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Research and Development

## Literature Review on Latex-Food Cross-Reactivity 1991-2006

Compiled by: Tom Grier  
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### **Differential allergen sensitization patterns in chestnut allergy with or without associated latex-fruit syndrome.**

Sánchez-Monge R, Blanco C, López-Torrejón G, Cumplido J, Recas M, Figueroa J, Carrillo T, Salcedo G.  
*J Allergy Clin Immunol.* 2006 Sep;118(3):705-10. Epub 2006 Jun 27.

**BACKGROUND:** Chestnut allergy has been almost exclusively considered in the context of the latex-fruit syndrome. Chestnut allergens not linked to latex hypersensitivity have not been studied. **OBJECTIVE:** We sought to explore whether differences in sensitization patterns between chestnut allergy with or without associated latex-fruit syndrome can be detected. **METHODS:** Twelve patients sensitized to chestnut but not to latex and 3 control patients with latex-chestnut allergy were analyzed. A major chestnut allergen was purified and characterized. IgE immunoblotting, specific IgE determination, and skin prick tests with 5 isolated allergens involved in food allergy or latex-fruit syndrome were also performed. **RESULTS:** A major 9-kd allergen was detected in chestnut extract, isolated, and identified as lipid transfer protein (LTP) Cas s 8. Specific IgE to this allergen was found in 91% (by means of IgE immunoblotting) and 58% (by means of ELISA) of sera from patients with chestnut but not latex allergy. Moreover, 66% of these patients had positive skin prick test responses to Cas s 8. Additionally, allergenic LTPs from peach fruit and *Artemisia vulgaris* pollen were also reactive. In contrast, avocado class I chitinase and latex hevein, allergens associated with the latex-fruit syndrome, showed no reaction. The opposite situation was exhibited by patients with latex-chestnut allergy. **CONCLUSIONS:** Patients with chestnut allergy with or without associated latex hypersensitivity present different patterns of major allergens (LTPs and class I chitinases, respectively). **CLINICAL IMPLICATIONS:** LTPs and class I chitinases can be used as diagnostic tools in patients with chestnut allergy to predict whether an associated latex sensitization and a risk of potential cross-reactivity with other plant foods and pollens exist.

### **Allergenic contribution of the IgE-reactive domains of the 1,3-beta-glucanase Ole e 9: diagnostic value in olive pollen allergy.**

Palomares O, Villalba M, Quiralte J, Rodríguez R.  
*Ann Allergy Asthma Immunol.* 2006 Jul;97(1):61-5.

**BACKGROUND:** Designing of methods for an accurate diagnosis is a main goal of allergy research. Olive pollen allergy is currently diagnosed using commercially available pollen extracts that do not allow identification of the molecules that elicit the disease. **OBJECTIVE:** To analyze the suitability of using the N- and C-terminal domains (NtD and CtD, respectively) of the 1,3-beta-glucanase Ole e 9, a major allergen from olive pollen, for in vitro diagnosis. **METHODS:** Serum samples from 55 olive-allergic patients were assayed using enzyme-linked immunosorbent assay to study hypersensitive patients with IgE reactivity to Ole e 9. The specific IgEs to NtD and CtD, obtained by recombinant technology, were determined by means of immunoblotting, enzyme-linked immunosorbent assay, and inhibition assays. **RESULTS:** Thirty-one of 33 serum samples from Ole e 9-allergic patients were IgE reactive to recombinant NtD (rNtD) (n = 26 [79%]), recombinant CtD (rCtD) (n = 22 [67%]), or both (n = 17 [52%]). Nine patients (27%) were exclusively reactive to rNtD and 5 (15%) to rCtD. Inhibition assays of IgE binding to Ole e 9 with a mixture of both domains abolished 90% of the binding, whereas 44% and 45% were abolished when rNtD and rCtD were used, respectively. **CONCLUSIONS:** Because sensitization to NtD or CtD of Ole e 9 could be correlated to vegetable food-latex-pollen cross-reactivity processes or to the exacerbation and persistence of asthma, respectively, these molecules could be used in vitro as markers of disease to classify patients and to design a patient-tailored immunotherapy approach.

### **Cross-reactive and species-specific immunoglobulin E epitopes of plant profilins: an experimental and structure-based analysis.**

Radauer C, Willeroider M, Fuchs H, Hoffmann-Sommergruber K, Thalhamer J, Ferreira F, Scheiner O, Breiteneder H.  
*Clin Exp Allergy.* 2006 Jul;36(7):920-9.

**BACKGROUND:** Profilins are cross-reactive plant allergens responsible for multiple pollen sensitization and pollen-associated food allergy. While it is assumed that profilins from different species are immunologically equivalent, some studies suggest partial or even lacking IgE cross-reactivity between certain profilins. **OBJECTIVE:** We aimed to obtain a

semi-quantitative assessment of the contributions of conserved and species-specific epitopes to IgE binding of plant profilins. **METHODS:** We compared model structures of profilins from timothy, mugwort, celery and bell pepper with crystal structures of birch and latex profilins. We predicted potential conformational epitopes that consisted of contiguous patches of at least 20% surface-exposed residues. Celery and timothy profilins were purified from their natural sources, and profilins from birch, mugwort, bell pepper and latex were expressed in *Escherichia coli*. The structural integrity of all purified proteins was confirmed by circular dichroism spectroscopy. IgE ELISAs and ELISA inhibitions using sera from 22 profilin-sensitized allergic patients were carried out. **RESULTS:** Peptide backbone conformations of all six profilins were highly similar. Nine variable epitopes and two containing high proportions of conserved residues were predicted. IgE from all sera bound to all tested profilins and the amounts were highly correlated. However, IgE inhibition experiments revealed that up to 60% of total IgE binding was mediated by species-specific epitopes. The extent of cross-reactivity among profilins from timothy, birch, latex and celery was greater than cross-reactivity to mugwort and bell pepper profilins. This pattern was mirrored by sequence similarities among one of the predicted variable epitopes. Patients with IgE to cross-reactive epitopes displayed allergic reactions to a greater number of plant foods than patients having IgE directed to species-specific epitopes. **CONCLUSION:** The large extent of cross-reactivity among plant profilins justifies using a single profilin for diagnosis. However, the fine specificity of IgE directed to variable epitopes may influence the clinical manifestation of profilin sensitization.

#### **Allergic memory of patients sensitized to castor bean after a long stimulation-free period.**

Marin V, Saraga J, Ariano R, Chouquet D, Dispard M, Bongrand P, Panzani RC.

*J Asthma*. 2006 Apr;43(3):193-8.

We have taken advantage of the temporary exposure of Marseilles population to castor bean seed proteins to follow 26 allergic patients more than 20 years after sensitization. Skin tests, specific immunoglobulin E (IgE) antibody assays, and specific immunoblots were performed. Skin test reactivity to *Ricinus Communis* and specific IgE concentrations decreased progressively and almost completely disappeared after 20 years. Specific IgE concentration displayed a fairly exponential decrease, with a half-life of 4.7 years. Thus, in the absence of any antigenic stimulation, directly by castor bean, or indirectly by cross-reactivity to other Euphorbiaceae, especially latex, IgE sensitization is bound to disappear.

#### **Crystal structure at 1.45-Å resolution of the major allergen endo-beta-1,3-glucanase of banana as a molecular basis for the latex-fruit syndrome.**

Receveur-Bréchet V, Czjzek M, Barre A, Roussel A, Peumans WJ, Van Damme EJ, Rougé P.

*Proteins*. 2006 Apr 1;63(1):235-42.

Resolution of the crystal structure of the banana fruit endo-beta-1,3-glucanase by synchrotron X-ray diffraction at 1.45-Å resolution revealed that the enzyme possesses the eightfold beta/alpha architecture typical for family 17 glycoside hydrolases. The electronegatively charged catalytic central cleft harbors the two glutamate residues (Glu94 and Glu236) acting as hydrogen donor and nucleophile residue, respectively. Modeling using a beta-1,3 linked glucan trisaccharide as a substrate confirmed that the enzyme readily accommodates a beta-1,3-glycosidic linkage in the slightly curved catalytic groove between the glucose units in positions -2 and -1 because of the particular orientation of residue Tyr33 delimiting subsite -2. The location of Phe177 in the proximity of subsite +1 suggested that the banana glucanase might also cleave beta-1,6-branched glucans. Enzymatic assays using pustulan as a substrate demonstrated that the banana glucanase can also cleave beta-1,6-glucans as was predicted from docking experiments. Similar to many other plant endo-beta-1,3-glucanases, the banana glucanase exhibits allergenic properties because of the occurrence of well-conserved IgE-binding epitopes on the surface of the enzyme. These epitopes might trigger some cross-reactions toward IgE antibodies and thus account for the IgE-binding cross-reactivity frequently reported in patients with the latex-fruit syndrome.

#### **[Four cases of pollen-food allergy syndrome suspected the cross reactivity including latex]**

Harada S, Yoshizaki Y, Kawasaki Y, Shimizu H.

*Alerugi*. 2005 Dec;54(12):1419-26.

[Article in Japanese]

**BACKGROUND:** Generally it is recognized that the occurrence of fruit allergy is attributed not to the sensitization of itself but to the cross reactivity with pollens or latex. But the relationship as to the sensitization between pollen and latex is obscure. So we aimed to investigate the relation of sensitization among pollens, fruits and latex. **METHODS:** We tried to

examine latex-specific IgE titer and practice skin prick test of latex for the patients of pollen-food allergy syndrome. RESULTS: It was confirmed that some patients of pollen-food allergy syndrome showed positive reactions against both specific IgE and skin prick test of latex, though they could tolerate latex products in their daily lives. We present here four patients of such clinical courses concretely. CONCLUSION: The patients of pollen-food allergy syndrome should be practiced examination about latex allergy, even if they can use latex products without any symptoms. And more if positive results are obtained, additional examination such as immunoblot and IgE RAST inhibition test are recommended to practice in order to clarify the unresolved problems, such as 1) which factor is the major allergen to cause cross-reactivity among these three factors? 2) what occurs if patients of same clinical courses with our cases continue to use latex products? Further investigation will be indispensable to resolve these problems in the future.

#### **Specific IgE response to purified and recombinant allergens in latex allergy.**

Kurup VP, Sussman GL, Yeang HY, Elms N, Breiteneder H, Arif SA, Kelly KJ, Bansal NK, Fink JN.

*Clin Mol Allergy*. 2005 Aug 10;3:11.;Print

BACKGROUND: In recent years, allergy to natural rubber latex has emerged as a major allergy among certain occupational groups and patients with underlying diseases. The sensitization and development of latex allergy has been attributed to exposure to products containing residual latex proteins. Although improved manufacturing procedures resulted in a considerable reduction of new cases, the potential risk for some patient groups is still great. In addition the prevalent cross-reactivity of latex proteins with other food allergens poses a major concern. A number of purified allergens and a few commercial kits are currently available, but no concerted effort was undertaken to evaluate them. METHODS: We studied 11 purified latex allergens, Hev b 1 to Hev b 10, and Hev b 13 along with several crude allergen extracts and two commercial ImmunoCAP assays to evaluate specific IgE antibody in the sera from latex allergic patients and controls. Health care workers and spina bifida patients with clinical symptoms of latex allergy, spina bifida patients without latex allergy, and non-atopic health care workers have been studied. RESULTS: The results suggest that Hev b 2, 5, 6, and 13 together identified over 80 percent health care workers with latex allergy, while Hev b 6 along with Hev b 1 or 3 detected specific IgE antibody in all sera studied from patients with spina bifida and latex allergy. The ImmunoCAP results using both Hev b 5 amplified and non-amplified closely agreed with the clinical diagnosis of latex allergy in health care workers and in spina bifida. CONCLUSION: Although the purified allergens and crude extracts reacted diversely with IgE from different patient groups, the results indicated that use of certain combinations of purified recombinant antigens will be useful in commercial kits or in in-house assays for detecting specific IgE antibody in the sera. The results suggest that a combination of Hev b 2, 3, 5, 6, and 13 together detected specific IgE in 80% of the sera from latex allergic patients. Both ImmunoCAPs correctly identified over 95% of latex allergic patients, however, showed reactivity with a few normal control subjects.

#### **IgE-reactive carbohydrate epitopes--classification, cross-reactivity, and clinical impact.**

Malandain H.

*Allerg Immunol (Paris)*. 2005 Apr;37(4):122-8.

A glycan-related IgE-reactivity has been demonstrated in most allergen sources, especially in plant kingdom. Recent progress in glycobiology has allowed a clearer classification of these glyco-epitopes. Unlike classical peptide chain-based epitopes, glyco-epitopes can share significant structural homologies beyond the limits of protein families. These glycoepitopes are thus prone to extensive cross-reactivity. They have been called Cross-reactive Carbohydrate Determinants or CCD. Many of these glyco-epitopes behave as "panepitopes", leading to cross-reactivity between products as distant as pollens and hymenoptera venoms. But CCD are not universally cross-reactive and they rather cluster into subgroups such as plant CCD or fungal CCD. Because a monovalent IgE-binding is sufficient in serum-based assays, glyco-epitopes and CCD are classically considered as a potential source of positive in vitro results without clinical significance. But some authors recently demonstrated that glyco-epitopes could induce a response at the cell level and suggested that they might play a role in vivo. As long as in vitro assays include glycan- and CCD-related IgE responses, laboratory results should be carefully interpreted in the light of existing knowledge about the glycomes of natural products. IgE-reactivity of the patient's serum can also be tested towards a glycoprotein model such as bromelain.

**1,3-beta-glucanases as candidates in latex-pollen-vegetable food cross-reactivity.**

Palomares O, Villalba M, Quiralte J, Polo F, Rodríguez R.  
*Clin Exp Allergy*. 2005 Mar;35(3):345-51.

**BACKGROUND:** 1,3-beta-glucanases (group 2 of pathogenesis-related proteins) are enzymes widely distributed among higher plants and have been recently proven to be significant allergens. **OBJECTIVE:** The aim of this work was to study the potential implication of 1,3-beta-glucanases in cross-reactivities among latex, pollen and vegetable foods. **METHODS:** The cDNA encoding the N-terminal domain (NtD) of Ole e 9, a major allergenic 1,3-beta-glucanase from olive pollen, was amplified by polymerase chain reaction and produced as a recombinant protein in *Pichia pastoris* (recombinant N-terminal domain, rNtD). Circular dichroism, ELISA, immunoblotting and immunoblotting inhibition experiments were carried out. Sera from olive pollen allergic patients and a rNtD-specific polyclonal antiserum were used. **RESULTS:** The NtD of Ole e 9 has been produced at high yield in the yeast *P. pastoris* and possesses 1,3-beta-glucanase activity. The expressed polypeptide conserves IgE and IgG immunodominant epitopes of the whole Ole e 9. A rNtD-specific polyclonal antiserum and sera from olive pollen allergic patients allowed detection of IgG and IgE reactive peptidic epitopes common to 1,3-beta-glucanase Ole e 9 in extracts from ash and birch pollen, tomato, potato, bell-pepper, banana and latex. **CONCLUSION:** rNtD and homologous glucanases are new molecules to be used in diagnostic protocols as they could help to identify allergic pollen patients who are at risk for developing allergic symptoms to fruits, vegetables and latex.

**Latex and chickpea (*Cicer arietinum*) allergy: first description of a new association.**

Branco Ferreira M, Pedro E, Meneses Santos J, Pereira dos Santos MC, Palma Carlos ML, Bartolomé B, Palma Carlos AG.  
*Allerg Immunol (Paris)*. 2004 Dec;36(10):366-71.

In this paper we describe the existence of cross-reactivity between allergens from latex and chickpea, a food from the Leguminosae family, which is common in the Mediterranean diet. We present the case report of a spina bifida boy with a clinical relevant food allergy to chickpea (oral syndrome + dysphonia), developing after the appearance of latex allergy symptoms (lip angioedema + intraoperative anaphylaxis). Specific IgE to latex and chickpea was demonstrated by skin prick tests, measurement of patient's serum specific IgE and IgE-immunoblotting. Cross-reactivity was studied by means of EAST-inhibition and western blotting-inhibition. A strong inhibition was observed in several IgE-binding bands when latex extract was used in solid phase and patient serum was preincubated with chickpea extract (chickpea extract as inhibitor phase). As far as we know, this is the first report of cross-reactivity between latex and chickpea, a food which should therefore be added to the extensive list of latex cross-reactive foods.

**Characterization of cross-reactive bell pepper allergens involved in the latex-fruit syndrome.**

Wagner S, Radauer C, Hafner C, Fuchs H, Jensen-Jarolim E, Wüthrich B, Scheiner O, Breiteneder H.  
*Clin Exp Allergy*. 2004 Nov;34(11):1739-46.

**BACKGROUND:** Between 30% and 50% of individuals who are allergic to latex products are also allergic to specific plant foods, a fact that is well documented as the latex-fruit syndrome. Simultaneous sensitization to latex and bell pepper has been previously reported. Although bell pepper fruits are frequently consumed raw, cooked or as a spice, little is known about the cross-reactive allergens. **OBJECTIVE:** In this study we wished to identify bell pepper allergens involved in the latex-fruit syndrome. **METHODS:** Sera of four patients who displayed clinical symptoms to latex and bell pepper were used in immunoblot studies on protein extracts of three different cultivars of fresh bell pepper and fresh *Hevea* latex. Cross-reactive allergens were identified by inhibition experiments using recombinant Hev b 8 (latex profilin), and natural Hev b 2 (latex beta-1,3-glucanase) in addition to the protein extracts. A novel cross-reactive IgE-reactive 30 kDa protein was subjected to sequence analysis. **RESULTS:** Three patients displayed IgE to profilins from bell pepper fruits and latex. Two patients possessed IgE to Hev b 2, a latex beta-1,3-glucanase, and a homologous protein in bell pepper. One patient possessed IgE reactive with a protein of 30 kDa identified by N-terminal sequencing as an l-ascorbate peroxidase and another patient to a protein of 38 kDa. Additionally, IgE binding proteins in two higher molecular weight ranges showed cross-reactive capacities. **CONCLUSION:** Our findings show on the molecular level that bell pepper is part of the latex-fruit syndrome. For the first time we have identified the major latex allergen Hev b 2, a beta-1,3-glucanase, and the bell pepper l-ascorbate peroxidase as cross-reactive allergens. We were also able to show that profilins are responsible for some of the IgE cross-reactivity.

**Sensitization to *Ficus benjamina*: relationship to natural rubber latex allergy and identification of foods implicated in the Ficus-fruit syndrome.**

Hemmer W, Focke M, Götz M, Jarisch R.  
*Clin Exp Allergy*. 2004 Aug;34(8):1251-8.

**BACKGROUND:** Ornamental *Ficus benjamina* (FB) has been recognized as a new indoor allergen. Little is known about the prevalence in moderately exposed subjects and the proposed association with fruit and Hevea latex hypersensitivity. **OBJECTIVE:** To study the prevalence of FB sensitization and the relationship with Hevea latex allergy, to identify cross-reacting fruits, and to characterize the responsible allergens. **METHODS:** A skin prick test solution prepared from FB latex (200 microg/mL) was included in our routine screening programme for suspect inhalant allergy. Patients reacting with the FB extract were further skin tested with exotic fruits by the prick-to-prick method. Inhibition of fig and FB CAP by FB latex, fig (*Ficus carica*), kiwi, the thiolproteases ficin and papain, Hevea latex and rHev b 6.02 (hevein) was performed in selected patients. **RESULTS:** Of 2662 patients with a positive skin test to any aeroallergen, 66 (2.5%) reacted with FB. Ten patients showed isolated sensitization to FB. Although FB-positive subjects were more often co-sensitized to Hevea latex than FB-negative (10.6% vs 3.8%,  $P < 0.01$ ), nearly 90% tested negative for Hevea latex. Sensitization to FB was specifically associated with positive skin tests to fresh fig (83%), dried fig (37%), kiwi fruit (28%), papaya (22%), avocado (19%), banana (15%), and pineapple (10%) ( $n = 54$ ). Clinical reactions were reported mainly from fresh and dried fig and kiwi (47%, 60%, and 64%, respectively, of skin test-positive patients), including seven patients with systemic reactions (urticaria, angioedema, asthma). CAP to fig in 11 patients with clinical fruit allergy was inhibited on average by 87% by FB latex, 89% by fresh fig, 80% by dried fig, 38% by kiwi (100 microg/mL each), and by 59% and 44% by ficin and papain (50 microg/mL), respectively. No inhibition was obtained with Hevea latex and rHev b 6.02. CAP to FB was inhibited on average by 95% by FB, 60% by fresh fig, 41% by ficin, 29% by papain, and less than 7% by rubber latex allergens. **CONCLUSIONS:** Sensitization to FB latex is found in 2.5% of atopic individuals and mostly occurs independently of Hevea latex allergy. Sensitization is commonly associated with allergic reactions to figs and other tropical fruits ('Ficus-fruit syndrome'). This cross-reactivity is mediated at least in part by thiolproteases.

**A major allergen from pollen defines a novel family of plant proteins and shows intra- and interspecies [correction of interspecie] cross-reactivity.**

Barral P, Batanero E, Palomares O, Quirarte J, Villalba M, Rodríguez R.  
*J Immunol*. 2004 Mar 15;172(6):3644-51.

Olive tree (*Olea europaea*) pollen is a main cause of allergy associated with extensive areas of Europe and North America. Ole e 10, a small (10.8 kDa) and acidic (pI 5.8) protein, has been identified as a major allergen from the olive pollen, isolated, and characterized. Circular dichroism analysis gave 17% alpha helix, 33% beta sheet, and 21% beta turn for its secondary structure. Based on amino acid sequences of tryptic peptides, the protein was cloned and sequenced. The allergen consists of a single polypeptide chain of 102 aa, with a signal peptide of 21 residues. Ole e 10 showed homology with the C-terminal domain of another olive allergen, Ole e 9 (1,3-beta-glucanase, 53% identity), with deduced sequences from *Arabidopsis thaliana* genes (42-46% identity) and with polypeptide segments (Cys boxes) of proteins involved in yeast development (Epd1/Gas-1p/Phr2 families; 42-43% similarity). Ole e 10 showed 55% prevalence for olive-allergic patients and exhibited an IgE response dependent on its conformation. Remarkable IgE cross-reactivity was detected with Ole e 9, but no correlation was observed between the individual IgE responses to both allergens. Ole e 10 shares IgE B cell epitopes with proteins from Oleaceae, Gramineae, Betulaceae, Chenopodiaceae, Cupressaceae, Ambrosia, and Parietaria pollens, latex, and vegetable foods, such as tomato, kiwi, potato, and peach. These data indicate that Ole e 10 is a new pan-allergenic plant protein that shows notable intra- and interspecies IgE cross-reactivity and is a powerful candidate to be involved in pollen-latex-fruit syndrome.

**Allergenic components of Indian jujube (*Zizyphus mauritiana*) show IgE cross-reactivity with latex allergen.**

Lee MF, Chen YH, Lan JL, Tseng CY, Wu CH.  
*Int Arch Allergy Immunol*. 2004 Mar;133(3):211-6. Epub 2004 Feb 16.

**BACKGROUND:** 'Latex-fruit syndrome' has been well documented. A prevalence of latex allergy among medical workers of 6.8-8.6% had been reported in Taiwan. However, there has been no study to determine the importance and type of fruit hypersensitivity in latex-allergic patients in Taiwan. This study aimed to identify the allergenic components of Indian jujube (*Zizyphus mauritiana*) and characterize the cross-reactivity of specific IgE antibodies to latex allergen. **METHODS:** Crude extracts were prepared from Indian jujube and from ammoniated natural rubber latex, and six medical workers and one

patient with a history of fruit allergy underwent skin testing with routine allergens, latex, Indian jujube and other fruits. Sera from two Indian jujube skin test-positive latex-allergic subjects were used for allergen-specific IgE, immunoblotting, immunoblot inhibition and enzyme-linked immunosorbent assay (ELISA) inhibition studies. RESULTS: Both patients had positive skin test responses and specific IgE assays to Indian jujube and latex extracts. Immunoblotting revealed that IgE from both subjects bound to a 42-kD latex protein and a 42-kD Indian jujube protein. In addition, IgE from one subject bound to a 30-kD Indian jujube protein. Preincubation of atopic sera with Indian jujube or latex extract demonstrated absent and/or marked inhibition of IgE binding. Moreover, anti-Indian jujube protein antibody-based ELISA was able to detect latex extracts. CONCLUSIONS: Our results add to findings regarding the 'latex-fruit syndrome' described in the literature, and further study of the cross-reacting allergens identified in Indian jujube may help to elucidate the mechanisms underlying this syndrome.

**The prevalence and diagnostic value of specific IgE antibodies to inhalant, animal and plant food, and ficus allergens in patients with natural rubber latex allergy.**

Ebo DG, Bridts CH, Hagendorens MM, De Clerck LS, Stevens WJ.

*Acta Clin Belg.* 2003 May-Jun;58(3):183-9.

BACKGROUND: It is well recognised that natural rubber latex allergy can be associated with serological cross-reactivity to plant allergens, especially tropical fruits and Ficus. In contrast, data on the frequency and clinical value of specific IgE antibodies against these allergens remain rare. In addition, little is known about the prevalence and diagnostic value of specific IgE antibodies to classical inhalant and animal allergens in NRL allergic patients. OBJECTIVE: The purpose of this study was to investigate the prevalence, the sensitivity, and the specificity of these different specific IgE antibodies in patients suffering from NRL allergy. METHODS: Serum samples of 42 NRL allergic adults were investigated. All had a history of NRL allergy confirmed by a positive skin test for latex and a positive latex-specific IgE. Samples were analysed for IgE antibodies against 9 plant food allergens (avocado, banana, chestnut, fig, kiwi, papaya, peanut, pineapple and tomato) and Ficus benjamina. A specific IgE quantification for 3 animal food allergens (codfish, cow's milk, egg's white) and 8 common inhalant allergens (Dermatophagoides pteronyssinus, birch pollen, timothy grass pollen, mugwort pollen, cat and dog epithelium, Aspergillus fumigatus and Cladosporium herbarum) was also performed. Because double blind placebo-controlled challenges could not be considered, for ethical reasons, patient's food allergy or immediate hypersensitivity for Ficus and inhalant allergens was documented by a standardised questionnaire. Diagnosis of atopy was based on a relevant history and the presence of a specific IgE antibody to at least one classical inhalant allergen. For some IgE determinations presence or absence of cross-reactivity was investigated by CAP-inhibition tests. RESULTS: A specific IgE antibody to at least one of the investigated inhalant and animal food allergens was found in respectively 76% and 12% of the serum samples. A plant food-specific IgE antibody was observed in 88% of the serum samples, most frequently to papaya (71%) and least frequently to kiwi (17%). Twenty-nine percent of the serum samples contained Ficus-IgE. According to the questionnaire and the threshold of 0.35 kUa/L, sensitivity of the plant food IgE antibodies varied between 0% for papaya and 73% for avocado. Specificity varied between 28% for papaya and 91% for kiwi. For Ficus-IgE sensitivity was 20% and specificity 70%. CONCLUSIONS: For inhalant and animal food allergens sensitivity and specificity of the IgE quantification correlated generally well with the values obtained in non-NRL allergic adults. Determination of specific IgE to the investigated plant foods and Ficus was not always a sensitive neither a specific test to establish the clinical diagnosis of this allergy.

**Detection of clinical markers of sensitization to profilin in patients allergic to plant-derived foods.**

Asero R, Mistrello G, Roncarolo D, Amato S, Zanoni D, Barocci F, Caldironi G.

*J Allergy Clin Immunol.* 2003 Aug;112(2):427-32.

BACKGROUND: A proper classification of patients allergic to plant-derived foods is of pivotal importance because the clinical features of allergic reactions to fruits and vegetables depend on the nature and characteristics of proteins responsible for sensitization. However, in normal clinical settings this is presently impossible. OBJECTIVE: We sought to detect clinical markers of sensitization to profilin. METHODS: Seventy-one patients allergic to fruits and vegetables but not sensitized to lipid transfer protein or natural rubber latex were studied. Food allergy was ascertained on the basis of clinical history and positive skin prick test responses with fresh foods, commercial extracts, or both. Allergies to foods that had caused less than 2 adverse reactions were confirmed by means of open oral challenge. IgE reactivity to rBet v 1/rBet v 2 and to natural Phleum species profilin were detected. Moreover, IgE to the 30- to 40-kd and 60- to 90-kd birch pollen-enriched fractions, which also can be involved in cross-reactivity phenomena, were measured in sera from 52 patients by means of ELISA. RESULTS: On the basis of in vitro tests, 24, 18, and 25 patients turned out to be sensitized to Bet v 1, Bet v 2, or both,

respectively. Four patients had negative test results for both allergens. Hypersensitivity to Bet v 2 was strongly associated with clinical allergy to citrus fruits (39% in patients monosensitized to Bet v 2 vs 4% in patients monosensitized to Bet v 1,  $P < .025$ ), melon or watermelon (67% vs 0%,  $P < .001$ ), banana (66% vs 8%,  $P < .001$ ), and tomato (33% vs 0%,  $P < .05$ ), whereas Bet v 1 sensitivity was associated with clinical allergy to apple (100% vs 39%,  $P < .001$ ) and hazelnut (56% vs 0%,  $P < .001$ ). The sensitivity of a history of allergy to gourd fruits, citrus fruits, tomato, banana, or a combination thereof as a means to detect profilin-hypersensitive patients was 85% (41/48). The specificity of an allergy to any of these fruits exceeded 85%, with positive predictive values ranging between 68% and 91%. **CONCLUSION:** In clinical settings in which laboratory investigations are not easily accessible, allergy to melon, watermelon, citrus fruits, tomato, and banana can be used as a marker of profilin hypersensitivity once a sensitization to natural rubber latex and lipid transfer protein is ruled out.

#### **Latex-fruit syndrome.**

Blanco C.

*Curr Allergy Asthma Rep.* 2003 Jan;3(1):47-53.

Natural rubber latex immunoglobulin E-mediated hypersensitivity is probably one of the most relevant challenges that has been faced in the treatment of allergies during recent years. Additionally, allergen cross-reactivity has arisen as another very important problem, in the difficulty in diagnosing it and in its clinical implications. It is clear that some latex allergens cross-react with plant-derived food allergens, the so-called latex-fruit syndrome, with evident clinical consequences. Although the foods most frequently involved are banana, avocado, kiwi, and chestnut, several others are also implicated. Investigations point to a group of defense-related plant proteins, class I chitinases, which cross-react with a major latex allergen, hevein, as the panallergens responsible for the syndrome. This review focuses on our current understanding of the latex-fruit syndrome.

#### **Evaluation of patatin as a major cross-reactive allergen in latex-induced potato allergy.**

Schmidt MH, Raulf-Heimsoth M, Posch A.

*Ann Allergy Asthma Immunol.* 2002 Dec;89(6):613-8.

**BACKGROUND:** Potential cross-reactions between natural rubber latex and fruit/vegetable specific immunoglobulin (IgE) antibodies have been reported for many years. This study was designed to investigate the molecular basis of acquired food sensitization focusing on the storage protein patatin and the patatin-like latex protein Hev b 7. **OBJECTIVE:** The amount of potato-specific IgE in the serum of latex-allergic health care workers and children with atopic dermatitis was determined to evaluate cross-reactivity between Hev b 7 and patatin. Additionally, the stability of potato patatin to digestion was investigated. **METHODS:** Human serum was tested on its reactivity to latex and potato proteins by IgE immunoblotting after one-dimensional (1-D) and 2-D electrophoresis. Latex- and potato-specific IgE concentrations were measured in fluorescence enzyme immunoassays (CAP, Pharmacia, Uppsala, Sweden). Further, potato patatin was chromatographically isolated to perform auto-inhibition tests. Stability of patatin to degradation was determined by digestion *in vitro*. **RESULTS:** Patatin was identified as major cross-reactive potato allergen by N-terminal sequencing. Seventy-five percent of the potato-sensitized people reacted with patatin in 1-D immunoblots, and 25% of the positive reactions to Hev b 7 could be blocked by preincubation of the patients' sera with purified potato patatin. Examination of children with atopic dermatitis showed that most sera contained patatin-specific IgE, whereas no Hev b 7-specific IgE was detected. Finally, patatin has been found partially stable to digestion *in vitro*. **CONCLUSIONS:** Patatin was identified as a major cross-reactive protein in latex-associated potato allergy and appears to be relevant for atopic dermatitis. Therefore, patatin could be a suitable marker for the determination of potato sensitization, and it may also constitute an important food allergen. Cross-reactivity between Hev b 7 and patatin was restricted to primarily latex-sensitized adults, suggesting a different mechanism of sensitization in children with atopic dermatitis.

#### **The latex-fruit syndrome.**

Wagner S, Breiteneder H.

*Biochem Soc Trans.* 2002 Nov;30(Pt 6):935-40.

Approximately 30-50% of individuals who are allergic to natural rubber latex (NRL) show an associated hypersensitivity to some plant-derived foods, especially freshly consumed fruits. This association of latex allergy and allergy to plant-derived foods is called latex-fruit syndrome. An increasing number of plant sources, such as avocado, banana, chestnut, kiwi, peach, tomato, potato and bell pepper, have been associated with this syndrome. The prevailing hypothesis is that allergen cross-

reactivity is due to IgE antibodies that recognize structurally similar epitopes on different proteins that are phylogenetically closely related or represent evolutionarily conserved structures. Several types of proteins have been identified to be involved in the latex-fruit syndrome. Two of these are plant defence proteins. Class I chitinases containing an N-terminal hevein-like domain cross-react with hevein (Hev b 6.02), a major IgE-binding allergen for patients allergic to NRL. A beta-1,3-glucanase was identified as an important latex allergen which shows cross-reactivity with proteins of bell pepper. Another important NRL allergen, Hev b 7, is a patatin-like protein that shows cross-reactivity with its analogous protein in potato. Furthermore, patients with allergy to plant-derived foods and associated pollinosis show a high frequency of IgE reactivity to the pan-allergen profilin, which may cause positive serum IgE determinations to NRL. Although there is much information about the plant-derived foods and some data about the allergens involved in the latex-fruit syndrome, it is not always clear whether latex sensitization precedes or follows the onset of food allergy.

**Allergies to cross-reactive plant proteins. Latex-fruit syndrome is comparable with pollen-food allergy syndrome.**

Yagami T.

*Int Arch Allergy Immunol.* 2002 Aug;128(4):271-9.

Both latex-fruit syndrome and oral allergy syndrome concomitant with pollinosis (pollen-food allergy syndrome) are considered to be caused by cross-reactivity between sensitizers and symptom elicitors. The cross-reactive food allergens relevant to these syndromes are mostly sensitive to heat and digestive enzymes. Such a vulnerable antigen cannot sensitize people perorally but provokes allergic reactions in already sensitized patients based on its cross-reactivity to the corresponding sensitizer. These types of food allergens are often called incomplete food allergens or nonsensitizing elicitors. Their features contrast with those of complete food allergens that have the capacity for peroral sensitization as well as symptom elicitation. Although highly antigenic and cross-reactive, carbohydrate epitopes do not generally elicit allergic reactions and often disturb in vitro IgE tests. Recent research has revealed that some of the cross-reactive allergens responsible for the two syndromes are proteins related to the defense responses of higher plants. Plant defense-related proteins are relatively conserved in the course of evolution and can supply cross-reactive epitopes. It is important to note that various stresses can stimulate the expression of these proteins, which implies that allergens increase in plants under stressful conditions like severe growing situations and exposure to some kinds of chemicals. Because defense-related proteins usually provide a plant with resistance to stresses, varieties that are apt to intensively induce such proteins are agriculturally valuable. Less toxic substances that cause crops to express defensive proteins are being investigated as a new type of agrochemical. Moreover, some defense-related proteins are going to be constantly produced in genetically modified plants. Even though these proteins can be useful agriculturally, their allergenicity should be evaluated carefully.

**[Prevalence of latex-fruit syndrome in health workers with latex allergy]**

Ramírez Cruz NE, Castrejón Vázquez MI, Espinoza Goldman MB, Martínez-Cairo Cueto S.

*Rev Alerg Mex.* 2002 Mar-Apr;49(2):46-51.

[Article in Spanish]

**BACKGROUND:** Prevalence of latex allergy in the general population is lesser than 1%. These patients have clinical and immunochemical cross-reactivity between latex and fruits; sometimes this has been referred to as the "latex-fruit-syndrome" (LFS); atopy was found to be a risk factor to sensitization to fruits. **OBJECTIVE:** To investigate the prevalence of LFS, in a group of health care workers with latex-allergy. **METHODS:** Hospital employees were initially screened for latex allergy with a questionnaire; these patients were divided into the following two groups: 1) health care workers with latex-allergy, classified into two subgroups: a) with a familial history of atopy; b) without a familial history of atopy, and 2) health care workers with familial history of atopy but without latex-allergy. Skin prick tests with latex and fruits extracts (kiwi, avocado, banana and chestnut) were done. **RESULTS:** Based in clinical history and with confirmation by skin testing, three patients of the health care workers' group with latex allergy have LFS (prevalence of 12.5%). Sensitivity and specificity for skin prick test in health care workers with latex-fruit syndrome were: latex, kiwi and chestnut sensitivity: 100%; latex and avocado specificity: 90%; chestnut and kiwi specificity: 100%. **CONCLUSION:** A low prevalence of latex-fruit syndrome was detected in our population. We found a higher prevalence in females with a history of atopy. Our findings were consistent with other literature reports.

**Latex allergy: historical perspective.**

Sussman GL, Beezhold DH, Liss G.

*Methods.* 2002 May;27(1):3-9.

The widespread use of powdered latex gloves, following the institution of universal precautions in 1987, increased the occurrence of a host of adverse reactions to natural rubber latex (NRL). Although the most common reactions are irritant or allergic dermatitis reactions to manufacturing chemicals, a spectrum of type I IgE-mediated reactions to NRL proteins are of great concern. IgE-mediated reactions range from contact urticaria to occupational asthma and anaphylaxis, resulting in significant morbidity and potential mortality. At-risk populations include highly exposed groups like health care workers and certain patient groups requiring extensive medical treatment. A significant complicating factor is the association with clinically significant adverse reactions to certain foods because of allergen cross-reactivity. Institution of policies to use only low-protein, powder-free gloves, has resulted in a dramatic reduction of visits to occupational health departments and workmen's compensation claims due to occupational asthma.

**IgE reactivity to profilin in pollen-sensitized subjects with adverse reactions to banana and pineapple.**

Reindl J, Rihs HP, Scheurer S, Wangorsch A, Hausteiner D, Vieths S.

*Int Arch Allergy Immunol.* 2002 Jun;128(2):105-14.

**BACKGROUND:** The so-called 'latex-fruit syndrome' is a well-documented phenomenon in cross-reactive allergies. By contrast, there is a lack of information about allergy to exotic fruits in patients with a predominant pollen sensitization. Since the ubiquitous protein profilin has been identified as an allergen in natural rubber latex as well as in pollen-related foods, the aim of this study was to investigate the role of profilin in allergy to certain exotic fruits. **METHODS:** Recombinant profilins from banana and pineapple were cloned by a PCR technique after isolation of total RNA using degenerated profilin-specific primers. The unknown 5' ends of copy DNA (cDNA) were identified by rapid amplification of 5'cDNA ends (5'-RACE) and expression in *Escherichia coli* BL21(DE3) cells. The recombinant profilins were purified by affinity chromatography using poly-(L)-proline as the solid phase. IgE-binding capabilities were characterized by means of immunoblot and Enzyme Allergosorbent Test (EAST). The cross-reactivity to birch pollen profilin and latex profilin was studied by EAST as well as by immunoblot inhibition experiments. **RESULTS:** Both banana and pineapple profilin were found to consist of 131 amino acid residues with high amino acid sequence identity to known allergenic pollen and food profilins (71-84%). IgE binding to the recombinant profilins was observed in 7/16 sera from subjects with suspected banana allergy (44%) and in 8/19 sera from subjects with suspected pineapple allergy (42%). Inhibition experiments indicated similar IgE reactivity of natural and recombinant allergens. In addition, high cross-reactivity to birch pollen profilin Bet v 2 and latex profilin Hev b 8 was demonstrated by immunoblot inhibition as well as EAST inhibition experiments. **CONCLUSIONS:** Since a high IgE-binding prevalence of about 40% was obtained in both banana and pineapple allergy, we conclude that profilin is an important mediator of IgE cross-reactivity between pollen and exotic fruits.

**Allergen cross-reactivity between proteins of the latex from *Hevea brasiliensis*, seeds and pollen of *Ricinus communis*, and pollen of *Mercurialis annua*, members of the Euphorbiaceae family.**

Palosuo T, Panzani RC, Singh AB, Ariano R, Alenius H, Turjanmaa K.

*Allergy Asthma Proc.* 2002 Mar-Apr;23(2):141-7.

Allergen cross-reactions among three strongly sensitizing Euphorbiaceae species, i.e., the rubber tree (*Hevea brasiliensis*), castor bean (*Ricinus communis*), and the Mediterranean weed *Mercurialis annua* were studied in Finnish patients (n = 25) allergic to natural rubber latex (NRL), but with no known exposure to castor bean or *M. annua*, and French patients allergic to castor bean (n = 26) or to *M. annua* (n = 9), but not to NRL. In immunoglobulin E (IgE)-immunoblotting, 28% of NRL-allergic patient sera recognized castor bean seed and 48% reacted to castor bean pollen proteins. Likewise, 35% of the NRL-allergic patient sera bound to *M. annua* pollen allergens. Nineteen percent of castor bean-allergic patients showed IgE to NRL and 8% to *M. annua* proteins. Sera from patients allergic to *M. annua* reacted in 44% to NRL, in 56% to castor bean seed, and in 78% to castor bean pollen proteins. In immunoblotting, castor bean seed extract inhibited the binding of NRL-reactive IgE to 20 kDa, 30 kDa of NRL, and 55 kDa of proteins; NRL extract, in turn, inhibited the binding of castor bean-reactive IgE to 14, 21-22, 29, and 32-34 kDa of castor bean proteins. In ELISA inhibition, NRL extract inhibited 33% of the binding of *M. annua*-reactive IgE of pooled sera to *M. annua* pollen. In conclusion, allergen cross-reactivity *in vitro* was observed among three botanically related Euphorbiaceae members, *H. brasiliensis*, *R. communis*, and *M. annua*, but the molecular specificity of the observed cross-reactions as well as their clinical significance remains to be elucidated. Allergen cross-reactivity should be taken into account in diagnostic work.

**Anaphylactic reaction to lychee in a 12-year-old girl: cross-reactivity to latex?**

Niggemann B, Reibel S, Hipler C, Wahn U.

*Pediatr Allergy Immunol.* 2002 Feb;13(1):64-7.

There are very few case reports on allergic reactions to lychee in the literature - so far only in adults. We report on a 12-year-old girl who developed swelling of lips, pruritus, generalized urticaria and dyspnea 30 min after eating a raw lychee. A second event occurred after eating a piece of cake covered with a fruit cocktail. All other foods were well tolerated. In infancy the girl had suffered from atopic dermatitis, which disappeared in childhood; for the previous 2 yr she had presented with seasonal allergic rhinoconjunctivitis. Upon oral provocation, she developed restlessness, flush, generalized urticaria and inspiratory stridor 50 min after eating half a lychee. The diagnostic work up showed a clear positive skin prick test to raw lychee and specific immunoglobulin E (IgE) in serum to latex but not to lychee. In the cellular antigen stimulation test (CAST) carried out with lychee extracts in several concentrations, the same positive results could be found confirming an allergic reaction. Cross-reactivity of lychee to latex was shown by inhibition experiments using the UniCAP 100-system. In conclusion, it seems worthwhile considering the rare allergy to lychee in the case of unclear food-allergic reactions and lychee should be added to the list of foods cross-reacting with latex.

**Cloning and molecular characterization of the Hevea brasiliensis allergen Hev b 11, a class I chitinase.**

O'Riordain G, Radauer C, Hoffmann-Sommergruber K, Adhami F, Peterbauer CK, Blanco C, Godnic-Cvar J, Scheiner O, Ebner C, Breiteneder H.

*Clin Exp Allergy.* 2002 Mar;32(3):455-62.

**BACKGROUND:** In the last 10 years type-I allergy against proteins from *Hevea brasiliensis* latex has become an acknowledged medical issue. Fruit-allergic patients represent one risk group for developing latex allergy. Class I chitinases have been identified from chestnut, avocado and banana as relevant allergens. The chitin binding (hevein) domain from these class I chitinases has been postulated to bear the important IgE binding epitopes. **OBJECTIVE:** To clone the cDNA of an allergenic latex class I chitinase, to express the recombinant protein and to determine its IgE cross-reactivity with hevein (Hev b 6.02). **METHODS:** A full-length cDNA coding for a class I chitinase has been isolated from *Hevea* latex RNA by reverse transcription followed by PCR. The chitinase encoding sequence has been subcloned into the pMAL expression vector and expressed in *E. coli* as a fusion protein to maltose binding protein. The highly enriched recombinant protein fraction has been tested for its IgE binding capacity in immunoblots and ELISA. Furthermore, the pathogenesis-related function of the recombinant protein was tested in a fungal growth inhibition assay. **RESULTS:** The *Hevea brasiliensis* latex chitinase, designated Hev b 11, displays 70% identity to the endochitinase from avocado and its hevein-domain 58% to hevein (Hev b 6.02). The recombinant Hev b 11-maltose binding protein is recognized by latex- and fruit-allergic patients with IgE binding in both, ELISA and immunoblots. Pre-incubation of sera with rHev b 11-maltose binding protein showed an overall 16% inhibition of subsequent binding to rHev b 6.02-maltose binding protein on solid phase. The growth of *F. oxysporum* was inhibited in a dose dependent manner by addition of rHev b 11-maltose binding protein to the culture. **CONCLUSIONS:** Hev b 11, a class I chitinase, is another allergen from *Hevea* latex with a chitin binding domain and displays a different IgE binding capacity compared with hevein.

**Tomato allergy in children and young adults: cross-reactivity with latex and potato.**

Reche M, Pascual CY, Vicente J, Caballero T, Martín-Muñoz F, Sanchez S, Martín-Esteban M.

*Allergy.* 2001 Dec;56(12):1197-201.

**BACKGROUND:** Several studies have shown that allergy to natural rubber latex is associated with cross-reactivity to certain foods such as tomato and potato. The objective was to investigate the clinical and immunologic differences between a group of patients with clinical allergy to tomato and latex and another which had only clinical allergy to tomato. We also aimed to assess, in vitro, the relationship of tomato and latex allergens, which could explain the cross-reactivity. **METHODS:** Forty patients with histories of adverse reactions to tomato and IgE-mediated hypersensitivity were enrolled in the study. Tomato, latex, and potato components were analyzed by SDS-PAGE immunoblotting. CAP and immunoblot inhibition were used to study allergen cross-reactivity. **RESULTS:** Patients from group A had a mean age of 13.2 years, and in group B the mean age was 21.7 years. In group B, 9/10 patients belonged to the latex-fruits syndrome. All patients of both groups tolerated potato. Immunoblotting patterns obtained with patients' sera from pool A showed IgE-binding bands to tomato ranging from 44 to 46 kDa and a triple band at 67 kDa. For latex, there was a strong binding at 44 kDa, and potato showed a strong band of 44 kDa and a 67-kDa triple band. In pool B, the binding to the band of 44 kDa in latex and tomato was more intense than in pool A.

In pool A, immunoblot inhibition with potato allergen showed an intense inhibition of the three allergens (potato, latex, and tomato); with latex, inhibition was partial and with tomato, a complete inhibition of tomato and latex was observed, and a partial inhibition of potato. In pool B, the inhibition pattern followed a similar tendency to pool A. The CAP inhibition confirmed the high rate of cross-reactivity between tomato, potato, and latex. CONCLUSIONS: In our study, tomato, potato, and latex showed a common band of 44-46 kDa probably corresponding to patatin. This protein could be implicated in the high cross-reactivity between tomato, latex, and potato observed in the immunoblot and CAP inhibition.

#### [Latex allergy. Diagnosis and therapeutic aspects]

Sánchez Palacios A.

*Allergol Immunopathol (Madr)*. 2001 Sep-Oct;29(5):212-21.

[Article in Spanish]

In the last two decades of the 20th century, latex allergy has reached epidemic proportions. Epidemiological studies demonstrate that 3-25 % of health personnel is allergic to latex. The main risk groups are health workers, machine operators in latex factories, and children with spina bifida and urogenital anomalies. From the allergenic point of view, latex contains 240 peptides but approximately 50 are able to react to IgE. Latex elongation factor Hevdl is the relevant allergen in patients with spina bifida. Prohevein (hev B6) behaves as a major allergen, since it reacts to IgE in most of the sera of patients with latex allergy. The nature of latex is complex; it is an allergenic mixture that depends on chemical, immunological and epidemiological variables. Latex proteins show strong cross reactivity with several proteins from fruit and vegetable grains such as avocado, potato, banana, tomato, chestnut, and kiwi. In vivo studies have shown that class I chitinase from avocado and chestnut behave as major allergens in allergic patients with latex-fruit syndrome. The clinical manifestations related to the use of latex products depend on the type of exposure, the amount of the allergen, and individual variability. The most useful diagnostic method is the skin prick test. Several perioperative guidelines are recommended in patients sensitized to latex as well as various alternatives to rubber gloves. An increasing number of studies describe the efficacy of etiological treatment (immunotherapy), using different guidelines and routes of administration. These preliminary data encourage the hope that in the near future immunomodulatory therapy will be available to mitigate against the latex allergy epidemic.

#### **Hev b 8, the *Hevea brasiliensis* latex profilin, is a cross-reactive allergen of latex, plant foods and pollen.**

Ganglberger E, Radauer C, Wagner S, Ríordáin G, Beezhold DH, Brehler R, Niggemann B, Scheiner O, Jensen-Jarolim E, Breiteneder H.

*Int Arch Allergy Immunol*. 2001 Jul;125(3):216-27.

**BACKGROUND:** Plant profilins are important pan-allergens. They are responsible for a significant percentage of pollen-related allergies. Limited information is available about their involvement in the latex-fruit syndrome and the cross-reactivities between latex and pollen. We aimed to clone and express the *Hevea brasiliensis* latex profilin to investigate its allergological significance and serological cross-reactivities to profilins from plant foods and pollens. **METHODS:** A DNA complementary to messenger RNA (cDNA) coding for the *Hevea* latex profilin, Hev b 8, was amplified by polymerase chain reaction from latex RNA. Recombinant (r)Hev b 8 was produced in *Escherichia coli* and used to screen sera from 50 latex-allergic health care workers (HCWs) with well-documented histories of food and pollen allergy and 34 latex-allergic spina bifida (SB) patients. The cross-reactivity of natural Hev b 8 and rHev b 8 with other plant profilins was determined by ELISA inhibition assays. A three-dimensional homology model of Hev b 8 was constructed based on known profilin structures. **RESULTS:** The cDNA of Hev b 8 encoded a protein of 131 amino acids with a predicted molecular mass of 14 kD. Twelve of the 50 HCWs and 2 of the 34 SB patients were sensitized to Hev b 8. All Hev b 8-sensitized patients showed allergic symptoms to pollen or plant foods. Cross-reactivities between profilins of latex, pollen and plant food were illustrated by their ability to inhibit IgE binding to rHev b 8. Homology modeling of Hev b 8 yielded a structure highly similar to Bet v 2, the birch pollen profilin, with the most distinct differences located at the N-terminus. **CONCLUSIONS:** We conclude that primary sensitization to latex profilin in the majority of cases takes place via pollen or food profilins. Additionally, pollinosis and food-allergic patients with profilin-specific IgE can be at risk of developing latex allergy.

**Allergy caused by ingestion of persimmon (*Diospyros kaki*): detection of specific IgE and cross-reactivity to profilin and carbohydrate determinants.**

Anliker MD, Reindl J, Vieths S, Wüthrich B.

*J Allergy Clin Immunol.* 2001 Apr;107(4):718-23.

**BACKGROUND:** Allergy to persimmon (*Diospyros kaki*) is very rare and not yet confirmed by means of double-blind, placebo-controlled, food-challenge (DBPCFC). Thus far, specific IgE to this fruit and cross-reactivity to pollen and other foods has not been determined. **OBJECTIVE:** The objective was to confirm allergy to persimmon in 3 patients with an according personal history and to characterize allergens and cross-reactivity of specific IgE antibodies to pollen and food allergens. One patient reacted with pruritus, penis edema, urticaria, and asthma; the second reacted with nausea and vomitus; and the third reacted with rhinoconjunctivitis, asthma, and stomachache after ingestion of persimmon. **METHODS:** Patients underwent skin prick testing with routine allergens, latex, persimmon, and other foods. Allergy to persimmon was confirmed by means of a DBPCFC. Specific serum IgE levels were measured with CAP-FEIA and the enzyme allergosorbent test (EAST) method. EAST and immunoblot inhibitions were carried out with persimmon; birch, grass, and ragweed pollen; latex; and N-glycans as inhibitors. **RESULTS:** All patients had positive skin test responses, DBPCFC and specific IgE assays to persimmon. Blot and EAST inhibition assays revealed IgE to cross-reactive profilin in one patient and IgE to cross-reacting carbohydrate determinants in all patients. **CONCLUSIONS:** This is the first report on 3 cases of allergy to persimmon verified by means of DBPCFC and detection of specific IgE. The sensitization is due to cross-reactive profilin and carbohydrate determinants.

**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.**

Seppälä U, Palosuo T, Kalkkinen N, Ylitalo L, Reunala T, Turjanmaa K.

*Allergy.* 2000 Mar;55(3):266-73.

**BACKGROUND:** Patients allergic to natural rubber latex (NRL) frequently show positive skin prick tests (SPT) and hypersensitivity reactions to various fruits, such as avocado, banana, and kiwi, as well as to vegetables such as potato. **METHODS:** Hev b 7 was purified from NRL "C-serum" and Sol t 1 from potato extract, and they were detected by immunoblotting. IgE antibodies to Hev b 7 and Sol t 1 were measured with ELISA in sera from 35 adults and 35 children allergic to NRL. ELISA inhibition and immunoblotting were used to study allergen cross-reactivity. The in vivo reactivity of Hev b 7 and Sol t 1 were demonstrated in the SPT. **RESULTS:** Seventeen (49%) of the 35 NRL-allergic adults had IgE antibodies to Hev b 7, in contrast to only one of the 35 NRL-allergic children. Fifteen (43%) of the NRL-allergic adults and 29 (83%) of the NRL-allergic children had IgE antibodies to Sol t 1. Ten (29%) of the adult sera showed IgE binding to both Sol t 1 and Hev b 7, and crosswise inhibition tests with pooled sera revealed marked cross-reactivity. In the SPT, both natural Hev b 7 and Sol t 1 were able to produce a wheal and flare reaction. **CONCLUSIONS:** One-half of the NRL-allergic adults, but only one of the NRL-allergic children, had IgE antibodies to natural Hev b 7. These results suggest that Hev b 7 is an important NRL allergen for adults, but not for children. Elucidation of the clinical importance of the observed cross-reactivity between Hev b 7 and Sol t 1 requires further studies.

**Latex allergy in the workplace.**

Toraason M, Sussman G, Biagini R, Meade J, Beezhold D, Germolec D.

*Toxicol Sci.* 2000 Nov;58(1):5-14.

While less than 1% of the general population is sensitized to latex, the U.S. Occupational Safety and Health Administration estimates that 8-12% of health-care workers are sensitized. The major source of workplace exposure is powdered natural rubber latex (NRL) gloves. NRL is harvested from HEVEA: brasiliensis trees and ammoniated to prevent coagulation resulting in the hydrolysis of the latex proteins. Prior to use in manufacturing, the latex is formulated by the addition of multiple chemicals. Thus, human exposure is to a mixture of residual chemicals and hydrolyzed latex peptides. Clinical manifestations include irritant contact dermatitis, allergic contact dermatitis (type IV), and type I immediate hypersensitivity response. Type I (IgE-mediated) NRL allergy includes contact urticaria, systemic urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, and anaphylaxis. Taking an accurate history, including questions on atopic status, food allergy, and possible reactions to latex devices makes diagnosis of type-I latex allergy possible. To confirm a diagnosis, either in vivo skin prick testing (SPT) or in vitro assays for latex-specific IgE are performed. While the SPT is regarded as a primary confirmatory test for IgE-mediated disease, the absence of a U.S. Food and Drug Administration-licensed HEVEA: brasiliensis latex extract has restricted its use in diagnosis. Serological tests have, therefore, become critically important as

alternative diagnostic tests. Three manufacturers currently have FDA clearance for in vitro tests, to detect NRL-specific IgE. The commercially available assays may disagree on the antibody status of an individual serum, which may be due to the assay's detecting anti-NRL IgEs to different allergenic NRL proteins. Sensitized individuals produce specific IgE antibody to at least 10 potent HEVEA: allergens, Hev b 1-Hev b 10, each of which differs in its structure, size, and net charge. The relative content and ratios of Hevs in the final allergen preparation most probably could effect diagnostic accuracy. The Hev proteins have been cloned and expressed as recombinant proteins. Sequencing demonstrates both unique epitopes and sequences commonly found in other plant proteins. Sequence homology helps to explain the cross reactivity to a variety of foods experienced by latex allergic individuals. The development of recombinant allergens provides reagents that should improve the diagnostic accuracy of tests for latex allergy. Although clinical and exposure data have been gathered on the factors affecting response in latex-allergic individuals, less is known regarding the development of sensitization. Coupled with in vitro dermal penetration studies, murine models have been established to investigate the route of exposure in the development of latex sensitization. Time-course and dose-response studies have shown subcutaneous, intratracheal, or topical administrations of non-ammoniated latex proteins to induce IgE production. Both in vitro penetration and in vivo studies highlight the importance of skin condition in the development of latex allergy, with enhanced penetration and earlier onset of IgE production seen with experimentally abraded skin. The diagnosis of latex allergy is complicated by these variables, which in turn hinder the development of intervention strategies. Further epidemiological assessment is needed to more explicitly define the scope, trends, and demographics of latex allergy. Diagnostic accuracy can be improved through greater knowledge of proteins involved in the development of latex allergy, and better documentation of the presently available diagnostic tests. In vivo and in vitro models can elucidate mechanisms of sensitization and provide an understanding of the role of the exposure route in latex allergy-associated diseases. Together, these efforts can lead to intervention strategies for reducing latex allergy in the workplace.

**Allergy caused by ingestion of zucchini (*Cucurbita pepo*): characterization of allergens and cross-reactivity to pollen and other foods.**

Reindl J, Anliker MD, Karamloo F, Vieths S, Wüthrich B.  
*J Allergy Clin Immunol.* 2000 Aug;106(2):379-85.

**BACKGROUND:** Allergy to zucchini (*Cucurbita pepo*), a member of the Cucurbitaceae family, has not previously been reported. We examined 4 patients complaining of allergic symptoms, such as oral allergy syndrome, nausea, diarrhea, or pruritus, after the intake of zucchini. **OBJECTIVE:** After the confirmation of food allergy, we wanted to characterize zucchini allergens and examine possible cross-reactions to pollen and food. **METHODS:** The patients underwent skin prick and prick-to-prick-testing with different allergens, including zucchini, latex, and birch, ragweed, and grass pollen. Moreover a double-blind, placebo-controlled, food challenge was performed to confirm food allergy. Total and specific serum IgE levels were determined by using CAP-FEIA and the enzyme allergosorbent test method (EAST), respectively. Proteins from zucchini reacting with patient IgE were detected by means of immunoblotting. To characterize cross-reacting IgE antibodies, immunoblot- and EAST-inhibition assays were carried out. **RESULTS:** All patients in this study had positive reactions to zucchini both in prick-to-prick tests and double-blind, placebo-controlled, food challenges. Specific serum IgE levels to zucchini were found in all cases. In blot- and EAST-inhibition assays IgE from two patients revealed binding to zucchini profilin at about 15 kd. Furthermore, in two cases, including one of the profilin-positive patients, IgE directed against cross-reacting carbohydrate determinants was detected. For one patient, no cross-reacting IgE could be found, but IgE from this patient reacted strongly with a zucchini protein at 17 kd. **CONCLUSIONS:** We report the first 4 cases of food allergy to zucchini. Zucchini allergens can cause systemic reactions and are at least partially heat stable. We suggest that allergy to zucchini can occur as a result of primary sensitization to zucchini, as well as to cross-reactions to the panallergen profilin and cross-reacting carbohydrate determinants.

**Class I chitinases, the panallergens responsible for the latex-fruit syndrome, are induced by ethylene treatment and inactivated by heating.**

Sánchez-Monge R, Blanco C, Perales AD, Collada C, Carrillo T, Aragoncillo C, Salcedo G.  
*J Allergy Clin Immunol.* 2000 Jul;106(1 Pt 1):190-5.

**BACKGROUND:** Class I chitinases have been identified as the major panallergens in fruits associated with the latex-fruit syndrome, such as avocado, banana, and chestnut. However, other plant foods containing these enzymes have not been related to this syndrome. **OBJECTIVE:** We sought out class I chitinases in the green bean, a legume that is known to express chitinases but is not associated with latex allergy, and examined whether the content or allergenic activity of chitinases can be modified by physical or chemical treatments. **METHODS:** IgE-binding proteins in untreated bean samples, as well as in

ethylene- and heat-treated samples, were detected by using a pool of sera from patients with latex-fruit allergy. Putative allergens were purified by cation-exchange chromatography and characterized by N-terminal sequencing, enzymatic activity assays, immunodetection with sera and antichitinase antibodies, and immunoblot inhibition tests. Skin prick tests with untreated and heated purified allergens were also carried out. RESULTS: An IgE-binding protein of 32 kd that was also recognized by antichitinase antibodies was detected in green bean extracts. This reactive component was strongly induced by ethylene treatment. The protein, designated PvChI, was identified as a class I chitinase closely related to the major avocado allergen Prs a 1. Immunoblot inhibition assays demonstrated cross-reactivity between both allergens. Purified PvChI induced positive skin prick test responses in 7 of 8 patients with latex-fruit allergy. Heat treatment of both Prs a 1 and PvChI produced a full loss of their allergenic capacities both in vitro and in vivo. No IgE-binding component was detected in the white mature bean in which the main isolated 32-kd protein corresponded to a nonreactive phytohemagglutinin. CONCLUSIONS: Ethylene treatment induces the expression of plant class I chitinases. The allergenic activity of plant class I chitinases seems to be lost by heating. This fact could explain why plant foods containing these putative allergens that are consumed after cooking are not usually associated with the latex-fruit syndrome.

#### **Latex type I sensitization and allergy in children with atopic dermatitis. Evaluation of cross-reactivity to some foods.**

Tücke J, Posch A, Baur X, Rieger C, Raulf-Heimsoth M.  
*Pediatr Allergy Immunol.* 1999 Aug;10(3):160-7.

Recent studies have demonstrated that allergy to natural rubber latex (NRL) is associated with cross-reactivity to certain foods. The aim of this study was to investigate the prevalence of NRL sensitization and allergy in children with atopic dermatitis (n=74). We also examined cross-reactions between latex and foods, and compared the frequency of suspected latex cross-reacting fruits in children with and without NRL-specific immunoglobulin E (IgE). Twelve of the 74 atopic children studied (16.2%; 95% confidence interval (CI), 8.7-26.6%) had circulating IgE antibodies to latex. These NRL-sensitized children were older and they showed significantly higher total IgE values ( $p<0.003$ ) when compared with the group of children without NRL sensitization. Of the specific food IgE evaluations, 18.4% (93 out of 505) were positive, and 69.9% were observed in the group of children with latex-specific IgE, most frequently to potato, tomato, sweet pepper, and avocado. An isolated latex-specific IgE response without food-specific IgE was never observed. Exclusively in the latex-positive group, conformity with the report of allergic symptoms after ingestion of food and increased food-specific IgE was found. Twenty children without proven latex sensitization showed increased food-specific IgE, most frequently to potato, banana, and chestnut. Avocado-specific IgE was never determined in this patient group. No significant differences were detected concerning the sensitization to potato, banana, and kiwi between NRL-sensitized children and the group of 20 children without latex-specific IgE. The competitive CAP inhibition using sera from children with specific IgE to both latex and food showed different cross-reactivities between latex and the specific food. A close relationship existed between latex and avocado (median inhibition: 100%), whereas sensitization to latex and kiwi seemed to be independent in our study group (inhibition:  $<25\%$ ). In particular, for potato, cross-reactivity and co-sensitization existed. Our study demonstrated that children with atopic dermatitis are a high-risk group for latex sensitization. Increasing age, additional sensitization to ubiquitous inhaled allergens, and enhanced total serum IgE values seemed to be important variables for latex sensitization and further sensitization to the latex-associated foods. Cross-reactivity and, in some cases, co-sensitization to specific fruits and vegetables, were observed.

#### **Fruit-pollen-latex cross-reactivity: implication of profilin (Bet v 2).**

Díez-Gómez ML, Quirce S, Cuevas M, Sánchez-Fernández C, Baz G, Moradiellos FJ, Martínez A.  
*Allergy.* 1999 Sep;54(9):951-61.

BACKGROUND: An association between allergy to fruits and latex, and between pollen and plant-derived food has been described. The cross-reactive structures responsible for these associations have not yet been completely elucidated. METHODS: IgE reactivity to the recombinant allergens Bet v 1 and Bet v 2, different pollens, natural latex, papain, and bromelain was investigated in 29 patients with allergy to fruits or vegetables who lived in an area without birch trees. RESULTS: Exactly 79.3% of patients were allergic to grass pollen, and two of them had clinical allergy to latex. Serum IgE reactivity (CAP) to birch pollen was found in 65% of patients, to Bet v 2 in 51.7%, to Bet v 1 in 3.4%, to latex in 58.6%, to bromelain in 51.7%, and to papain in 17.2% of patients. All subjects with positive IgE to Bet v 2 had also reactivity to latex, grass, olive tree, birch, and mugwort pollens. The six patients not allergic to pollen did not show IgE reactivity to latex, Bet v 1, or Bet v 2. A significant correlation was found between CAP to latex with Bet v 2 ( $r=0.86$ ,  $P<0.001$ ), with birch ( $r=0.86$ ,  $P<0.001$ ), and with ryegrass ( $r=0.81$ ,  $P<0.001$ ). Immunoblotting using nine sera with positive CAP to birch pollen showed IgE-binding to a 15-kDa band that was recognized by antiprofilin monoclonal antibody. Bet v 2 CAP could be inhibited up to

52% by ryegrass and up to 23% by mugwort. CAP to latex was almost completely inhibited by ryegrass pollen with sera from five subjects without symptoms due to latex, whereas no inhibition was observed with serum from one patient with allergy to latex. CONCLUSIONS: Patients with allergy to plant-derived food and associated pollinosis showed a high frequency of IgE reactivity to Bet v 2, which may cause positive serum IgE determinations to latex and birch pollen due to the presence of cross-reactive epitopes. IgE reactivity to Bet v 2 may serve as an indicator of broad sensitization.

**Class I endochitinase containing a hevein domain is the causative allergen in latex-associated avocado allergy.**

Posch A, Wheeler CH, Chen Z, Flagge A, Dunn MJ, Papenfuss F, Raulf-Heimsoth M, Baur X.

*Clin Exp Allergy*. 1999 May;29(5):667-72.

**BACKGROUND:** In the medical literature immunoglobulin (Ig)E-mediated sensitization to avocado is rarely reported. On the other hand, more than 50% of subjects having IgE-mediated natural rubber latex allergy are sensitized to avocado fruit as demonstrated by skin-prick testing and/or specific IgE measurements and about 10-20% report hypersensitivity reactions after ingesting avocado. **OBJECTIVE:** The underlying pathomechanism of latex-associated avocado allergy is still unknown. The conserved hevein domain of the major latex allergen prohevein (Hev b 6.01) is a ubiquitous chitin-binding protein structure that can be found in several plant proteins and may be responsible for the observed cross-reactivity between latex and avocado fruit. **METHODS:** Chitin-binding avocado proteins (CBAPs) were isolated by affinity-chromatography and their IgE-binding characteristics were studied by immunoblotting using the sera from 15 avocado-sensitized latex patients. Inhibition experiments using isolated hevein and CBAPs as inhibitor solutions were performed to study the immunological cross-reactivity between both protein species and to assess the role of the CBAPs as mediators in latex-associated avocado allergy. **RESULTS:** In 80% of avocado-sensitized subjects (n = 15), IgE antibodies directed against a 31-kDa allergen were detected by immunoblotting. This IgE-binding protein was identified by protein sequencing to be a class I endochitinase containing a hevein domain at the N-terminus. Purified native and digested (using simulated gastric fluid) endochitinase were able to completely block all avocado-specific IgE antibodies in six out of seven avocado patients. **CONCLUSIONS:** Sensitization to endochitinase class I containing a hevein domain is the main underlying pathomechanism in latex-mediated avocado allergy.

**Latex allergy: a patient and health care system emergency.**

Kelly KJ, Walsh-Kelly CM.

*Ann Emerg Med*. 1998 Dec;32(6):723-9.

Latex allergy, an IgE-mediated reaction to proteins retained in finished natural rubber latex products, has become one of the most pervasive problems in medicine. Latex allergy has resulted in death, progressive asthma, severe food allergy from cross-reactivity, and disability of health care professionals with the accompanied loss of self-esteem and income from their inability to work in their chosen profession. This article reviews the risks of latex allergy and proposes strategies for prevention and management of the problem.

**Cross-reactivity between latex and sweet pepper due to prohevein.**

Gallo R, Roncarolo D, Mistrello G.

*Allergy*. 1998 Oct;53(10):1007-8.

**Identification of hevein (Hev b 6.02) in Hevea latex as a major cross-reacting allergen with avocado fruit in patients with latex allergy.**

Chen Z, Posch A, Cremer R, Raulf-Heimsoth M, Baur X.

*J Allergy Clin Immunol*. 1998 Sep;102(3):476-81.

**BACKGROUND:** Recent studies demonstrated that allergy to natural rubber latex is frequently associated with hypersensitivity to avocado fruit. The responsible cross-sensitizing allergen has not been identified. **OBJECTIVE:** The purpose of this study was to investigate the cross-reactivity of a latex major allergen, hevein, with avocado proteins. **METHODS:** Serum samples from 118 health care workers (HCWs) allergic to latex (HCW group) and 78 patients with spina bifida (SB) allergic to latex (SB group) were included in this study. Anti-hevein and anti-avocado IgE antibodies were measured by enzyme-linked allergosorbent assay. Cross-reactivity of hevein to avocado proteins was assessed by inhibition of the IgE binding in individual patients' sera containing IgE antibodies to both hevein and avocado. **RESULTS:** The

prevalence of seropositive IgE antibodies to avocado was found to be strongly associated with the presence of hevein-specific IgE antibodies in subjects of both groups ( $P < .001$ ). Sixty-seven of 91 (73%) subjects from the HCW group and all 19 subjects in the SB group with positive IgE antibodies to hevein also had elevated IgE values to avocado. Competitive RAST inhibition with 42 sera showed that IgE binding to avocado could be completely inhibited in 27 (64%) sera by preincubation with hevein. By contrast, the degrees of inhibition of IgE to hevein by avocado extract ranged from 0% to 36% ( $n = 16$ ). These results indicate that sensitization to avocado in most patients allergic to latex is caused exclusively by IgE-binding epitopes present in hevein. Results of immunoblots and immunoblot inhibition with 11 serum samples confirmed that a 30-kd protein in avocado was the major IgE-binding component; the IgE-binding reactivity to this protein could be inhibited by hevein in all sera tested. **CONCLUSION:** Hevein is the major cross-reacting allergen with avocado in subjects with latex allergy.

#### **Cross-reactivity between buckwheat and latex.**

De Maat-Bleeker F, Stapel SO.

*Allergy*. 1998 May;53(5):538-9.

#### **Plant defense-related enzymes as latex antigens.**

Yagami T, Sato M, Nakamura A, Komiyama T, Kitagawa K, Akasawa A, Ikezawa Z.

*J Allergy Clin Immunol*. 1998 Mar;101(3):379-85.

**BACKGROUND:** Latex allergy is an increasing hazard to people who frequently come into contact with latex products. Of interest concerning this immediate-type allergy is the cross-reactivity to various vegetable foods and pollen. Despite its high prevalence, no adequate explanation has been provided for the cross-reactive antigens. **OBJECTIVE:** We have hypothesized that a series of plant defense-related proteins act as latex allergens, as well as vegetable food allergens. To evaluate this hypothesis, hydrolytic enzymes that are very likely to take on defensive roles in rubber trees were examined for their antigenicity. **METHODS:** By applying chromatographic procedures, defense-related enzymes were separated from nonammoniated latex (NAL). Their antigenicity was examined by immunoblotting and ELISA with sera containing IgE antibodies to crude latex proteins. **RESULTS:** Three kinds of hydrolytic enzymes (basic beta-1,3-glucanases [35, 36.5, and 38 kd], a basic chitinase/lysozyme [29.5 kd], and an acidic esterase [44 kd]) were separated from NAL. They were recognized by IgE antibodies from a significant number of patients allergic to latex. The basic beta-1,3-glucanases and the acidic esterase were also strongly recognized by IgE antibodies from several atopic subjects who were allergic to various vegetable foods rather than latex products. **CONCLUSION:** It was ascertained that the three defense-related enzymes separated from NAL constituted part of the latex antigens. Taking together the well-known serologic or immunologic relationships and amino acid sequence similarities of defense-related proteins coming from phylogenetically distant plant species, we can suspect their universal antigenicity and cross-reactivity.

#### **Asthma caused by Ficus benjamina latex: evidence of cross-reactivity with fig fruit and papain.**

Díez-Gómez ML, Quirce S, Aragonese E, Cuevas M.

*Ann Allergy Asthma Immunol*. 1998 Jan;80(1):24-30.

**BACKGROUND:** Ficus benjamina or weeping fig is a plant used increasingly for indoor decoration that can cause allergic rhinitis and asthma. **OBJECTIVE:** We report a clinical and immunologic study in a patient with perennial asthma caused by F. benjamina latex in whom several episodes of angioedema of the oropharyngeal tract and tongue followed ingestion of figs and kiwi. **METHODS:** Hypersensitivity to latex from F. benjamina and from Hevea brasiliensis, fig fruit, kiwi, papain, and bromelain was investigated by means of skin prick test, specific IgE determination by CAP, histamine release test, and bronchial provocation test to F. benjamina latex. CAP-inhibition assays were carried out to study possible cross-reactivity among these antigens. **RESULTS:** Hypersensitivity to F. benjamina latex, fig, kiwi, and proteases was demonstrated by means of skin prick test, determination of specific IgE and histamine release test. Bronchial provocation test with F. benjamina latex resulted in a dual asthmatic reaction, confirming the etiologic role of this plant. A rise of eosinophil cationic protein in patient's serum was observed 21 hours after bronchial challenge, suggesting activation of eosinophils. Inhibition assays showed that F. benjamina latex as liquid-phase inhibited up to 95% the CAP to fig and up to 57% the CAP to papain. Neither sensitization nor cross-allergenicity with H. brasiliensis latex was found. **CONCLUSIONS:** Hypersensitivity to F. benjamina latex may cause IgE-mediated respiratory allergy. The association with allergy to fig and papain is likely due to the existence of cross-reactive allergen structures.

**IgE epitope analysis of the hevein preprotein; a major latex allergen.**

Beezhold DH, Kostyal DA, Sussman GL.

*Clin Exp Immunol.* 1997 Apr;108(1):114-21.

We have previously identified the hevein preprotein as a common allergen for latex allergic healthcare workers. The B cell epitopes in the hevein protein that are recognized by IgE of latex-allergic individuals have not been identified. In this study, we examined the hevein preprotein using epitope mapping. Overlapping synthetic peptides of 10 amino acids (two aa overlap) were synthesized on a derivatized cellulose membrane using Fmoc chemistry. The peptide spots were probed with pooled sera from 10 latex-allergic patients, and the IgE-reactive peptides identified with anti-IgE MoAbs. We identified six B cell epitopes within the full length hevein preprotein which bound IgE from latex-allergic patients. Two were located in the N-terminal 5-kD hevein domain and four were observed in the 14-kD C-domain. A broad epitope was located between the N-terminal amino acids 13-24. This epitope had nearly complete homology to wheat germ agglutinin (WGA). Immunological cross-reactivity to WGA was confirmed by Western blot analysis with purified WGA, and this reactivity could be inhibited by latex proteins or WGA. Of the five remaining epitopes, four had homologies to other proteins in the pathogenesis-related family of plant proteins (PR-4). The data demonstrate that hevein has multiple IgE epitopes. The significant homology of these epitopes to a broad family of plant defence proteins further explains the increased prevalence of food allergies in latex-allergic individuals.

**A nurse with anaphylaxis to stone fruits and latex sensitivity: potential diagnostic difficulties to consider.**

Weiss SJ, Halsey JF.

*Ann Allergy Asthma Immunol.* 1996 Dec;77(6):504-8.

**BACKGROUND:** There have been several recent reports describing a cross-reactivity between latex and antigens derived from a number of fruits, including those of the stone fruit family. The relationships between the allergic reactions to the antigens from these plant products are still being defined. **OBJECTIVE:** To characterize the IgE reactivity of a patient who had anaphylactic reactions following the ingestion of several members of the stone fruit family (ie, plum, peach, and nectarine) and had a positive clinical history for latex allergy. **METHODS:** The patient's serum was tested for the presence of specific IgE for latex, stone fruits, and a panel of other foods reported to be cross-reactive with latex. Prick testing was also performed with freshly prepared extracts from the implicated fruits. Finally, the immunochemical relationship between this patient's fruit and latex sensitivity was investigated by RAST inhibition. **RESULTS:** The patient had strongly positive skin tests to the freshly prepared fruit extracts but the in vitro food-specific IgE tests were equivocal or very low positive. In vitro latex-specific IgE tests were strongly positive. The stone fruit extracts were shown to be inhibitors of the patient's latex specific IgE by RAST inhibition. **CONCLUSION:** Skin testing with freshly prepared fruit extracts was more sensitive than the in vitro tests with this patient. The inhibition data support an immunochemical relationship between the patient's latex allergy and sensitivity to stone fruits.

**Latex hypersensitivity in emergency medical service providers.**

Safadi GS, Corey EC, Taylor JS, Wagner WO, Pien LC, Melton AL Jr.

*Ann Allergy Asthma Immunol.* 1996 Jul;77(1):39-42.

**BACKGROUND:** Emergency medical service providers have a high degree of exposure to latex products. Patients utilizing emergency medical services can be allergic to latex products used during rescue efforts. **OBJECTIVE:** To determine the prevalence of latex hypersensitivity among emergency medical service providers. **METHODS:** Study questionnaires were distributed to a group of emergency medical service providers. Skin prick testing was performed using latex, common aeroallergens, and food extracts. Patch testing was done using latex and individual rubber additives. Serum latex-specific IgE was also measured. **RESULTS:** A total of 93 completed surveys were collected. Average exposure to latex in the work environment was 8.2 years. Eighty-four (90%) used latex gloves routinely at work. Of those, thirteen (14%) gave history of reaction to latex gloves. Sixty-two percent were not aware of the possibility of latex allergy in themselves or their patients. Forty-one (44%) had skin testing. Of those, four (10%) had positive prick tests for at least one of the four latex preparations used. Five had positive skin tests to avocado extract without supporting clinical history. Two had positive skin tests to banana, one with supporting clinical history for banana allergy. No food cross-reactivity with latex was demonstrated. Latex-specific serum correlated with prick skin test results. No positive reactions were noted with patch testing. **CONCLUSIONS:** A significant percentage of emergency medical service providers were not aware of the occupational risk of latex allergy or

the potential risk in their patients. A positive prick skin test for latex was present in 4 of 41 (10%), representing one-third of those who reported symptoms from latex exposure.

#### **Oral allergy syndrome induced by chestnut (*Castanea sativa*)**

Antico A.

*Ann Allergy Asthma Immunol.* 1996 Jan;76(1):37-40.

Comment in: *Ann Allergy Asthma Immunol.* 1996 Sep;77(3):254. PMID: 8814053.

**BACKGROUND:** Oral allergy syndrome is a distinctive type of allergy to food resulting from direct contact between food and the oral mucosa. Normally, it affects patients who are allergic to pollens. It can be challenged by testing for hypersensitivity to fresh fruit or vegetables in well-known associations. Oral allergy syndrome rarely occurs in patients with other types of allergies, or to food not associated with pollens. Only occasionally does chestnut cause hypersensitivity. There are only a few reported cases, depending on cross-reactivity in previously latex-hypersensitive patients. Oral allergy syndrome to chestnut in a patient with respiratory allergy to *Dermatophagoides* is therefore unusual and worth reporting. **OBJECTIVES:** To describe the clinical features and their differences from previously reported cases and to analyze the techniques and methodologic problems related to in vivo and in vitro diagnosis. **METHODS:** Case report. Skin tests with commercial and freshly made extracts and by the prick-by-prick method. Challenge test. Specific IgE antibody assay. Prausnitz-Küstner reaction. **RESULTS:** The challenge with fresh food confirmed an oral allergy syndrome to chestnut. Clear symptoms of rhinoconjunctivitis and asthma set in as well. Skin tests with several commercial extracts and the prick-by-prick test were negative and so was specific IgE assay in serum by RAST and other immunoenzymatic methods. Skin prick test with a freshly prepared extract of fresh chestnut and the passive transfer reaction were positive. **CONCLUSIONS:** The case of oral allergy syndrome to chestnut reported here appears to be a manifestation of immediate IgE-dependent hypersensitivity.

#### **Latex allergy in a child with banana anaphylaxis.**

Cinquetti M, Peroni D, Vinco A, Zoppi G.

*Acta Paediatr.* 1995 Jun;84(6):709-10.

Allergy to latex and to banana is probably uncommon. Cross-reactivity between these two antigens has been recently demonstrated, but the clinical association of allergic reactions to latex contact and banana ingestion is extremely rare. We report a 3-year-old boy who developed an anaphylactic reaction following banana ingestion and who presented an associated immediate hypersensitivity to latex.

#### **Allergy to latex, avocado pear, and banana: evidence for a 30 kd antigen in immunoblotting.**

Lavaud F, Prevost A, Cossart C, Guerin L, Bernard J, Kochman S.

*J Allergy Clin Immunol.* 1995 Feb;95(2):557-64.

Allergens of natural latex, latex gloves, avocado pear, and banana extracts were investigated by an immunoblotting technique in sera of patients experiencing associated latex and fruit allergies. Extracts were separated by sodium dodecyl-sulfate-polyacrylamide gel electrophoresis and electroblotted onto nitrocellulose. After incubation with patients' sera, IgE antibodies were revealed by a goat anti-human IgE alkaline-phosphatase conjugate. Seventeen serum samples from patients with well-documented latex allergy were studied. Among these patients, 10 demonstrated an allergy to avocado pear sometimes associated with banana. In sera from patients with latex and fruit allergy, prominent IgE binding was revealed at about 30 kd with latex and fruit extracts. Serum controls remained negative. Cross-inhibition of immunoblotting confirmed that this main allergen is linked to a common epitope present in latex and fruits. This must be related to clinical findings and previous observations of cross-reactivity.

**Latex anaphylaxis.**

Ebo DG, Stevens WJ, De Clerck LS.

*Acta Clin Belg.* 1995;50(2):87-93.

In the past decade, immediate hypersensitivity to latex has been accepted as a serious problem. The proteins that are present in natural rubber are considered to be the responsible antigens, and the hypersensitivity responses induced include contact and generalized urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, life threatening anaphylaxis and death. So far, children with spina bifida or severe urogenital defects, health care workers, and rubber industry employees appear to be at greater risk than the general population. Since 1991 several reports and cross-reactivity studies have demonstrated an association between latex allergy and allergy to certain fruits, especially banana, avocado and kiwi. Because our knowledge of the major allergens is still incomplete, standardised in vitro and in vivo tests are not yet readily available. Therefore, the clinician should rely on a medical history, physical examination, and reliable serological tests to confirm diagnosis of latex anaphylaxis. Because of possible systemic reactions to skin prick testing and provocation tests, these methods should be restricted to patients with a compelling history and an inconclusive serologic test result. Preventive measures are the key to successful and safe management of patients with latex anaphylaxis.

**Latex allergy: clinical features and cross-reactivity with fruits.**

Blanco C, Carrillo T, Castillo R, Quiralte J, Cuevas M.

*Ann Allergy.* 1994 Oct;73(4):309-14.

Comment in: *Ann Allergy.* 1994 Oct;73(4):277-81. PMID: 7943993.

**BACKGROUND:** Latex IgE-mediated allergy is an important medical problem, but its clinical characteristics and association with food allergies are not well defined. **OBJECTIVE:** Our objectives were to determine the clinical features of latex-allergic patients, and latex-associated food hypersensitivities. **METHODS:** A prospective study was performed in our outpatient clinic. It consisted of a clinical questionnaire, skin prick tests with aeroallergens and foods, skin test with a latex extract, determination of total and specific IgE by CAP/RAST methods, and RAST inhibition. Latex and food allergies were diagnosed on the basis of a suggestive clinical history and a positive skin test with the corresponding allergen. **RESULTS:** Twenty-five patients were diagnosed as having latex allergy. Their mean age was 33 +/- 9.0 years, with female predominance (23:2). There were nine greenhouse and six hospital workers. Latex-induced reactions included systemic anaphylaxis in nine patients (36%). Average total IgE was 161 kU/L, and it was within normal limits in 16 cases. Latex skin prick tests had excellent diagnostic precision with no adverse reactions, and CAP for latex diagnostic sensitivity was 80%. Forty-two food allergies were diagnosed in 13 of our patients (52%), and 23 of these consisted of systemic anaphylaxis. The most frequent food hypersensitivities were to avocado (9), chestnut (9), banana (7), kiwi (5) and papaya (3). Through RAST-inhibition, cross-reactivity among latex, avocado, chestnut, and banana was demonstrated. **CONCLUSIONS:** In our experience, latex allergy affects middle-aged women in certain professions at increased risk. Our data suggest the existence of a "latex-fruit syndrome," because 52% of our latex allergic patients had allergies to certain fruits.

**Cross-reactivity of food allergens in latex allergy.**

Kurup VP, Kelly T, Elms N, Kelly K, Fink J.

*Allergy Proc.* 1994 Jul-Aug;15(4):211-6.

Allergy resulting from exposure to latex proteins has been reported with increasing frequency in certain patient and occupational groups. Patients with latex allergy demonstrate cross-reactivity with some food allergens. Although amino acid homology of a few polypeptides from food and latex have been reported, no information is available comparing food and latex allergens. In the present study, we have obtained antibody from latex-sensitive patients by affinity absorption with various food and latex allergen extracts. The antibodies were then evaluated for reactivity with various antigens by ELISA. The results indicated that IgE cross-reactivity existed between different latex and food antigens. Hence, care should be exercised during evaluation of patients, as the clinical response may not be directed to the primary sensitizing antigen and may represent cross-reactivity of antigens.

**[Food-induced anaphylaxis in latex allergy]**

Abeck D, Börries M, Kuwert C, Steinkraus V, Vieluf D, Ring J.

*Hautarzt*. 1994 Jun;45(6):364-7.

[Article in German]

Contact urticaria and anaphylactic reactions to latex-containing rubber products are being recognized with increasing frequency in all kinds of medical disciplines. Recently a number of reports have been published describing anaphylactic reactions to food items in patients with latex allergy. The cases of three patients who developed anaphylactic reactions to both latex and food items are presented, and the importance of the association of latex and cross-reactivity with food items is stressed. The food items that led to anaphylactic reactions were banana and avocado; banana, avocado and buckwheat; and banana, avocado and tomato. The cross-reactivity of latex to buckwheat and tomato has not been reported before.

**Banana allergy in patients with immediate-type hypersensitivity to natural rubber latex: characterization of cross-reacting antibodies and allergens.**

Mäkinen-Kiljunen S.

*J Allergy Clin Immunol*. 1994 Jun;93(6):990-6.

**BACKGROUND:** An association between allergy to latex and banana has been reported. Even though cross-reacting IgE antibodies have been demonstrated, in no study has the existence of structurally similar allergens been confirmed. In the present study banana allergy was studied in a large series of patients with latex allergy. Specific IgE antibodies were characterized for cross-reactivity and compared with pollen RAST results. Latex and banana extracts were investigated for common antigens and allergens. **METHODS:** Latex-, banana-, and pollen-specific (birch, timothy, mugwort) IgE were measured in 47 sera from patients with latex allergy. Thirty-one patients were skin prick tested with banana and questioned for possible reactions after eating bananas. Several RAST inhibition and immunosorbent inhibition studies were used to characterize cross-reacting IgE antibodies. Structurally similar antigens and allergens were evaluated with crossed-line immunoelectrophoresis and crossed-line radioimmunoelectrophoresis, respectively. **RESULTS:** Latex RAST results were positive in 31 (66%) and banana RAST results were positive in 26 (55%) of the 47 sera. Of the 31 latex RAST-positive sera, 25 (81%) were also banana RAST-positive. Results from latex RAST correlated significantly with results from banana RAST ( $p < 0.001$ ), but not with those from pollen RAST ( $p > 0.05$ ). Banana skin prick test results were positive in 11 (35%) of the 31 patients tested. Symptoms after eating bananas were reported by 16 (52%) of the 31 patients. In inhibition studies the binding of IgE antibodies to solid-phase banana and to several latex preparations was inhibited by latex and banana, respectively. In crossed-line immunoelectrophoresis at least one antigen from banana fused with an antigen from latex, which also bound IgE antibodies in autoradiography (crossed-line radioimmunoelectrophoresis). **CONCLUSIONS:** Patients with latex allergy have symptoms caused by banana and show positive skin test and specific IgE test results. Cross-reacting IgE antibodies were confirmed by several inhibition techniques. For the first time, a structurally similar antigen/allergen was demonstrated.

**Sensitization from chestnuts and bananas in patients with urticaria and anaphylaxis from contact with latex.**

Fernández de Corres L, Moneo I, Muñoz D, Bernal G, Fernández E, Audicana M, Urrutia I.

*Ann Allergy*. 1993 Jan;70(1):35-9.

Comment in: *Ann Allergy*. 1993 Jan;70(1):1-2. PMID: 8424590.

We present eight patients allergic to latex and fruit (chestnut and banana), seven of whom are women, and aged 17 to 42 years (mean 25 years). Four had family and five personal atopic histories. The total IgE varied from 41 to 520 Ku/L (mean 263). The symptoms followed ingestion of fruit (anaphylaxis) in four patients and contact with rubber (contact urticaria and anaphylaxis) in the other four. Skin prick test (SPT) with latex and radioallergen sorbent test to latex were positive in all the patients. Histamine release (HR) to latex was carried out on six patients and was positive in three. In the six patients with symptoms after having eaten chestnuts the SPT was positive and specific IgE was detected in five of them. Histamine release to chestnuts was positive in three of the six patients tested and one of them (-SPT and + IgE) tolerated the fruit. Two out of five patients with symptomatic banana allergy had negative SPT with banana while the test was positive in one patient who tolerated this fruit, this being the only case with specific IgE to banana. Histamine release with banana was only positive in one case. The important correlation between SPT, RAST, and HR results to latex and chestnut together with the total inhibition of the chestnut RAST with a serum pool by preincubation with latex suggests cross-reactivity among these allergens.

**Partial cross-reactivity between latex and banana allergens.**

Ross BD, McCullough J, Ownby DR.

*J Allergy Clin Immunol.* 1992 Sep;90(3 Pt 1):409-10.

Comment in: *J Allergy Clin Immunol.* 1992 Sep;90(3 Pt 1):279-81.

**Cross-reactivity between latex and banana.**

M'Raihi L, Charpin D, Pons A, Bongrand P, Vervloet D.

*J Allergy Clin Immunol.* 1991 Jan;87(1 Pt 1):129-30.