

***Hevea brasiliensis* Latex Allergens: Current Panel and Clinical Relevance**

Stefan Wagner Heimo Breiteneder

Center of Physiology and Pathophysiology, Department of Pathophysiology, Medical University of Vienna,
Vienna, Austria

Key Words

Hevea brasiliensis allergens · Latex allergy ·
Recombinant allergens · Prevalence of latex allergens

Abstract

Latex allergy has been studied in detail in Europe and the US over the past two decades, resulting in specific guidelines that succeeded in reducing its incidence in high-risk populations within the medical field. How these developments have affected high-risk populations outside the health care scenario is an important unanswered question. In addition, a second wave of latex allergy may occur in nations that are striving to attain higher economic and technologic standards, including population-dense countries such as China. Therefore, the application of *Hevea* allergens in novel diagnostic assays and the development of specific latex immunotherapy will provide new opportunities for latex allergy research. In this review, we summarize current knowledge on the immunological properties of the 13 officially accepted *Hevea brasiliensis* latex allergens.

Copyright © 2005 S. Karger AG, Basel

Introduction

The latex allergy epidemic has come and gone, at least in the highly industrialized countries of Europe and North America. It was caused in part by the adoption of precau-

tion measures in response to the increase in viral infections such as hepatitis and HIV in the late 1980s and 1990s [1]. Present-day low prevalence rates in the USA and in Finland suggest that the peak of the latex allergy epidemic is over at least for health care workers (HCWs) [2]. This is by and large due to the preventive measures implemented following the recommendations of several reputable research teams as well as task forces of European and American Allergy Associations.

Outside the health care field, the situation seems to be different. Eighteen percent of flower greenhouse workers reported immediate symptoms associated with wearing latex gloves [3]. A study from Spain involving skin prick test screening showed that 6% of construction workers had latex allergy [4]. Latex allergy is also more frequent in patients with food allergy. A higher percentage of latex allergy (10.4%) was found in latex-exposed individuals with food allergy than in those without (5.6%) [5]. In general, atopic patients are more susceptible to latex allergy than nonatopic individuals [6]. It is quite possible that the prevalence of latex allergy in such risk groups outside the medical field has developed in a different way. Nevertheless, forefront research on latex allergy and the individual latex allergens has decreased and slowed down considerably. Justifiably so?

There are population-dense countries around the world that are striving to attain the economical and technological status that is the norm in Europe and the US. So the question arises whether the history of latex allergy will repeat itself. Recent data on the high prevalence of

latex allergy in Taiwan [7], Turkey [8], and Poland [9] show that the increased use of latex products in these fast-developing countries may lead to the emergence of a new epidemic. Although the occurrence of latex allergy among health care workers and workers in the diverse branches of industry with frequent latex exposure is still not documented in the literature, China, India and Mexico can be expected to encounter increased incidences of latex allergy. Education and prevention measures will need to be installed, but this will only be possible with a time lag. Therefore, improved surveillance and testing in these countries will be necessary to evaluate any new emergence of latex allergy.

Although latex allergy represented a hot topic in allergy research for a rather long period of time, specific immunotherapy must still be considered as an experimental treatment [10, 11]. Accurate diagnosis of latex allergy, whenever possible in a component-resolved way, is of great importance for the development and application of any specific immunotherapy. At present, the skin prick test (SPT) is considered the most reliable test for the diagnosis of latex allergy [12–14]. It is in this context that we review the current status of knowledge about the thirteen officially accepted latex allergens (www.allergen.org) and present available data on their frequency of recognition or reactivity in different study populations.

Hev b 1 (Rubber Elongation Factor)

Hev b 1, a small protein of 137 amino acid residues with a molecular mass of 14.6 kDa, was the first latex allergen characterized on the molecular level [15]. Alenius et al. [16] reported a relatively low frequency of IgE antibodies to purified Hev b 1 with the exception of spina bifida (SB) patients. In IgE immunoblot studies, these authors observed that 67% of sera of SB patients displayed Hev b 1-specific IgE whereas none of the sera of latex-allergic individuals showed any reactivity. Using nHev b 1 in ELISA, a prevalence of 18% could be observed in latex-allergic individuals. Yeang et al. [17] produced a recombinant Hev b 1 in *Escherichia coli* that did not bind IgE of 19 latex-allergic individuals in immunoblot studies. There is only one study that recognizes Hev b 1 not only as a major allergen for SB patients but also as an important latex allergen for HCWs. In this study, 81% of the SB patients and 50% of the HCWs showed IgE reactivity to Hev b 1 [18]. More recent studies performed with natural and recombinant Hev b 1 clearly demonstrated that Hev b 1 was one of the major allergens of

Hevea latex for SB patients with prevalences ranging from 54 to 100%, but that it was less important for HCWs and other latex-allergic individuals with prevalences ranging from 13 to 32% [19–21].

Hev b 2 (β -1,3-Glucanase)

The basic β -1,3-glucanase isolated from *Hevea* latex was first described by Sunderasan et al. [22] as the Hev b 2 allergen which appeared as a doublet of 34 kDa in SDS-PAGE and was recognized by IgE antibodies of a latex-allergic patient. The cDNA of Hev b 2 codes for a protein of 374 amino acid residues with N-terminal and C-terminal extensions that are cleaved off, resulting in a mature protein of 35.1 kDa with one putative N-glycosylation site [23]. Hev b 2 seems to be a major allergen of *Hevea* latex with prevalences ranging from 38 to 65% [19, 21]. Yagami et al. [24] described that the carbohydrate structures of Hev b 2 were the major IgE-binding epitopes. Based on these findings, it is not surprising that in one study performed with a recombinant Hev b 2 expressed in *E. coli* only 7% positive responses were detectable in SPTs [25]. Nor did Raulf-Heimsoth et al. [26] observe any responses to their recombinant Hev b 2.

Wagner et al. [27] recently observed on a molecular level that Hev b 2 cross-reacted with a homologous protein of bell pepper, indicating that Hev b 2 is one of the latex allergens involved in the latex-fruit syndrome.

Hev b 3

Hev b 3 is one of the latex allergens that is mainly associated with latex allergy in SB patients. A cDNA clone encoding a protein of 204 amino acid residues with a predicted molecular mass of 22.3 kDa has been described [28]. Hev b 3 showed 47% sequence identity with Hev b 1 [28]. The protein was produced as a recombinant protein in *E. coli* and a prevalence of 83% in SB patients was found in IgE immunoblot experiments [28]. Cross-reactivity of Hev b 3 and Hev b 1 was described as well [28]. Natural and recombinant Hev b 3 proteins were used in several studies revealing similar prevalences. For SB patients, prevalences ranged from 77 to 100% and from 7 to 32% for HCWs and latex-allergic individuals [19–21, 25]. Interestingly, prevalence data of Hev b 3 highly correlate with the data obtained for Hev b 1, indicating that these proteins contain very similar IgE epitopes.

Hev b 4 (Cyanogenic Glucosidase)

Hev b 4 comprises a triplet of IgE-binding proteins of molecular masses of 50–57 kDa. Sunderasan et al. [29] have recently described the component with the highest molecular mass of this protein complex as a cyanogenic glucosidase. Studies with natural Hev b 4 have demonstrated that this protein was an important allergen for HCWs as well as SB patients. Kurup et al. [19] performed ELISA and RAST studies with nHev b 4. The prevalences obtained with RAST assays were lower than those obtained with ELISAs. RAST data ranged from 30 to 46% for SB patients and from 23 to 61% for HCWs versus 77% for SB patients and 65% for HCWs with ELISAs. Natural Hev b 4 was also used in SPTs with latex-allergic HCWs revealing a prevalence of 39% [21].

Hev b 5

Hev b 5 was characterized as an IgE-binding protein by two research groups at the same time. Both groups described a cDNA encoding a protein consisting of 151 amino acid residues with a predicted molecular mass of 16 kDa [30, 31]. Slater et al. [31] produced Hev b 5 as a recombinant protein with the maltose-binding protein as fusion component and performed RAST assays revealing a prevalence of 92% for HCWs and 56% for SB patients. Further studies were performed with recombinant Hev b 5 molecules. In CAP-FEIA tests, 68% of HCWs and 33% of SB patients showed reactivity to Hev b 5 [20]. In SPT studies prevalences of 62 and 65% were determined [21, 25].

Hev b 5 is one of the most important allergens of *Hevea* latex and therefore indispensable for the diagnosis of latex allergy. Pharmacia Diagnostics has reported a lower sensitivity of their latex ImmunoCAP due to the lack of Hev b 5. Retesting of patients' sera with the ImmunoCAP preparation spiked with a recombinant Hev b 5 showed that some of the responses were stronger and some sera testing negative became positive [32].

Hev b 6

Hev b 6.01 (prohevein) is a precursor protein consisting of 187 amino acid residues that contains two domains, a 4.7-kDa amino-terminal domain (Hev b 6.02 or hevein), and a 14-kDa carboxy-terminal domain (Hev b 6.03). The precursor protein and both domains are

present as distinct proteins in *Hevea* latex. Alenius et al. [33] identified prohevein as a major latex allergen for HCWs as well as SB patients. Banerjee et al. [34] produced all three Hev b 6 molecules as recombinant proteins with the maltose-binding protein as fusion component and demonstrated, based on ELISA experiments, that most of the IgE-binding domains were located on Hev b 6.02 with additional IgE epitopes on Hev b 6.03. For SB patients, prevalences up to 50% were obtained indicating that Hev b 6 was also an important allergen for those children. Ylitalo et al. [35] tested nHev b 6.01 and nHev b 6.02 with sera of SB patients or other latex-allergic children with prevalences from 58 to 86%. Additional studies also revealed high prevalences for SB patients ranging from 30 to 69% [19, 20]. From these data one might conclude that Hev b 6 is as important for SB patients as Hev b 1 or Hev b 3. For HCWs and other latex-allergic adults, Hev b 6 is the most important allergen besides Hev b 5 with prevalences ranging from 40 to 88% obtained in several studies [19–21, 25, 34].

Hev b 6.02 shows sequence identities of more than 50% to hevein domains of class I chitinases from fruits. This may explain why Hev b 6 seems to be the most important allergen involved in the latex-fruit syndrome. Cross-reactivity of Hev b 6.02 with various fruit class I chitinases such as those from avocado and banana has been described (reviewed in Wagner and Breiteneder [36]).

Hev b 7 (Patatin-Like Protein)

Beezhold et al. [37] first described a 46-kDa protein from fresh natural rubber latex that was recognized by IgE of HCWs. Kostyal et al. [38] and Sowka et al. [39] have cloned and expressed Hev b 7 in both *E. coli* and *Pichia pastoris*. The two Hev b 7 proteins of 43 kDa can be described as two isoforms because they differ in their sequences by only seven amino acid residues. In IgE immunoblot studies, Sowka et al. [39] reported a prevalence of 11% for their recombinant protein. Seppälä et al. [40] observed that 49% of latex-allergic individuals and less than 1% of latex-allergic children displayed IgE to purified Hev b 7. They concluded from their results that Hev b 7 is not an important latex allergen for children. In following studies using sera of SB patients it could be demonstrated that Hev b 7 is an important allergen for SB patients, with prevalences ranging from 15 to 77% [19, 41]. Recent studies have shown that for HCWs and other latex-allergic individuals Hev b 7 seems to be an impor-

tant allergen, with prevalences ranging from 23 to 45% [19, 21, 25].

Hev b 7 shows about 50% sequence identity with the important potato allergen patatin (Sola t 1), indicating a potential cross-reactivity to this plant-derived food. Cross-reactivity between Hev b 7 and potato patatin was demonstrated with latex- and potato-allergic individuals [42]. Furthermore, proteins of 44–46 kDa in tomato, potato and *Hevea* latex, possibly patatin and patatin-like proteins, showed cross-reactivity [43].

Hev b 8 (Profilin)

Plant profilins are important pan-allergens but there is an ongoing discussion about the clinical relevance of IgE binding to profilin that has to be distinguished from cross-reactive IgE binding without evoking allergic symptoms. Hev b 8 was first identified as an IgE-binding protein by IgE inhibition studies [44]. Two Hev b 8 isoforms were then described and produced as recombinant proteins in *E. coli* [45, 46]. One cDNA was derived from *Hevea* leaf RNA that encoded a protein of 131 amino acid residues with a predicted molecular mass of 14.2 kDa [45] and another from *Hevea* latex also encoding a protein of 131 amino acid residues but a predicted molecular mass of 14 kDa [46]. Both recombinant Hev b 8 isoforms revealed similar IgE reactivity. The ‘leaf’ Hev b 8 was recognized by sera of 20% of HCWs and 12% of SB patients in CAP assays [45], the ‘latex’ Hev b 8 by sera of 24% of HCWs and 6% of SB patients in Western blot analyses [46]. In a third study, a recombinant Hev b 8 with the maltose-binding protein as fusion component was used for SPT studies yielding a prevalence of 3% [25].

Hev b 8 seems to be involved in the latex-fruit syndrome as cross-reactivity could be demonstrated to profilins from celery tuber [46], banana and pineapple [47], and bell pepper [27].

Hev b 9 (Enolase)

Hev b 9 was first identified as an IgE-binding protein of *Hevea* latex by microsequencing of protein spots after two-dimensional electrophoresis and Western blot with latex-allergic patients’ sera [48]. The complete cDNA of this protein encoding an enolase of 445 amino acid residues with a calculated molecular mass of 47.6 kDa was described [49]. The cDNA showed sequence identities of about 60% to Alt a 11 and Cla h 6, important allergens of

the molds *Alternaria alternata* and *Cladosporium herbarum*. Hev b 9 was produced as a recombinant protein in *E. coli* and showed a prevalence of 14.5% in Western blot analyses using sera of 110 latex-allergic subjects [49]. Furthermore, it could be demonstrated in the same study that Hev b 9 shared IgE epitopes with Alt a 11 and Cla h 6, indicating a possible cross-reactivity. Hev b 9 was also produced as a recombinant protein in *E. coli* with the maltose-binding protein as fusion component [20]. Coupled to ImmunoCAPs, sera of SB patients and HCWs were investigated, resulting in no response for the SB patients and 10% positive responses for the HCWs [20].

Hev b 10 (Manganese Superoxide Dismutase)

Hev b 10 was first identified as an IgE-binding protein of *Hevea* latex in the same study as Hev b 9 [48]. The cDNA encoding a protein of 206 amino acid residues with a predicted molecular mass of 22.9 kDa was then described and showed 49% identity with Asp f 6, the MnSOD from *Aspergillus fumigatus* [50]. A recombinant Hev b 10 produced in *E. coli* showed a prevalence of 27% when used in Western blot analysis with sera of latex-allergic subjects. In addition, cross-reactivity to Asp f 6 was described [50]. Hev b 10 was also produced as a recombinant protein in *E. coli* with the maltose-binding protein as fusion component [51]. This protein was used in EASTs with sera of SB patients and HCWs and showed a prevalence of 10% for SB patients and of 0% for HCWs. The same protein was also used in CAP-FEIA experiments using sera of SB patients and HCWs. In this study, the prevalence for the SB patients was 0% and 3% for the HCWs [20].

Hev b 11 (Class I Chitinase)

Fruit class I chitinases containing a small N-terminal hevein domain are described as the most important pan-allergens associated with the latex-fruit syndrome (reviewed in Wagner and Breiteneder [36]). Two cDNAs of *Hevea* latex class I chitinases have been described, one derived from *Hevea* latex coding for a protein of 295 amino acid residues and a molecular mass of 33 kDa [52] and another derived from *Hevea* leaves (Hev b 11.0102) also encoding a protein of 295 amino acid residues but with a predicted molecular mass of 31.6 kDa [53]. Comparison of the amino acid residues revealed differences in eight positions. In sequence analysis, the latex sap Hev b 11

showed 70% identity with Pers a 1, the class I chitinase from avocado, and 58% identity of its chitin-binding domain with hevein (Hev b 6.02) [52]. The chitin-binding domain of the 'leaf' Hev b 11 showed 56% sequence identity with Hev b 6.02 [53]. Both proteins were produced as recombinant proteins in *E. coli* with the maltose-binding protein as fusion component [52, 53]. In Western blot analyses the 'latex' Hev b 11 showed a prevalence of 19% [52], whereas the 'leaf' Hev b 11 showed a prevalence of 29% in CAP assays [53]. O'Riordain et al. [52] could demonstrate that the 'latex' Hev b 11 was weakly cross-reactive with Hev b 6.02, but there are no data about a possible cross-reactivity with fruit class I chitinases.

Hev b 12 (Lipid Transfer Protein)

Lipid transfer proteins are important cross-reactive allergens, especially in plant-derived foods. Recently, Beezhold et al. [54] described the cDNA of a lipid transfer protein of *Hevea* latex encoding a protein of 116 amino acid residues with a calculated molecular mass of 9.3 kDa. The same research group produced Hev b 12 as a recombinant protein in *E. coli* with glutathione S-transferase as fusion component. In Western blot analysis, 24% of latex-allergic individuals displayed Hev b 12-specific IgE. There are no data about potential cross-reactivity.

Hev b 13 (Early Nodule-Specific Protein)

Recently, Arif et al. [55] have characterized an early nodule-specific protein (ENSP) as the main IgE-binding protein in the 42- to 46-kDa range of *Hevea* latex allergens. The cDNA of Hev b 13 contained two possible open reading frames. The cDNA thus coded for two possible proteins, one consisting of 391 amino acid residues and a calculated molecular mass of 43.3 kDa, and the second consisting of 372 amino acid residues and a calculated molecular mass of 41.2 kDa. With the longer open reading frame, a signal peptide was predicted resulting in a mature protein of 40.4 kDa. The molecular mass of the native Hev b 13 was 42.9 kDa as described by mass spectrometry [55]. The authors speculated that the discrepancy between these molecular masses was due to glycosylation as the Hev b 13 sequence contained three putative N-glycosylation sites. Hev b 13 seems to be a very important allergen for SB patients as well as HCWs. In one study, EAST experiments were performed, with nHev

Table 1. Panel of latex allergens and frequency of reactivity of SB patients and other latex-allergic children

Allergen	Patients	Source	Method	Frequency %	Ref.
Hev b 1	6 SB	n	IB	67	16
	62 SB	n	EAST	81	18
	58 SB	r	CAP	93	61
	13 SB	n	ELISA	100	19
			RAST	54–85	19
	9 SB	r	CAP	100	20
Hev b 2	13 SB	n	ELISA	54	19
			RAST	38–46	19
Hev b 3	35 SB	r	IB	83	28
	13 SB	n	ELISA	100	19
			RAST	77–85	19
	9 SB	r	CAP	78	20
Hev b 4	13 SB	n	ELISA	77	19
			RAST	30–46	19
Hev b 5	57 SB	r	RAST	56	31
	9 SB	r	CAP	33	20
Hev b 6	25 SB	r (6.01)	ELISA	48	34
	25 SB	r (6.02)	ELISA	56	34
	25 SB	r (6.03)	ELISA	28	34
	30 LAC	n (6.01)	ELISA	86	35
	12 SB	n (6.01)	ELISA	58	35
	30 LAC	n (6.02)	ELISA	63	35
	12 SB	n (6.02)	ELISA	58	35
	13 SB	r (6.01)	ELISA	69	19
			RAST	30–38	19
	9 SB	r (6.01)	CAP	44	20
Hev b 7	35 LAC	n	ELISA	<1	40
	13 SB	r	ELISA	77	19
			RAST	15–23	19
	38 SB	n	IB	40	41
Hev b 8	17 SB	r	CAP	12	45
	34 SB	r	IB	6	46
	9 SB	r	CAP	0	20
Hev b 9	9 SB	r	CAP	0	20
Hev b 10	20 SB	r	EAST	10	51
	9 SB	r	CAP	0	20
Hev b 11	no data				
Hev b 12	no data				
Hev b 13	11 SB	n	EAST	75	56

SB = Spina bifida; LAC = latex-allergic children; n = natural; r = recombinant; IB = IgE immunoblot.

Table 2. Panel of latex allergens and frequency of reactivity of HCWs and other latex-allergic individuals

Allergen	Patients	Source	Method	Frequency %	Ref.
Hev b 1	30 LAI	n	IB	<1	16
	45 LAI	n	ELISA	18	16
	103 HCW	n	EAST	50	18
	71 HCW	r	CAP	23	61
	31 HCW	n	ELISA	32	19
			RAST	13–19	19
	40 HCW	r	CAP	23	20
	62 HCW	n	SPT	23	21
Hev b 2	31 HCW	n	ELISA	65	19
			RAST	48–61	19
	29 LAI	r	SPT	7	25
	62 HCW	n	SPT	63	21
Hev b 3	15 LAI	r	IB	27	28
	31 HCW	n	ELISA	32	19
			RAST	19	19
	29 LAI	r	SPT	7	25
	40 HCW	r	CAP	12.5	20
	62 HCW	n	SPT	24	21
Hev b 4	31 HCW	n	ELISA	65	19
			RAST	23–61	19
	62 HCW	n	SPT	39	21
Hev b 5	13 HCW	r	RAST	92	31
	29 LAI	r	SPT	62	25
	40 HCW	r	CAP	68	20
	62 HCW	r	SPT	65	21
Hev b 6	25 HCW	r (6.01)	ELISA	84	34
	25 HCW	r (6.02)	ELISA	88	34
	25 HCW	r (6.03)	ELISA	40	34
	31 HCW	r (6.01)	ELISA	55	19
			RAST	45	19
	29 LAI	r (6.01)	SPT	66	25
	40 HCW	r (6.01)	CAP	75	20
	62 HCW	n (6.01)	SPT	63	21
Hev b 7	36 LAI	r	IB	11	39
	25 LAI	n	ELISA	49	40
	31 HCW	r	ELISA	42	19
			RAST	23–45	19
	29 LAI	r	SPT	41	25
	62 HCW	n (7.01)	SPT	45	21
Hev b 8	29 LAI	r	SPT	3	25
	25 HCW	r	CAP	20	45
	50 HCW	r	IB	24	46
	40 HCW	r	CAP	10	20
Hev b 9	110 LAI	r	IB	15	49
	40 HCW	r	CAP	10	20
Hev b 10	15 LAI	r	IB	27	50
	20 HCW	r	EAST	0	51
	40 HCW	r	CAP	3	20
Hev b 11	57 LAI	r	IB	19	52
	58 LAI	r (11.0102)	CAP	29	53
Hev b 12	37 LAI	r	IB	24	54
Hev b 13	53 HCW	n	EAST	87	56
	62 HCW	n	SPT	63	21

HCW = Health care worker; LAI = latex-allergic individual; n = natural; r = recombinant; IB = IgE immunoblot.

b 13 yielding prevalences of 75% in SB patients and 87% for HCWs [56]. In another study using nHev b 13 in SPTs, a prevalence of 63% was found in HCWs [21]. To date, no data are available on the influence of possible N-glycans on IgE binding.

Conclusions and Future Prospects

This review of the available knowledge on 13 *Hevea* latex allergens (summarized in tables 1, 2) clearly shows that there are opportunities for further research. Two-dimensional gel electrophoresis of *Hevea* proteins followed by IgE immunoblotting has revealed the existence of further allergens [48, 57, 58]. Progress in diagnosis using recombinant allergens may only be limited by the ability to express these allergens for use in high throughput diagnostic screening assays.

On the other hand, a change of paradigm may favor the use of partially enriched or purified natural allergens. No reliable recombinant proteins are available for Hev b 2, 4 and 13. In addition, the role and importance of glycosylation for allergenicity remains an unanswered question for Hev b 2 and 13. Therefore, a recent SPT study of latex-allergic HCWs relied on the use of purified natural *Hevea* latex allergens [21].

The performance and reproducibility of diagnostic assays are highly dependent on the allergen content of the reagents used. Low diagnostic sensitivity was related to poorly represented and/or denatured allergens such as Hev b 5 [59]. Although the quality of latex extracts has improved in recent years, there is still room for further developments [60]. In the future, the reagents of choice may well consist of a combination of recombinant and natural allergens.

In the next few years, it is possible that large new markets for latex allergy diagnostics and specific immunotherapy will open up. It is reasonable to assume that this will provide a new incentive for basic as well as applied latex allergy research.

Acknowledgement

The support of the Austrian Science Fund (grant SFB F01802) is gratefully appreciated.

References

- Ownby DR: A history of latex allergy. *J Allergy Clin Immunol* 2002;110:S27–S32.
- Reunala T, Alenius H, Turjanmaa K, Palosuo T: Latex allergy and skin. *Curr Opin Allergy Clin Immunol* 2004;4:397–401.
- Carrillo T, Blanco C, Quirarte J, Castillo R, Cuevas M, Rodriguez de Castro F: Prevalence of latex allergy among greenhouse workers. *J Allergy Clin Immunol* 1995;96:699–701.
- Conde-Salazar L, Gatica ME, Barco L, Iglesias C, Cuevas M, Valks R: Latex allergy among construction workers. *Contact Dermatitis* 2002;47:154–156.
- Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F: Population study of food allergy in France. *J Allergy Clin Immunol* 2001;108:133–140.
- Nettis E, Micale G, Fanelli M, Serio G, Colanardi MC, Ferrannini A, Tursi A: Atopy and risk factors for latex sensitization in a selected population. *Allergy Asthma Proc* 2003;24:185–191.
- Chen YH, Lan JL: Latex allergy and latex-fruit syndrome among medical workers in Taiwan. *J Formos Med Assoc* 2002;101:622–626.
- Ozkan O, Gokdogan F: The prevalence of latex allergy among health care workers in Bolu (Turkey). *Dermatol Nurs* 2003;15:543–547, 554.
- Dudek W, Palczynski C, Walusiak J, Krakowiak A, Wittczak T, Ruta U: Natural rubber latex-specific IgE and total serum IgE level in Polish blood donors (abstract). *Allergy* 2003;58:S353.
- Pereira C, Pedro E, Tavares B, Ferreira MB, Carrapatoso I, Rico P, Loureiro G, Rodrigues F, Santos MC, Palma-Carlos AG, Chieira C: Specific immunotherapy for severe latex allergy. *Allerg Immunol (Paris)* 2003;35:217–225.
- Sastre J, Fernandez-Nieto M, Rico P, Martin S, Barber D, Cuesta J, de las Heras M, Quirce S: Specific immunotherapy with a standardized latex extract in allergic workers: A double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2003;111:985–994.
- Ebo DG, Stevens WJ, Bridts CH, De Clerck LS: Latex-specific IgE, skin testing, and lymphocyte transformation to latex in latex allergy. *J Allergy Clin Immunol* 1997;100:618–623.
- Palosuo T, Makinen-Kiljunen S, Alenius H, Reunala T, Yip E, Turjanmaa K: Measurement of natural rubber latex allergen levels in medical gloves by allergen-specific IgE-ELISA inhibition, RAST inhibition, and skin prick test. *Allergy* 1998;53:59–67.
- Kim KT, Safadi GS, Sheikh KM: Diagnostic evaluation of type I latex allergy. *Ann Allergy Asthma Immunol* 1998;80:66–70.
- Czuppon AB, Chen Z, Rennert S, Engelke T, Meyer HE, Heber M, Baur X: The rubber elongation factor of rubber trees (*Hevea brasiliensis*) is the major allergen in latex. *J Allergy Clin Immunol* 1993;92:690–697.
- Alenius H, Kalkkinen N, Yip E, Hasmin H, Turjanmaa K, Makinen-Kiljunen S, Reunala T, Palosuo T: Significance of rubber elongation factor as a latex allergen. *Int Arch Allergy Immunol* 1996;109:362–368.
- Yeang HY, Cheong KF, Sunderasan E, Hamzah S, Chew NP, Hamid S, Hamilton RG, Cardosa MJ: The 14.6 kd rubber elongation factor (Hev b 1) and 24 kd (Hev b 3) rubber particle proteins are recognized by IgE from patients with spina bifida and latex allergy. *J Allergy Clin Immunol* 1996;98:628–639.
- Chen Z, Posch A, Cremer R, Raulf-Heimsoth M, Rihs HP, Baur X: Purification and characterization of rubber elongation factor (Hev b 1) from Hevea latex that acts as a major allergen in latex-allergic patients with spina bifida (abstract). *Allergy* 1997;52:79.
- Kurup VP, Yeang HY, Sussman GL, Bansal NK, Beezhold DH, Kelly KJ, Hoffman DR, Williams B, Fink JN: Detection of immunoglobulin antibodies in the sera of patients using purified latex allergens. *Clin Exp Allergy* 2000;30:359–369.
- Raulf-Heimsoth M, Rozynek P, Lundberg M, Cremer R, Maryska S, Bruning T, Rihs HP: Individual latex allergen sensitization profiles in spina bifida patients and health care workers using a panel of recombinant latex allergens coupled to ImmunoCAP (abstract). *J Allergy Clin Immunol* 2002;106:S283.
- Bernstein DI, Biagini RE, Karnani R, Hamilton R, Murphy K, Bernstein C, Arif SA, Berendts B, Yeang HY: In vivo sensitization to purified *Hevea brasiliensis* proteins in health care workers sensitized to natural rubber latex. *J Allergy Clin Immunol* 2003;111:610–616.
- Sunderasan E, Hamzah S, Hamid S, Ward MA, Yeang HY, Cardosa MJ: Latex B-serum β -1,3-glucanase (Hev b 2) and a component of the microhelix (Hev b 4) are major latex allergens. *J Nat Rubber Res* 1996;10:82–99.
- Chye ML, Cheung KY: Beta-1,3-glucanase is highly expressed in laticifers of *Hevea brasiliensis*. *Plant Mol Biol* 1995;29:397–402.
- Yagami T, Osuna H, Kouno M, Haishima Y, Nakamura A, Ikezawa Z: Significance of carbohydrate epitopes in a latex allergen with beta-1,3-glucanase activity. *Int Arch Allergy Immunol* 2002;129:27–37.
- Yip L, Hickey V, Wagner B, Liss G, Slater J, Breiteneder H, Sussman G, Beezhold D: Skin prick test reactivity to recombinant latex allergens. *Int Arch Allergy Immunol* 2000;121:292–299.
- Raulf-Heimsoth M, Rihs HP, Bruning T: Latex: A new target for standardization. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankfurt* 2003;94:107–115.
- Wagner S, Radauer C, Hafner C, Fuchs H, Jensen-Jarolim E, Wuthrich B, Scheiner O, Breiteneder H: Characterization of cross-reactive bell pepper allergens involved in the latex-fruit syndrome. *Clin Exp Allergy* 2004;34:1739–1746.
- Wagner B, Krebitz M, Buck D, Niggemann B, Yeang HY, Han KH, Scheiner O, Breiteneder H: Cloning, expression, and characterization of recombinant Hev b 3, a *Hevea brasiliensis* protein associated with latex allergy in patients with spina bifida. *J Allergy Clin Immunol* 1999;104:1084–1092.
- Sunderasan E, Ward MA, Yeang HY: Isolation and characterization of latex cyanogenic glucosidase in *Hevea brasiliensis*. *J Rubber Res* 2002;5:244–252.
- Akasawa A, Hsieh LS, Martin BM, Liu T, Lin Y: A novel acidic allergen, Hev b 5, in latex. Purification, cloning and characterization. *J Biol Chem* 1996;271:25389–25393.
- Slater JE, Vedvick T, Arthur-Smith A, Trybul DE, Kekwick RG: Identification, cloning, and sequence of a major allergen (Hev b 5) from natural rubber latex (*Hevea brasiliensis*). *J Biol Chem* 1996;271:25394–25399.
- Lundberg M, Chen Z, Rihs HP, Wrangsjö K: Recombinant spiked allergen extract. *Allergy* 2001;56:794–795.
- Alenius H, Kalkkinen N, Lukka M, Reunala T, Turjanmaa K, Makinen-Kiljunen S, Yip E, Palosuo T: Prohevein from the rubber tree (*Hevea brasiliensis*) is a major latex allergen. *Clin Exp Allergy* 1995;25:659–665.
- Banerjee B, Wang X, Kelly KJ, Fink JN, Sussman GL, Kurup VP: IgE from latex-allergic patients binds to cloned and expressed B cell epitopes of prohevein. *J Immunol* 1997;159:5724–5732.
- Ylitalo L, Alenius H, Turjanmaa K, Palosuo T, Reunala T: IgE antibodies to prohevein, hevein, and rubber elongation factor in children with latex allergy. *J Allergy Clin Immunol* 1998;102:659–664.
- Wagner S, Breiteneder H: The latex-fruit syndrome. *Biochem Soc Trans* 2002;30:935–940.
- Beezhold DH, Sussman GL, Kostyal DA, Chang NS: Identification of a 46-kD latex protein allergen in health care workers. *Clin Exp Immunol* 1994;98:408–413.
- Kostyal DA, Hickey VL, Noti JD, Sussman GL, Beezhold DH: Cloning and characterization of a latex allergen (Hev b 7): homology to patatin, a plant PLA2. *Clin Exp Immunol* 1998;112:355–362.
- Sowka S, Wagner S, Krebitz M, Arijia-Mad-Arif S, Yusof F, Kinacian T, Brehler R, Scheiner O, Breiteneder H: cDNA cloning of the 43-kDa latex allergen Hev b 7 with sequence similarity to patatins and its expression in the yeast *Pichia pastoris*. *Eur J Biochem* 1998;255:213–219.
- Seppala U, Palosuo T, Kalkkinen N, Ylitalo L, Reunala T, Turjanmaa K: IgE reactivity to patatin-like latex allergen, Hev b 7, and to patatin of potato tuber, Sol t 1, in adults and children allergic to natural rubber latex. *Allergy* 2000;55:266–273.

- 41 Wagner B, Buck D, Hafner C, Sowka S, Niggemann B, Scheiner O, Breiteneder H: Hev b 7 is a *Hevea brasiliensis* protein associated with latex allergy in children with spina bifida. *J Allergy Clin Immunol* 2001;108:621–627.
- 42 Schmidt MH, Raulf-Heimsoth M, Posch A: Evaluation of patatin as a major cross-reactive allergen in latex-induced potato allergy. *Ann Allergy Asthma Immunol* 2002;89:613–618.
- 43 Reche M, Pascual CY, Vicente J, Caballero T, Martin-Munoz F, Sanchez S, Martin-Esteban M: Tomato allergy in children and young adults: Cross-reactivity with latex and potato. *Allergy* 2001;56:1197–1201.
- 44 Vallier P, Balland S, Harf R, Valenta R, Deviller P: Identification of profilin as an IgE-binding component in latex from *Hevea brasiliensis*: Clinical implications. *Clin Exp Allergy* 1995;25:332–339.
- 45 Rihs HP, Chen Z, Rozynek P, Baur X, Lundberg M, Cremer R: PCR-based cloning, isolation, and IgE-binding properties of recombinant latex profilin (rHev b 8). *Allergy* 2000;55:712–717.
- 46 Ganglberger E, Radauer C, Wagner S, Riordain G, Beezhold DH, Brehler R, Niggemann B, Scheiner O, Jensen-Jarolim E, Breiteneder H: Hev b 8, the *Hevea brasiliensis* latex profilin, is a cross-reactive allergen of latex, plant foods and pollen. *Int Arch Allergy Immunol* 2001;125:216–227.
- 47 Reindl J, Rihs HP, Scheurer S, Wangorsch A, Haustein D, Vieths S: IgE reactivity to profilin in pollen-sensitized subjects with adverse reactions to banana and pineapple. *Int Arch Allergy Immunol* 2002;128:105–114.
- 48 Posch A, Chen Z, Wheeler C, Dunn MJ, Raulf-Heimsoth M, Baur X: Characterization and identification of latex allergens by two-dimensional electrophoresis and protein microsequencing. *J Allergy Clin Immunol* 1997;99:385–395.
- 49 Wagner S, Breiteneder H, Simon-Nobbe B, Susani M, Krebitz M, Niggemann B, Brehler R, Scheiner O, Hoffmann-Sommergruber K: Hev b 9, an enolase and a new cross-reactive allergen from hevea latex and molds. Purification, characterization, cloning and expression. *Eur J Biochem* 2000;267:7006–7014.
- 50 Wagner S, Sowka S, Mayer C, Cramer R, Focke M, Kurup VP, Scheiner O, Breiteneder H: Identification of a *Hevea brasiliensis* latex manganese superoxide dismutase (Hev b 10) as a cross-reactive allergen. *Int Arch Allergy Immunol* 2001;125:120–127.
- 51 Rihs HP, Chen Z, Rozynek P, Cremer R: Allergenicity of rHev b 10 (manganese-superoxide dismutase). *Allergy* 2001;56:85–86.
- 52 O'Riordain G, Radauer C, Hoffmann-Sommergruber K, Adhami F, Peterbauer CK, Blanco C, Godnic-Cvar J, Scheiner O, Ebner C, Breiteneder H: Cloning and molecular characterization of the *Hevea brasiliensis* allergen Hev b 11, a class I chitinase. *Clin Exp Allergy* 2002;32:455–462.
- 53 Rihs HP, Dumont B, Rozynek P, Lundberg M, Cremer R, Bruning T, Raulf-Heimsoth M: Molecular cloning, purification, and IgE-binding of a recombinant class I chitinase from *Hevea brasiliensis* leaves (rHev b 11.0102). *Allergy* 2003;58:246–251.
- 54 Beezhold DH, Hickey VL, Kostyal DA, Puhl H, Zuidmeer L, van Ree R, Sussman GL: Lipid transfer protein from *Hevea brasiliensis* (Hev b 12), a cross-reactive latex protein. *Ann Allergy Asthma Immunol* 2003;90:439–445.
- 55 Arif SA, Hamilton RG, Yusof F, Chew NP, Loke YH, Nimkar S, Beintema JJ, Yeang HY: Isolation and characterization of the early node-specific protein homologue (Hev b 13), an allergenic lipolytic esterase from *Hevea brasiliensis* latex. *J Biol Chem* 2004;279:23933–23941.
- 56 Raulf-Heimsoth M, Yeang HY, Sander I, Rozynek P, Arif SA, Fleischer C, Cremer R, Bruning T, Rihs HP: Is ENSP (Hev b 13) the missing latex allergen to fill the gap in the repertoire of isolated allergens for the determination of sensitization profiles? (abstract). *J Allergy Clin Immunol* 2003;111:S95.
- 57 Posch A, Chen Z, Dunn MJ, Wheeler CH, Petersen A, Leubner-Metzger G, Baur X: Latex allergen database. *Electrophoresis* 1997;18:2803–2810.
- 58 Yagami T, Haishima Y, Tsuchiya T, Tomitaka-Yagami A, Kano H, Matsunaga K: Proteomic analysis of putative latex allergens. *Int Arch Allergy Immunol* 2004;135:3–11.
- 59 Chen Z, Rihs HP, Slater J, Paupore EJ, Schneider EM, Baur X: The absence of Hev b 5 antigen may cause false negative results in serologic assays for latex-specific IgE antibodies (abstract). *J Allergy Clin Immunol* 2000;106:83.
- 60 Hamilton RG, Peterson EL, Ownby DR: Clinical and laboratory-based methods in the diagnosis of natural rubber latex allergy. *J Allergy Clin Immunol* 2002;110:S47–S56.
- 61 Rihs HP, Chen Z, Schumacher S, Rozynek P, Cremer R, Lundberg M, Raulf-Heimsoth M, Petersen A, Baur X: Recombinant Hev b 1: large-scale production and immunological characterization. *Clin Exp Allergy* 2000;30:1285–1292.