

Allergens and Allergic Diseases in Children

KUO-WEI YEH

The prevalence of allergic diseases is increasing gradually. Exposure to allergens is one of the trigger factors for symptoms in sensitized individuals. House dust mites and cockroach are the two most common indoor aeroallergens in Taiwan. There are wide differences in the numbers in different locations and in different seasons of these allergens. Sensitization to food allergens is prominent in young infants and can predict further aeroallergen sensitization. However, whether early exposure to allergens might develop or prevent allergic diseases in later childhood requires further research. Up to the present, allergen avoidance has demonstrated no prominent clinical efficacy in the improvement of allergic symptoms, although it is able to reduce allergen load in the environment. In a clinical regard, allergen avoidance should still be included as a part of treatment plans and be well explained to patients. (Acta Paediatr Tw 2006; 47:169-74)

Key words: allergen, atopy, allergic disease

People are usually exposed to foreign substances in various settings. These substances, which stimulate the production of immunoglobulin E (IgE) in a genetically disposed individual, are called allergens. Allergens are soluble proteins or glycoprotein of a molecular weight of 10 to 50 kDa. Up to the present, the allergen nomenclature has been maintained by the Allergen Nomenclature Committee of the International Union of Immunological Societies (IUIS). Allergens are designated by the first three letters of the genus, followed by a space, then the first letter of species, followed by another space, trailed by an Arabic numeral. The Arabic number represents the order the allergen has been isolated or the clinical importance. For example, *Der p 1* and *Der f 1* are the allergens of *Dermatophagoides pteronyssinus* (*Der p*) and *Dermatophagoides farinae* (*Der f*), respectively, and are important allergens causing allergic symptoms.

Asthma, allergic rhinitis, and atopic dermatitis are very common allergic diseases among children. The prevalence of allergic diseases is increasing gradually throughout the world. Although there have been reports that it might reach a plateau in western countries,^{1,2} the increasing prevalence of asthma and allergic rhinitis is still prominent in Taiwan.³⁻⁵ Allergy is a hypersensitivity reaction to a specific allergen initiated by immunological

mechanisms, although there are some nonimmunological factors triggering allergic symptoms. Despite the facts that allergens might be one of the risk factors for the development of allergic disorders and allergen avoidance can reduce the allergen load, whether clinical symptoms improve by this approach is still debated.

ALLERGENS AND THE INDOOR ENVIRONMENT

In different phenotypes of allergic disorders, house dust mites play a major role in triggering not only airway diseases but also skin manifestations. Dust mites, living on human dander, are ubiquitous in the home, and cannot be seen via the naked eye. They are around 0.3 mm in length. One person produces 0.5-1.0 grams of dander each day; however, thousands of mites can live on only 250mg of human dander for months. Airborne mite allergens with particle sizes = 10 μ m can be detected only when the indoor environment is disturbed, and they fall on ground rapidly after disturbance. Unlike commercial advertisements, air filtration devices or ionizers cannot reduce the mite levels indoors, because most of the time mites are on the floor or on mattresses instead of being distributed throughout the air. However, allergens from pets are carried both

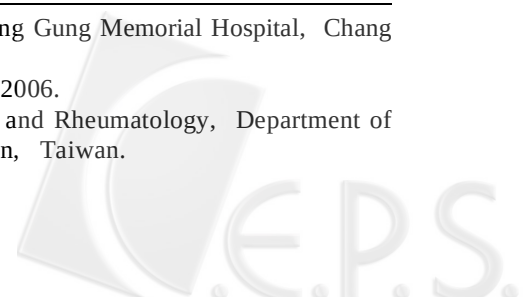
Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chang Gung Memorial Hospital, Chang Gung Children's Hospital, and Chang Gung University, Taoyuan, Taiwan.

Received: July 30, 2006. Revised: August 20, 2006. Accepted: August 31, 2006.

Address reprint requests to: Dr. Kuo-Wei YEH, Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chang Gung Children's Hospital, No. 5, Fu-Hsin Street, Taoyuan, Taiwan.

TEL : 886-3-3281200 ext. 8969

FAX : 886-3-3274843



by large particles ($= 10\mu\text{m}$) and by small particles ($< 5\mu\text{m}$).⁶ The small particles still remain in the air after environmental disturbance. In this regard, air filtration devices are useful in cleaning up pet allergens as well as passive smoke. The most efficient filter is HEPA (High Efficiency Particulate Air), where 99.97% of particles of $0.3\mu\text{m}$ in size can be removed from the air.

The indoor humidity level is associated with the growth of mites and their number in house. House dust mites do not proliferate at 45% relative humidity at 20–23°C.⁷ In a temperate climate, it is practical to maintain an indoor relative humidity of less than 51% during the humid summer season, and this results in significant reductions in mite and allergen levels.⁸ In a case control study in Kaohsiung, of the many indoor environmental factors included in this study, only home dampness demonstrated an association with asthma (adjusted odds ratio=1.77–2.65).^{9,10} Yang, *et al* demonstrated that indoor dampness may not only lead to the development of asthma or other respiratory diseases, but may exacerbate the symptoms.¹¹ The relationship between dampness and asthma exacerbation or disease development might be associated with dust mites. For control of dust mite exposure, it is reasonable to reduce indoor dampness and humidity by dehumidifiers instead of air cleaners as mentioned above. The control of indoor humidity to under 45% is an important measure in reducing the amount of dust mites and their growth. In humid climatic regions like Taiwan, using air conditioning and dehumidifiers to maintain indoor relative humidity around 50%, leading to the suggestion of controlling dampness in order to reduce mite growth.

In clinical practice, it is commonly suggested to wash sheets, duvets or clothes in warm water to remove mite allergens. It takes at least 55 °C to kill 80% of mites, although it requires 120–140°C to denature the mite allergens.¹² However, this practice is not practical in Taiwan because there are few temperature adjustable washing machines in the home, and it is inconvenient to otherwise prepare hot water for washing clothes in daily life. Direct sun exposure of bedding can kill mites,¹³ although this is also not convenient in the urban lifestyle in Taiwan. The mite numbers in duvets reduce significantly from 410/m³ to 6/m³ after hot tumble drying for 1 hour, but neither *Der p 1* concentrations in duvet dust samples nor total dust weights are significantly altered by tumble drying.¹⁴ Tumble dryers can be possibly an alternative choice of mite control, although more evidence through continued research is still required. Encasings with impermeable covers on bedding material, such as mattresses, is an alternative choice in avoiding allergen exposure. Mahakittikun, *et al* demonstrated that only encasings with a pore size of 2–10 μm with tightly woven microfiber covers can prevent the passage of mites,

still having a good level of comfort and air permeability.

¹⁵ Recent studies and meta-analyses have confirmed that encasements might be an effective method in avoiding allergen contact, although the clinical effect on patients has not proven promising.^{16,17}

ALLERGEN SENSITIZATION AND ITS EVOLUTION WITH AGE IN TAIWAN

Although mites are the major allergen worldwide, there are wide differences in the numbers in different locations and in different seasons. Mites are also one of the most common allergens in Taiwan. In general, 79.3% to 82.5% of asthmatic children are sensitive to mites^{18,19}, however, up to 97.6% of atopic children are sensitive who have had all clinical presentations of asthma, allergic rhinitis and atopic dermatitis.¹⁹ Most patients are sensitive to different species of mites at the same time instead of a single mite allergen (2.4% only for *Der p*, and 2.9% only for *Der f*). The mean number of mites is greater in August through November and lowest in July.²⁰ In terms of different parts in Taiwan, the incidence of sensitization of *Der p*, *Der f*, cockroach, feather, shrimp, crab, and peanut are higher in atopic subjects at an age of 18 years in northern Taiwan, also with significant differences when compared to age-matched subjects in southern Taiwan.²¹ However, the sensitization rate to *Der p* is much lower in Kin-Men, an off-shore island, than in Taipei (25.7% vs. 90.6%). Ragweed pollen is a much more important allergen in Kin-Men.²² Sensitization to *Der f* and *Der p* presents no difference between children (below 16 years old) and adults in Taiwan (from 57.4% to 63.6%).²³ The duration of development of IgE-mediated sensitivity depends on the interaction of the host immune status and allergen amount. It takes several months to years to be sensitized after exposure to mites. It is expected that young children have a lower percentage of mite sensitivity. In a previous study in southern Taiwan, in children at an age below 3, 44% of them were sensitive to mites, although the rate rose up to 90% after an age of 3 years old.²¹ Hypersensitivity to egg white or milk during infancy are also usually high responders to inhalants during childhood. Therefore, it is usually suggested to check aeroallergens beyond 3 years of age, clinically in terms of evolution of sensitization. Previous studies in Taiwan have shown that mite allergies occur more frequently (96.8%) in patients with an age of 11 to 20 years.²⁴ Among food allergens, milk and egg white have been demonstrated to be more frequently found in patients below 10 years old.^{24,25} Another investigation also showed that crab, milk and egg white are prominent food allergens in those 2 to 6 years old in Taiwan.²⁶ In an

investigation in young children below the age of 3 in Singapore, the prevalence of sensitization was highest for cow's milk (45.9%), followed by egg white (38.7%), dust mites *Der p* (31.4%) and *Blomia tropicalis* (*Blo t*) (25.5%). This study also produced a similar trend where sensitization to ingested allergens was significantly more prevalent in children aged 1 year or younger than in older children (70.4% of those below 1 year, and 50% of those aged 1-3 years; $p < 0.02$). The prevalence of sensitization to food allergens is higher compared to inhalant allergens in young children in Singapore.²⁷ According to the above investigations, specific IgE antibodies against milk and egg are most frequent during the first 2 years of life, whereas IgE against inhalant allergens is predominant later in childhood. Clinical sensitization to egg white and milk and subsequent tolerance appeared early in childhood, whereas allergy to inhalants appeared later and did not disappear.²⁸ IgE antibodies to allergens of egg white or milk in infants can predict sensitization to inhalant allergens before 7 years of life. A positive reaction to specific IgE antibody against egg white in infants at 6 months of age can prove to be significant predictors of future positive reactions to mite IgE during the first 5 years of life. The positive and negative predictive values were both 85%.^{29,30} Besides early sensitization to food, it has also been emphasized that family history is also an important factor in the prediction of later aero-sensitization in childhood.^{31,32} In clinical practice, in young children below 3 years old at high risk of atopy, it has been suggested that checking for food allergens first is a good practice. If sensitization to food is expressed in young infants, prevention of aeroallergen exposure should also be suggested as early as possible.

In addition to *Der p* and *Der f*, *Blo t* is also an important mite species in the tropical and sub-tropical regions of the world. *Blo t* 5 is a major allergen with up to a 70% sensitization rate in *Blo t* allergic populations, such as in Brazil, Hong Kong, Singapore and even Taiwan.³³⁻³⁵ It accounts for 44.3% of the total number of mites in house dust samples. It has around a 73% positive rate among asthma patients in Taiwan among different studies.^{18,36} Concomitant sensitizations to *Blo t* and *Der. p* occurs in 63.3% of asthmatic patients in our country.³⁶ *Dermatophagoides microcera* (*Der m*) is another allergen seldom reported. In Taiwan, its prevalence of sensitization was 79.5% in children, and concomitant sensitization to *Der p* and *Der f* was 84.5% and 87.5% respectively.³⁷

Cockroach is the second most common aeroallergen in Taiwan. Among atopic patients, 57.5% of patients with asthma and 50.7% of patients with allergic rhinitis are sensitive to cockroach extracts.³⁸ They may constitute a risk factor for asthma attacks, resulting in

hospitalization.³⁹ Its debris or excretions after death can evaporate into the air and cause allergic symptoms after inhalation. This airborne allergen also becomes significant after 3 years of age. There is no difference in this allergen between adult and children groups (17.6% vs. 18.2%).²³ Gold *et al* followed up a cohort of 499 children with asthmatic or allergic parents. *Blag 1* or 2 (cockroach) allergen levels in the family room was a significant predictor of having two or more wheezing episodes in the first year of life.⁴⁰ Children with asthma also had significantly lower pulmonary function, as they were sensitized to cockroach.⁴¹

ALLERGEN SENSITIZATION AND AVOIDANCE ON DEVELOPMENT OF ALLERGIC DISEASES

Allergic diseases are associated with gene and environmental interaction. The development of different phenotypes may manifest at different stages of childhood. Whether early exposure to allergens develops different phenotypes of atopic disorders is controversial. According to the Tucson Children Respiratory Study, a longitudinal cohort of 1246 children, made up of 18% children, had persistent wheezing at an age of 6, who also had eczema before the age of 2. Eczema may be the first clinical presentation of the allergic march.⁴² A cohort study involving 1314 children born in Germany (German Multicentre Atopy Study, MAS) did not find any relationship between allergen sensitization and wheezing during the first 2 years of life, and even during the development of asthma at 7 years of age.⁴³ In a study in the United Kingdom, only 29% of children with persistent wheezing at 4 years old were found sensitive to at least one common aeroallergen.⁴⁴ In a cohort study, exposure to 2 µg/g of dust mites was the threshold for sensitization of allergic children, although it was even higher than 20 µg/g for the threshold of non-allergic children.⁴⁵ However, other reports suggest that the threshold of mite concentration inducing airway hyper-responsiveness in highly susceptible children is 10-100 times lower than 2 µg/g.⁴⁶ In a cohort of British children at risk for allergic disease because of family history, there was a trend toward an increasing degree of sensitization at the age of 11 with greater exposure of more than 10 µg/g of dust during infancy.⁴⁷ A study for the relationship between early exposure to allergens and atopic diseases in later life in Taiwan revealed that exposure to a mite allergen concentration of 1 µg/g of dust may be associated with a higher incidence of AD ($p=0.0156$); the presence of *Der p 1* IgE antibody at 18 months of age was associated with a higher incidence of asthma ($p=0.0001$); and children sensitized to egg whites at 18 months of age have an increased risk of

developing atopic dermatitis at 3 years of age ($p=0.0187$).⁴⁸

Many controlled studies have demonstrated that the reduction of house dust mite exposure reduces clinical symptoms of asthma,^{49,50} although other meta-analyses of published data or clinical trials have not demonstrated the benefits to asthmatic patients.^{51,52} The procedure of environmental allergen control can reduce allergen load in daily surroundings, although whether it has benefits in clinical outcomes of patients needs further research.

In addition to newly developed treatments for controlling allergic diseases, hopefully, physicians or scientists can find better intervention strategies in delaying the allergic march. Several clinical trials suggest reducing exposure to house dust mites during infancy to prevent the development of asthma in later childhood. In reducing mite exposure in infants with atopic dermatitis who are sensitized to egg white and milk but not mites, such children have shown lower increases of IgE to mites compared with a control group after 1 year of intervention.⁵³ Different studies have contradictory explanations depending on the exposure dose of allergens, the timing of exposure, the characteristics of allergens and host susceptibility. It has to be prudent to apply the results into clinical practice. The effect of environmental factors on the development of allergic sensitization and asthma is still controversial.⁵⁴

A critical variable in the evaluation of the relationships between allergens and allergic symptoms is the age at the assessment of the studies. The intervention and outcomes evaluated vary among these trials. However, it appears that only concentration on the avoidance of house dust mites cannot produce benefits in the onset of asthma or allergic diseases in later childhood, though this intervention has proven useful in reducing the mite amount around the household in several cohort studies.⁵⁵⁻⁵⁹

There is evidence that environmental interventions are able to reduce allergen load, although susceptible hosts exposed to allergens would experience exacerbated allergic symptoms. However, it is hard to draw a conclusion that allergen avoidance can definitely impede the development of allergic diseases or improve clinical outcomes in susceptible atopic patients.

CONCLUSION

Allergic diseases are common in children. Except for asthma and rare occasions of anaphylaxis, most allergic diseases are not life-threatening. However, they can influence patients' quality of life for a long time. Several devices or formulations declare their preventive or therapeutic effect on allergic diseases, although they

require further scientific research and evidence, instead of commercial advertisement, to support their efficacy. Being a doctor or a member of a medical staff, it is prudent to interpret any updated information on allergic disease. It is also an obligation and responsibility to deliver accurate and scientific-based (not quasi-scientific) information to patients.

REFERENCES

1. von HL, Haahtela T. Signs of reversing trends in prevalence of asthma. *Allergy* 2005; **60**:283-92.
2. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**:733-43.
3. Yan DC, Ou LS, Tsai TL, Wu WF, Huang JL. Prevalence and severity of symptoms of asthma, rhinitis, and eczema in 13- to 14-year-old children in Taipei, Taiwan. *Ann Allergy Asthma Immunol* 2005; **95**:579-85.
4. Liao MF, Huang JL, Chiang LC, Wang FY, Chen CY. Prevalence of asthma, rhinitis, and eczema from ISAAC survey of schoolchildren in Central Taiwan. *J Asthma* 2005; **42**:833-7.
5. Kao CC, Huang JL, Ou LS, See LC. The prevalence, severity and seasonal variations of asthma, rhinitis and eczema in Taiwanese schoolchildren. *Pediatr Allergy Immunol* 2005; **16**:408-15.
6. Custovic A, Simpson A, Pahdi H, Green, RM, Chapman, MD, Woodcock A. Distribution, aerodynamic characteristics, and removal of the major cat allergen Fel d 1 in British homes. *Thorax* 1998; **53**:33-8.
7. Munir AK, Björkstén B, Einarsson R, et al. Mite allergens in relation to home conditions and sensitization of asthmatic children from three climatic regions. *Allergy* 1995; **50**:55-64.
8. Arlian LG, Neal JS, Morgan MS, Vyszenski-Moher DL, Rapp CM, Alexander AK. Reducing relative humidity is a practical way to control dust mites and their allergens in homes in temperate climates. *J Allergy Clin Immunol* 2001; **107**:99-104.
9. Yang CY, Tien YC, Hsieh HJ, Kao WY, Lin MC. Indoor environmental risk factors and childhood asthma: a case-control study in a subtropical area. *Pediatr Pulmonol* 1998; **26**:120-4.
10. Yang CY, Lin MC, Hwang KC. Childhood asthma and the indoor environment in a subtropical area. *Chest* 1998; **114**:393-7.
11. Yang CY, Chiu JF, Chiu HF, Kao WY. Damp housing conditions and respiratory symptoms in primary school children. *Pediatr Pulmonol* 1997; **24**:73-7.
12. Cain G, Elderfield AJ, Green R, et al. The effect of dry heat on mite, cat, and dog allergens. *Allergy* 1998; **53**:1213-5.
13. Tovey ER, Woolcock AJ. Direct exposure of carpets to sunlight can kill all mites. *J Allergy Clin Immunol* 1994; **93**:1072-4.
14. Mason K, Riley G, Siebers R, Crane J, Fitzharris P. Hot tumble drying and mite survival in duvets. *J Allergy Clin Immunol* 1999; **104**:499-500.
15. Mahakittikun V, Komoltri C, Nochot H, Angus AC, Chew FT. Laboratory assessment of the efficiency of encasing materials against house dust mites and their allergens.

- Allergy 2003; **58**:981-5.
16. Recer GM. A review of the effects of impermeable bedding encasements on dust-mite allergen exposure and bronchial hyper-responsiveness in dust-mite-sensitized patients. *Clin Exp Allergy* 2004; **34**:268-75.
 17. Woodcock A, Forster L, Matthews E, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003; **349**: 225-36.
 18. Chou TY, Wu KY, Shieh CC, Wang JY. The clinical efficacy of in vitro allergen-specific IgE antibody test in the diagnosis of allergic children with asthma. *Acta Paediatr Taiwan* 2002; **43**:35-9.
 19. Lo SF, Chiang BL, Hsieh KH. Analysis of total IgE and allergen-specific IgE antibody levels of allergic children in Taiwan. *Acta Paediatr Taiwan* 1997; **38**:375-80.
 20. Chang YC, Hsieh KH. The study of house dust mites in Taiwan. *Ann Allergy* 1989; **62**:101-6.
 21. Chiang W, Tsai IF, Tsai WC, Chen BH. Effect of age on allergen responses of allergic patients in southern Taiwan. *Kaohsiung J Med Sci* 2004; **20**:323-9.
 22. Tsai JJ, Kao MH, Huang SL. Comparison of major aeroallergens in Taipei and Kin-Men. *J Formos Med Assoc* 1997; **96**:985-9.
 23. Hsu CL, Chiang BL, Kuo SH. Specific allergen tests in asthmatic patients: a comparison between adults and children. *Thorac Med* 2004; **19**:82-91.
 24. Tsai JJ, Chen WC. Different age of asthmatic patients affected by different aeroallergens. *J Microbiol Immunol Infect* 1999; **32**:283-8.
 25. Tsai JJ, Chen WC. Relation of different food allergens to different age of asthmatic patients. *J Microbiol Immunol Infect* 1999; **32**:47-51.
 26. Lee CS, Tang RB, Chung RL. The evaluation of allergens and allergic diseases in children. *J Microbiol Immunol Infect* 2000; **33**:227-32.
 27. Khoo J, Shek L, Khor ES, Wang DY, Lee BW. Pattern of sensitization to common environmental allergens amongst atopic Singapore children in the first 3 years of life. *Asian Pac J Allergy Immunol* 2001; **19**:225-229.
 28. Hattevig G, Kjellman B, Bjorksten B. Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children. *Pediatr Allergy Immunol* 1993; **14**:182-6.
 29. Nickel R, Kulig M, Forster J et al. Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997; **99**: 613-7.
 30. Sasai K, Furukawa S, Muto T, Baba M, Yabuta K, Fukuwatari Y. Early detection of specific IgE antibody against house dust mite in children at risk of allergic disease. *J Pediatr* 1996; **128**:834-40.
 31. Kulig M, Bergmann R, Niggemann B, Burow G, Wahn U. Prediction of sensitization to inhalant allergens in childhood: evaluating family history, atopic dermatitis and sensitization to food allergens. The MAS Study Group. Multicentre Allergy Study. *Clin Exp Allergy* 1998; **28**:1397-403.
 32. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999; **103**:1173-9.
 33. Baqueiro T, Carvalho FM, Rios CF, dos Santos NM, cantara-Neves NM, Medical Student Group. Dust mite species and allergen concentrations in beds of individuals belonging to different urban socioeconomic groups in Brazil. *J Asthma* 2006; **43**:101-5.
 34. Yi FC, Lee BW, Cheong N, Chua KY. Quantification of Blo t 5 in mite and dust extracts by two-site ELISA. *Allergy* 2005; **60**:108-12.
 35. Sun BQ, Wu A, Chan A, Chik S, Wong D, Zhong NS. House dust mite allergen (Derp1 and Blo t5) levels in asthmatics' home in Hongkong. *Chin Med Sci J* 2004; **19**:185-8.
 36. Tsai JJ, Wu HH, Shen HD, Hsu EL, Wang SR. Sensitization to *Blomia tropicalis* among asthmatic patients in Taiwan. *Int Arch Allergy Immunol* 1998; **115**:144-9.
 37. Huang HW, Lue KH, Wong RH, Sun HL, Sheu JN, Lu KH. Distribution of allergens in children with different atopic disorders in central Taiwan. *Acta Paediatr Tw* 2006; **47**:127-34.
 38. Lan JL, Lee DT, Wu CH, Chang CP, Yeh CL. Cockroach hypersensitivity: preliminary study of allergic cockroach asthma in Taiwan. *J Allergy Clin Immunol* 1988; **82**: 736-40.
 39. Gelber LE, Seltzer LH, Bouzoukis JK, Pollart SM, Chapman MD, Platts-Mills TA. Sensitization and exposure to indoor allergens as risk factors for asthma among patients presenting to hospital. *Am Rev Respir Dis* 1993; **147**:573-8.
 40. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills TA, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. *Am J Respir Crit Care Med* 1999; **160**:227-36.
 41. Lin YC, Su HJ, Hsiue TR, Lee CH, Chen CW, Guo YL. Levels of house dust mite-specific IgE and cockroach-specific IgE and their association with lower pulmonary function in Taiwanese children. *Chest* 2002; **121**:347-53.
 42. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; **332**:133-8.
 43. Lau S, Illi S, Sommerfeld C et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000; **356**:1392-7.
 44. Tariq SM, Matthews SM, Hakim EA, Steven M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998; **101**:587-93.
 45. Kuehr J, Frischer T, Meinert R, et al. Mite allergen exposure is a risk for the incidence of specific sensitization. *J J Allergy Clin Immunol* 1994; **94**:44-52.
 46. Dreborg S. Mite allergens. Collection, determination, expression of results, and risk levels for sensitization and symptom induction. *Allergy* 1998; **53**(48 Suppl):88-91.
 47. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (*Der p 1*) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990; **323**:502-7.
 48. Huang JL, Chen CC, Kuo ML, Hsieh KH. Exposure to a high concentration of mite allergen in early infancy is a risk factor for developing atopic dermatitis: a 3-year follow-up study. *Pediatr Allergy Immunol* 2001; **12**:11-6.
 49. van der HS, Kauffman HF, Dubois AE, de Monchy JG. Allergen-avoidance measures in homes of house-dust-mite-allergic asthmatic patients: effects of acaricides and mattress encasings. *Allergy* 1997; **52**:921-7.
 50. Carswell F, Birmingham K, Oliver J, Crewes A, Weeks J. The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children—a double-blind controlled trial. *Clin Exp Allergy* 1996; **26**:386-96.
 51. Gotzsche PC, Johansen HK, Schmidt LM, Burr ML. House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2004; **4**:CD001187.

52. Woodcock A, Forster L, Matthews E, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003; **349** (3):225-36.
53. Nishioka K, Yasueda H, Saito H. Preventive effect of bedding encasement with microfine fibers on mite sensitization. *J Allergy Clin Immunol* 1998; **101**:28-32.
54. Wickman M, Melen E, Berglund N, et al. Strategies for preventing wheezing and asthma in small children. *Allergy* 2003; **58**:742-7.
55. Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005; **116**:49-55.
56. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003; **58**:489-93.
57. Woodcock A, Lowe LA, Murray CS, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004; **170**:433-9.
58. Horak F, Jr., Matthews S, Ihorst G, et al. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational **randomized, controlled birth-cohort study**—24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004; **34**:1220-5.
59. Koopman LP, van Strien RT, Kerkhof M, et al. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med* 2002; **166**:307-13.

