

Spider-mite allergy and asthma in fruit growers

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Asthma and allergic diseases caused by domestic mites such as house dust mites and storage mites are major health problems worldwide. In contrast to domestic mites, spider mites are outdoor phytophagous mites causing significant damage to fruit leaves throughout the world. After several case reports of spider mite-induced asthma and allergy, cross-sectional surveys have demonstrated that spider mites are important allergens in the development of asthma and rhinitis in fruit farmers.

Interestingly, epidemiological surveys have also demonstrated that spider mites are common sensitizing allergens that are related to the prevalence of asthma and rhinitis, even in the non-farming population exposed to spider mites. Protein analysis has demonstrated that crude extracts derived from spider mites contain several major allergens, and that N-terminal amino acid sequencing of the major allergens is not homologous with any previously characterized domestic mite allergens, suggesting that major allergens derived from spider mites are unique in terms of cross-reactivity to domestic mites. Taken together, these findings suggest that spider mites are important allergens in the development of asthma among the exposed non-farming population as well as among fruit farmers themselves, and that allergens derived from spider mites may be novel allergens. *Curr Opin Allergy Clin Immunol* 2:103–107. © 2002 Lippincott Williams & Wilkins.

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Abbreviation

HLA human leukocyte antigen

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Introduction

Many agents in the working environment can cause asthma, and in 1980, their total number was reported to exceed 200 [1]. With the introduction of new materials into working environments and increased awareness on the part of physicians, the list continues to grow over time. The phylum Arthropoda is divided into three main classes, Insecta, Arachnida, and Crustacea, and approximately 30% of individuals who are exposed become sensitized to them. Domestic mites such as house dust mites and storage mites, which are included in the class Arachnida, are the most important allergens in the development of asthma and allergic diseases worldwide [2,3]. In contrast to domestic mites, which belong to the suborder Astigmata, spider mites (family *Tetranychidae*) are outdoor phytophagous mites that damage fruit leaves throughout the world, and belong to the suborder Prostigmata of the order Acari [4] (Table 1). Spider mites rapidly develop injurious populations in early spring, damaging fruit leaves and in some cases causing defoliation. Most spider mites feed to a depth of approximately 100 μm , and completely remove cell contents so that no oxidized cytoplasm can develop. One generation of spider mites requires approximately 2 weeks at optimum spring temperatures of between 30°C maximum and 19°C minimum, which allows approximately 10–12 generations per year [4]. Although predaceous mites attack spider mites, the predator complex most common in the world does not usually control spider mites, particularly when spray programmes of organic phosphates or sulphur upset natural control [5,6]. In fact, although spider mites were negligible pests in fruit cultivation before World War II, the number of these mites has increased in the fruit cultivation industry since pesticides were introduced to eliminate fruit insects [7]. Surveys have demonstrated [8–10] that the European red mite (*Panonychus ulmi*) and the two-spotted spider mite (*Tetranychus urticae*) are the most common pests in apple farms, *T. urticae* is the most common in pear farms, green houses and herbaceous plants, and, as shown in Fig. 1, the citrus red mite (*Panonychus citri*) is most common in citrus farms.

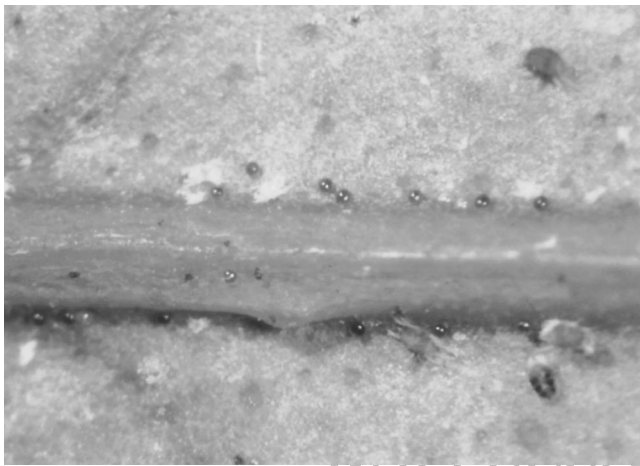
Reunala *et al.* [11] first described allergic reactions to *T. urticae* in two patients suffering from rhinitis, conjunctivitis and contact urticaria, who worked in a greenhouse. Subsequently, Delgado *et al.* [12] described a case of *T. urticae*-induced occupational asthma and rhinoconjunctivitis confirmed by specific bronchial challenge. Meanwhile, Kroidl *et al.* [13] first described six patients with *P.*

Table 1. Family relationship between spider mites and domestic mites

Order	Suborder	Family	Genus	Species
Acari	Astigmata	Pyroglyphidae	<i>Dermatophagoides</i>	<i>D. pteronyssinus</i> <i>D. farinae</i>
			<i>Euroglyphus</i>	<i>E. maynei</i>
		Glycyphagidae	<i>Glycyphagus</i>	<i>G. domesticus</i>
			<i>Lepidoglyphus</i>	<i>L. destructor</i>
			<i>Blomia</i>	<i>B. tropicalis</i>
		Acaridae	<i>Acarus</i>	<i>A. siro</i>
			<i>Tyrophagus</i>	<i>T. putrescentiae</i>
	Prostigmata	Tetranychidae (spider mites)	<i>Tetranychus</i>	<i>T. urticae</i>
			<i>Panonychus</i>	<i>P. ulmi</i>
				<i>P. citri</i>

Previously published by Kim et al. [16].

Figure 1. Citrus red mites on citrus leaf (original)



Prevalence of spider-mite allergy in fruit farmers

From our own cross-sectional survey in 181 citrus farmers in Korea [15], the most common sensitizing allergen was *P. citri* (16.5%), followed by cockroach (11.0%), *Dermatophagoides pteronyssinus* (9.9%), and *Dermatophagoides farinae* (9.3%), whereas 9% of the citrus farmers revealed a positive skin response only to *P. citri*. Of the 181 farmers, 22 (12.1%) were diagnosed as asthmatic on the basis of the results of a questionnaire investigating asthma symptoms and on bronchial hyperresponsiveness to methacholine (Table 2). Of these 22 asthmatic individuals, 12 (54.5%) yielded a positive skin response to *P. citri*, and 11 (50%) were *P. citri*-sensitive asthmatic individuals whose asthmatic symptoms had initially developed after work and had been aggravated in the workplace. The sensitization to *P. citri* was also significantly related to the prevalence of rhinitis. These results confirm that *P. citri* is the most important allergen in the development of asthma and rhinitis in citrus farmers.

ulmi-induced occupational asthma among the inhabitants of a fruit-growing area. After these case reports, the first case of *P. citri*-induced occupational asthma was confirmed by specific bronchial challenge, and the clinical characteristics of some 16 patients were described [14]. The asthmatic symptoms in patients with *P. citri* occupational asthma were found to be aggravated in late spring and autumn, when populations of *P. citri* increased, and the asthmatic severity of more than half of the asthmatic patients was confirmed to be severe. The latent period from initial exposure to the onset of asthma symptoms was more than 10 years, a period longer than in those with asthma caused by other occupational agents, especially low molecular weight chemical agents.

This review aimed to determine the prevalence of spider mite-induced allergy and asthma in fruit farmers and the non-farming population, to assess the risk factors for the development of spider-mite allergy, and evaluate the characteristics of allergens derived from spider mites.

Another cross-sectional study [16] demonstrated that *P. ulmi* and *T. urticae*, the most common apple leaf mites, were the most common sensitizing allergens in 725 apple farmers, of whom more than 5% had an isolated skin response to the spider mites. That survey also revealed that the incidence of work-related asthma and rhinitis symptoms was higher in farmers with positive skin responses to spider mites than in those with negative responses. The two epidemiological surveys suggested that spider mites, especially *P. citri*, *P. ulmi* and *T. urticae*, are important causative allergens in the development of occupational asthma among fruit farmers.

Prevalence of spider-mite allergy among the non-farming population

Recent investigations have demonstrated that spider mites are important allergens for the development of asthma and rhinitis in non-farming populations. Jee et al. [17] described the clinical significance of *T. urticae*-derived allergens in asthmatic non-farmers living around pear farms. One-third of these asthmatic individuals

Table 2. Prevalence of citrus red mite-induced asthma and allergic rhinitis in citrus farmers

	Asthma (n = 22)	Allergic rhinitis (n = 35)	Total (n = 181)
Age, mean (range), years	52.2 (29–70)	45.6 (18–77)	50.1 (18–87)
Sex (male/female)	12/10	19/16	78/103
Occupational history, mean (range), years	23.8 (9–40)	22.2 (9–40)	23.7 (5–40)
Skin prick test ^a	59.0%	100%	25.9%
<i>D. pteronyssinus</i>	27.2%	40%	9.9%
<i>D. farinae</i>	22.7%	34.2%	9.3%
Tree pollen	0%	0%	0%
Grass pollen	0%	2.8%	1.1%
Ragweed	0%	2.8%	1.1%
Mugwort	9%	8.5%	3.3%
<i>Alternaria</i> spp.	4.5%	2.8%	1.1%
Animal epithelium	0%	0%	0%
Cockroach	18.1%	34.2%	11.0%
<i>P. citri</i>	54.5%	68.5%	16.5%
<i>P. citri</i> -sensitive asthma ^b	50%	28.6%	6%

^aWheal formed by one or more allergenes $\geq$ wheal formed by histamine (1 mg/ml).

^bAsthmatic subjects with positive skin responses to *P. citri* and work-related respiratory symptoms.

were sensitized to *T. urticae*, of whom approximately two-thirds exhibited significant bronchoconstriction after the inhalation of *T. urticae* extracts. The asthmatic symptoms of the *T. urticae*-asthmatic individuals were aggravated seasonally, especially in summer and early autumn, at which time the levels of *T. urticae* densities on pear leaves are highest, suggesting that *T. urticae* may be an important causative allergen among asthmatic individuals living around pear farms, who suffer summer-season aggravation of asthmatic symptoms.

Cross-sectional surveys in children living near citrus farms [18,19•] have demonstrated that *P. citri* was the second most common sensitizing allergen after house dust mites, and that sensitization to *P. citri* was significantly related to bronchial hyperresponsiveness, even in the absence of asthma symptoms [20]. These findings suggest that spider mites such as *P. citri* are common sensitizing outdoor allergens and important causative allergens in the development of asthma among exposed children living in rural areas.

Risk factors for the development of spider-mite allergy

Both environmental exposure to allergens and genetic predisposition have been known to be potential determinants for sensitization to a causative allergen. Although such sensitization requires exposure to only a small dose, it is nevertheless possible that high exposure may be associated with an increased risk of sensitization. The results from a follow-up study by Sporik *et al.* [21] showed that exposure to high levels of house dust mite allergen increased the risk of sensitization. As for outdoor spider mites, children who had either frequently visited fruit farms, or had been living near them, had enhanced skin responses to spider mites [19•]. These findings indicate that environmental exposure is a major determinant for the risk of sensitization to spider mites, and

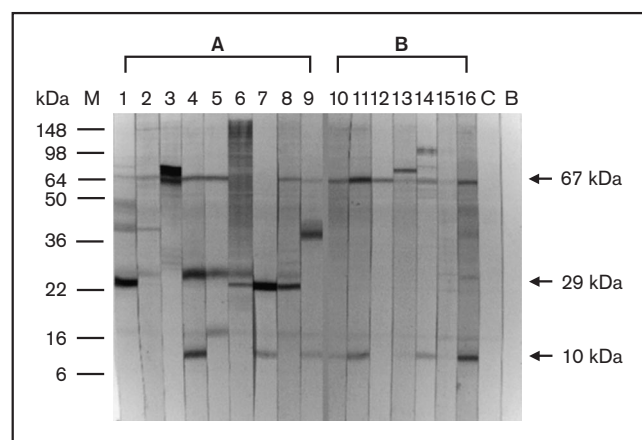
when combined with the prevalence data for spider-mite allergy, suggest that spider-mite allergy may be a common problem even among the non-farming population, especially those living near fruit farms.

Human leukocyte antigen (HLA) class II genes are likely candidates for controlling the immune response to specific allergens. In general, significant associations are found only with highly purified simple allergens [22,23]. The results of one of our own association studies [24•] showed that *P. citri*-induced asthma displayed a strong positive association with HLA-DRB1*0701. Our most recent association study has found that the HLA-DRB1*0701 allele was significantly associated with sensitization to citrus red mite, but not with asthma symptoms themselves, and that any HLA-DQ alleles were not significantly associated with sensitization to citrus red mite (Y.K. Kim, unpublished data). These findings suggest that the HLA-DRB1*0701 allele may be an important risk factor for sensitization to *P. citri*.

Characteristics of spider mite-derived allergens

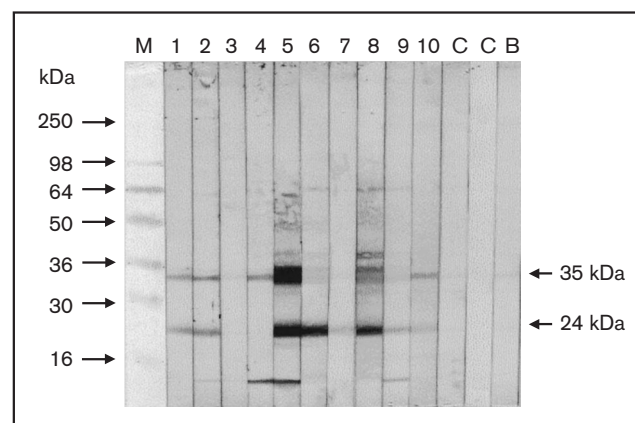
There is an agreement among researchers on the suggestion that the closer the taxonomic relationship between species, the greater the level of cross-allergenicity. Spider mites belong to the order Acari, the suborder Prostigmata, and the spider mite family *Tetranychidae*. Citrus red mites and European red mites belong to the genus *Panonychus*, and two-spotted spider mites to the genus *Tetranychus* (Table 1). Meanwhile, domestic mites such as house dust mites and storage mites, also of the order Acari, belong to the suborder Astigmata. Because of the wide domestic exposure in some populations, many investigators have evaluated the allergenic cross-reactivity between house dust mites and storage mites. Park *et al.* [25] reported a marked inhibition of *Tyrophagus putrescentiae*-specific IgE with *D. pteronyssinus*

Figure 2. IgE-immunoblot analysis of *Tetranychus urticae* extracts in sera from pear farmers with *T. urticae*-induced occupational asthma (original)



(a) A sera from farmers sensitized to both *T. urticae* and house dust mites. (b) Sera from farmers sensitized to only *T. urticae*. (c) Control serum; M, standard marker; B, buffer.

Figure 3. IgE-immunoblot analysis of *Panonychus citri* extracts in sera from citrus farmers with *P. citri*-induced occupational asthma



Previously published by Kim *et al.* [30*].

Lanes 1–10: sera from citrus farmers. C, control serum; B, buffer control; M, marker proteins.

extract, but found that *D. pteronyssinus*-specific IgE was not inhibited by *T. putrescentiae* in Korean urban areas. The authors suggested that many allergenic determinants of *T. pteronyssinus* may be cross-reactive to *Dermatophagoides* spp. A number of studies have been performed to determine the allergenic cross-reactivity between spider mites and domestic mites.

Burches *et al.* [26] reported that specific IgE to *T. urticae* could not be detected in the absence of specific IgE to *D. pteronyssinus*. However, Astarita *et al.* [27] reported that *T. urticae*-specific IgE binding was not inhibited by *D. pteronyssinus* in farm workers. Our study [15] revealed that *P. citri*-specific IgE binding was partly inhibited by *D. pteronyssinus* extract in citrus farmers with positive skin responses to both *P. citri* and *D. pteronyssinus*, whereas only minimal inhibitions were noted with additions of *D. pteronyssinus* in farmers with isolated skin responses to *P. citri*. Our recent study [28*] also demonstrated that although *P. ulmi*-specific IgE binding was completely inhibited by *P. citri*, it was only partly inhibited by *T. urticae*, *T. putrescentiae* and *D. pteronyssinus*, in decreasing order, whereas *T. urticae*-specific IgE binding was only partly inhibited by *P. citri*, *P. ulmi*, *T. putrescentiae* and *D. pteronyssinus*, in decreasing order. These findings indicate that spider mite-derived extracts contain species-specific allergens, in addition to those allergens that are shared in common with domestic mites.

Crude *D. pteronyssinus* allergens are a source of many allergens. Extracts have been shown to contain as many as 32 different IgE-binding components, as assessed by sodium dodecylsulphate–polyacrylamide gel electro-

phoresis and immunoblotting [29]. In the case of allergens derived from outdoor spider mites, both *T. urticae* and *P. ulmi*-derived crude extracts contained more than 10 different IgE-binding components in apple farmers and, among these, at least three IgE-binding components were found to be major allergens by sodium dodecylsulphate–polyacrylamide gel electrophoresis and IgE immunoblotting [28*]. *T. urticae*-derived extracts also contained a number of IgE-binding components in pear farmers with *T. urticae* asthma, with three (10 000, 29 000 and 67 000 M_r) of them bound in more than 50% of asthmatic patients (Fig. 2) (Y.K. Kim, unpublished data). Similar to *T. urticae* and *P. ulmi*, *P. citri*-derived crude extracts contained five IgE-binding components, as determined by the study of 10 citrus farmers with *P. citri* asthma, with two (24 000 and 35 000 M_r) of them being major allergens [30*] (Fig. 3). N-terminal amino acid sequencing of the major allergens of *T. urticae* and *P. citri* was not homologous with any previously characterized allergens [30*], suggesting that the major allergens derived from spider mites are unique in terms of cross-reactivity to domestic mites.

Conclusion

Spider mites are outdoor phytophagous mites that incur a severe economic effect on agriculture and have been found to be distributed worldwide. Epidemiological studies have demonstrated that spider mites are important allergens in the development of work-related asthma and rhinitis in fruit-cultivating farmers, after several case reports of occupational allergy to spider mites. Moreover, outdoor spider mites are not only common sensitizing allergens, but have also been associated with the development of asthma and rhinitis

among the non-farming population exposed to spider mites. Although predaceous mites do indeed attack spider mites, the mites are usually not well controlled by the current predator complex, and consequently their numbers have increased substantially in the fruit-cultivation industry since pesticides were introduced to eliminate fruit moths. These environmental changes may well play a role in the recently noted increase in the prevalence of asthma and allergic diseases.

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