that 10 of them lived in homes containing detectable mites (mean ca. 190 g^{-1}) whereas 19 randomly selected, non-sensitised controls had no detectable mites in their homes, giving an odds-ratio for sensitisation if mites were present of >20. By way of contrast, Marks *et al.* (1995b) in Sydney, Australia, found 41% of 80 children were sensitised to dust mites (current asthma 15%) and that there was actually a slightly higher Der p 1 concentration in homes of children who were not sensitised to dust mites (64 μg g^{-1}) than in those who were (41 μg g^{-1}). In areas of low dust mite populations, sensitised people receive seasonal variation in exposure and may not have symptoms and bronchial hyperreactivity all year. In areas of high dust mite populations, sensitised people receive continued high dose exposure, enough to maintain bronchial hyperreactivity for most of the time (Peat *et al.,* 1996). Demonstration of a dose-response relationship between allergen exposure, sensitisation and asthma depends on there being sufficient variation in allergen concentration, seasonally or between homes, for a broad range of asthma severity to become manifest. This variation in exposure is likely to be highest in areas that have most homes with few or no mites and a few homes with a great many, rather than in areas where almost all homes have large numbers of mites (Marks, 1998). So, in areas of low dust mite populations, the range of disease severity is likely to be high, from mild to severe; and a dose-response is demonstrable. In areas of high dust mite populations, the range of disease severity is lower because most people with asthma have more severe symptoms and a dose-response is not evident (see Figure 8.20), suggesting there is an upper threshold for exposure beyond which increasing exposure

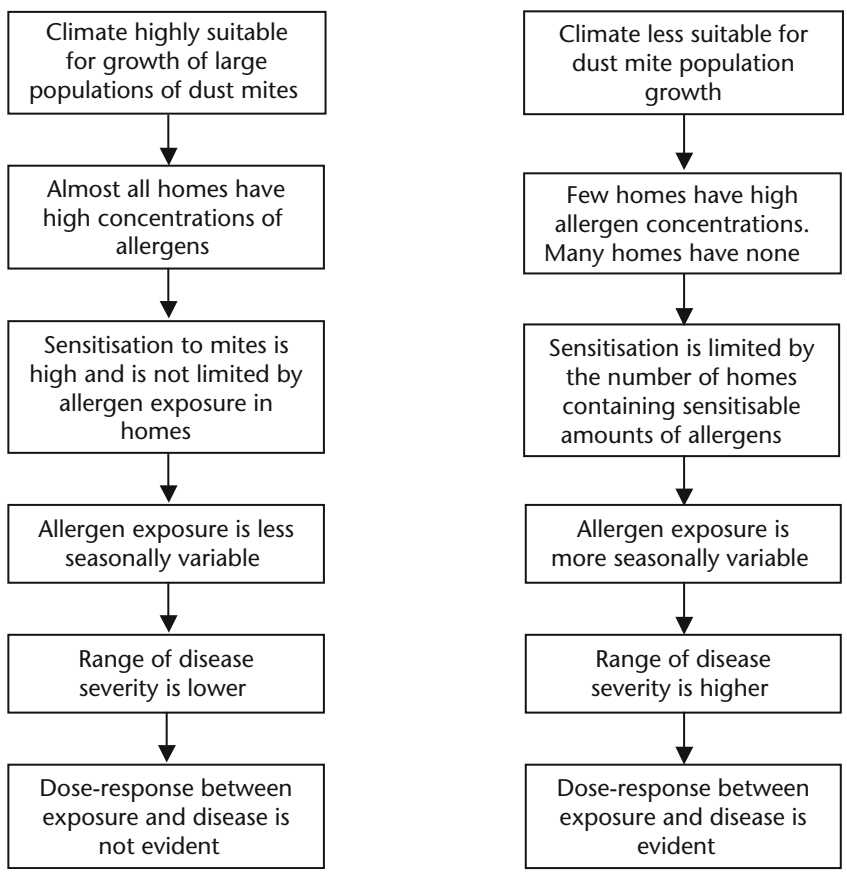

Figure 8.20 Conceptual model of the influence of macroclimate on mite allergen exposure and the prevalence of sensitisation to dust mites and the severity of mite-mediated atopic asthma.

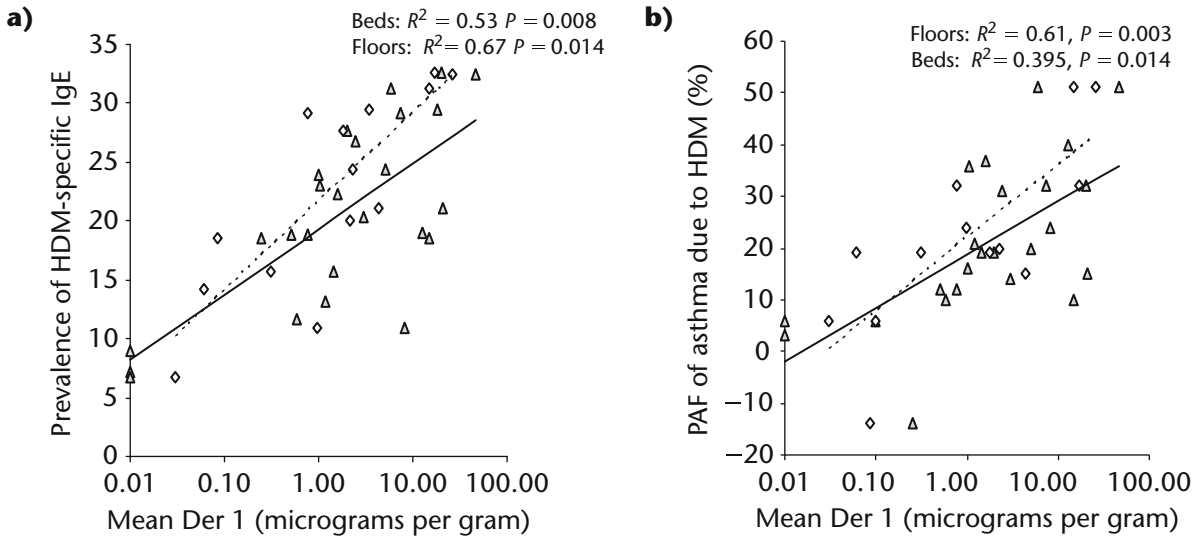

Figure 8.21 Relationship between allergen concentrations in beds (triangles, solid lines) and floors (diamonds, dashed lines) from Appendix 4 and **a)** sensitisation to dust mites based on prevalence of mite-specific IgE; **b)** the population-attributable fraction of asthma due to sensitisation to dust mites from the European Community Respiratory Health Survey (ECRHS; Sunyer *et al.*, 2004).

does not cause further risk of sensitisation or disease. Marks (1998) reckons this level is around 10 μg g^{-1}. It follows that even with allergen avoidance methods that can achieve large reductions in exposure, patients in areas of low exposure are likely to benefit more: an 80% reduction of 10 μg g^{-1} Der 1 still leaves a concentration that would be considered high for most places in the temperate latitudes of the Northern Hemisphere.

The European Community Respiratory Health Survey included 48 centres in 22 countries. Prevalence of mite-specific IgE has been determined and the attributable fraction of asthma due to sensitisation to mites has been calculated for 36 centres involving almost 13 600 volunteers in 16 countries (Sunyer *et al.*, 2004). Of these, 28 centres had matching data on mite allergen concentrations (shown in Appendix 4), most of which were determined by Zock *et al.* (2006) as part of ECRHS Phase II (though not all of these were used herein). There were statistically significant positive correlations between Der 1 concentrations in both beds and floors and the prevalence of mite-specific IgE as well as the mite-attributable fraction of asthma (see Figure 8.21). At a mean of 10 μg g^{-1} Der 1, prevalence of mite-specific IgE was 28%, almost twice that at 0.1 μg g^{-1}, and mite-attributable asthma was 35%, over four times as high. These relationships indicate there is probably a log.-linear dose-response relationship between mite allergen exposure and both prevalence of sensitisation and mite-mediated asthma in adults in this large trans-regional study. The International Study of Asthma and Allergies in Childhood had 28 centres with data on the population-attributable fraction of asthma due to a positive skin-prick test or allergen-specific IgE (Weinmayer *et al.*, 2007). But corresponding allergen concentrations (Appendix 4) were available for only nine of them, so a similar analysis was not attempted.

8.9 Changes in exposure to mite allergens?

It has been suggested there has been an increase in dust mite population density and allergen concentrations in homes since the 1970s (e.g. Sporik *et al.*, 1990; Woolcock *et al.*, 1995). Petrova and Zheltikova recorded an increase in frequency of mites in Moscow apartments between 1983 and 1997, but a decrease in mean abundance. Halmai (1984) claimed there was a significant increase in frequency and abundance of *D. farinae* between 1969 and 1984 in Hungary, but statistical analyses were lacking. Neither of these studies was based on repeated-measures sampling, whereas the longest repeated-measures surveys of allergen concentrations, though more recent, show no increase over 6–8 years (Topp *et al.*, 2003; Antens *et al.*, 2006; Crisafulli *et al.*, 2007).

But current patterns of mite allergen exposure are probably quite different now from what they were 100 years ago or more. Before the advent of improved food storage and hygiene, people ran a daily risk of

acquiring a not inconsiderable part of their daily fat and protein intake from the consumption of insect and mite pests of stored products. There is anecdotal evidence that stored products mites were more common in urban homes than they are today (Chapter 4), so probably the spectrum of allergen exposure was more diverse. In the 19th century, airborne particles in cities would have included quite a lot of horse dung, together with its bacterial endotoxins (see Figure 4.17). Insect and mite contaminants of food were a fact of life in Westernised countries until the implementation of food standards and packaging around the 1950s. In many parts of the world where cereals, pulses, dried fish and meat are sold loose, they still are. The regular ingestion by a sizeable proportion of the human population of insects, mites and their frass would represent a marked difference both in route of exposure and allergen spectrum, especially bearing in mind that oral administration of allergen can induce immune tolerance. If people used not to get asthma so much in the past because their immune system was steered towards Th1 responses by increased prevalence of childhood infections, then maybe also there was less asthma around because people naturally desensitised themselves as they ate.

There have been major changes in housing design in the last 40 years. The building of energy-efficient homes (predominantly a phenomenon of developed countries with temperate climates in the Northern Hemisphere), which are insulated, double-glazed, centrally heated, and with low ventilation, was triggered partly by the oil crisis of the 1970s and the need to conserve heating fuel. Fitted carpets have become the standard floor covering in many homes, whereas before the 1960s, linoleum, polished floorboards and rugs were standard. These changes in housing design have resulted in warmer, moister homes and it has been claimed that the more favourable domestic microclimate encouraged the development of large populations of dust mites. This, in turn, has led to a boom in dust mite allergen exposure which has been cited as a possible reason for the recent increase in asthma prevalence. So goes the story. But the data on housing risk factors (see 8.6 above) does not support it. Apparently, people spend more time indoors on average than they did 40 years ago. According to Platts-Mills *et al.* (1996) human behavioural factors that may contribute to the increase in the prevalence and severity of asthma include poor standards of domestic cleanliness, passive smoking, lack of exercise and obesity. People spend more time in front of the television or computer, less time exercising outdoors or engaged in manual toil; they eat more processed food containing more saturated fat, and less antioxidant-containing fresh fruit and vegetables; and have less contact with soil and less exposure to beneficial bacteria.

These lifestyle changes are linked in part to increasing affluence. Increased prevalence of asthma and atopy has been associated with higher gross national product per capita (Stewart *et al.,* 2001) and with lower intake of cereals, nuts, vegetables and plant starches (Ellwood *et al.,* 2001). But in urban societies it is people on low incomes who tend to eat worst, exercise least and have the highest rates of morbidity and mortality (Syme, 1986). Exposure to a so-called 'modern' or 'Western' lifestyle is frequently invoked as a factor that explains increases in asthma prevalence and is linked to increasing urbanisation (Figure 8.22) and rural depopulation and dietary shifts associated with urban living in developing countries (Weinberg, 1999; Hooper *et al.,* 2008), and to higher social class and income in developed ones (Heinrich *et al.,* 1998). Asthma is of higher prevalence in Westernised countries, but developing countries may have a higher burden of asthma morbidity because they contain a much higher proportion of world population.

There is now widespread acceptance that the temperature of the planet is increasing and that climate change is taking place as a result of anthropogenic greenhouse gas emissions. A great deal of research effort has been devoted to predicting the biological effects of global climate change, focusing on the effects on ecosystem diversity, pests of crops and arthropod vectors of diseases of humans and domesticated animals. The issue is that warming does not automatically equate to higher population densities of mites. On balance, it is too early to say what will happen with dust mite populations, though increased prevalence of asthma has been linked to climate change (Beggs and Bambrick, 2005). In Chapter 4 we saw that the best predictor of abundance of dust mites at the regional scale was the estimated daily rate of evaporation, a site-specific function of temperature, rainfall, elevation and latitude. In most climate change models, predictions of changes in evaporation are much less certain than predictions of changes in temperature. Global average precipitation projections show increases with time as the hydrological cycle is enhanced by global warming, with higher latitudes having increased precipitation, the tropics having least

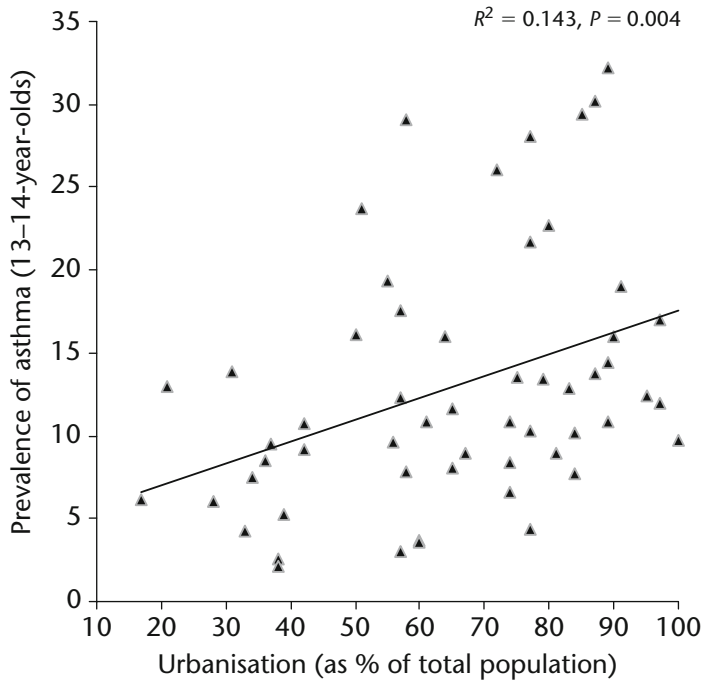

Figure 8.22 The relationship between prevalence of asthma among 13–14-year-old adolescents and urbanisation in 56 countries. Asthma prevalence data from ISAAC Steering Committee (1998), urbanisation from country population data, World Bank Group (http://www.worldbank.org/data/countrydata/countrydata.html).

and the subtropics showing little or no change (Johns *et al.,* 2003). Some regions are predicted to get markedly dryer with reduced average summer rainfall by 2080, including most of Europe (Buonomo *et al.,* 2005), though certain areas (the central and eastern Mediterranean, central Spain, central and eastern Continental Europe and southern Scandinavia) are predicted, paradoxically, to receive a higher frequency of heavy rainfall events despite strong summer drying.

In conclusion, mites are important in asthma and allergies but they are only part of the story. Diet and certain foods, exposure to microorganisms and other allergens, urbanisation, changes in social and economic status and lifestyle all seem to have a role in relation to the prevalence of allergies and allergic diseases. All of this makes mites seem like a smaller part of a much bigger picture than at the time of the First International Workshop on mites and asthma in 1987. This is probably a good thing, for there is no reason to believe that interactions between the environment and human disease should be characterised by simple, linear phenomena governed by only a few factors. Mites need to be seen within the appropriate context of a bigger, more complex set of interacting determinants than we ever imagined 20 years ago.