Allergen Data Collection - Update:

Hazelnut *(Corylus avellana)*

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Hazelnut *(Corylus avellana)*

Authors in alphabetical order [contact information]

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Abstract

Two fundamentally different types of allergy to hazelnuts have been identified. The more frequent type is associated with pollens from trees of the order Fagales (birch, alder, hazel, hornbeam, and oak), the other less common type is not associated with pollen allergy. Symptoms of hazelnut allergy in subjects with pollinosis are usually milder immediate-type reactions at the mucosa of lips, tongue and throat (oral allergy syndrome). In contrast in hazelnut allergic subjects without concomitant pollinosis more severe systemic reactions can occur. Even deaths confirmed as due to hazelnut allergy have been reported. Prevalence of IgE-mediated adverse reactions to hazelnut in tree pollen allergic patients can be higher than 70%. In Switzerland more than one third of food allergic adults suffer from hazelnut allergy. Hazelnut is often used as a food ingredient in, for example pastry, confectionary products and ice cream. Hazelnut oils which are not fully refined may potentially be a threat for nut allergic individuals.

Useful tests in the diagnosis of hazelnut allergy include skin tests and determination of specific IgE, when positive. In contrast specificity and negative predictive values of these tests are not valid to exclude a hazelnut allergy.

Hazelnut allergens closely related to birch pollen allergens Bet v 1 and Bet v 2 and allergens not related to pollen have been identified in both in subjects with pollinosis and in subjects without pollinosis. Up to now four isoforms of the major allergen Cor a 1 have been identified in hazel pollen (Cor a 1.01 to Cor a 1.03) and hazelnuts (Cor a 1.04), which are cross- reactive to the pathogenesis-related protein Bet v 1. A 14-kDa hazelnut allergen showed cross- reactivity to birch profilin (Bet v 2). These birch-related allergens are labile to heat and enzymatic digestion. One of the allergens not related to pollens belongs to the group of lipid-transfer proteins which were recently identified as plant-pan allergens. These allergenic proteins were demonstrated to be stable against heat treatment.

Detailed information on prevalence, symptoms, and diagnostic features of hazelnut allergy as well as cross-reactivities, molecular biological and allergenic properties of the major hazelnut and hazel pollen allergens are reviewed in tabular form. The terms "nuts" or "tree nuts" refer to shell (nut) fruits of various botanical families. In the present Allergen Data Collection nuts or tree nuts include almond, brazil nut, cashew nut, hazelnut, pecan nut, pistachio, and walnut. Unless stated otherwise, peanuts, chestnut, and coconuts are not included.
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Contents

1 Prevalence of Hazelnut Allergy

Prevalence data are based on different diagnostic procedures. While the prevalence of sensitization (sensitivity) can be estimated by SPT, RAST, and immunoblot, a clinical relevant sensitization (allergy) is evaluated by convincing history (anamnesis) or food challenge tests (ideally by DBPCFC).

1.1 General Population

Prevalences within the author's selected populations are listed. Those that are assigned randomly selected ("unselected") with numbers more than 500 may be regarded as representative of the "general population". Inclusion criteria may involve circumstances not related to atopic predisposition according to current knowledge.

Country / Subjects	Allergy / Sensitivity	References
Australia, Victoria a) 332 unselected new-born infants b) 4078 children with suspected peanut or tree nut allergy (age < 14 years) (study 1990-96) c) 620 children at risk of atopy (followed from birth for 2 years)	hazelnut 0.18% (frequency of almond allergy in b), corrected for prevalence ratio to peanut allergy in b) and c), extrapolated by risk of atopy in a)	Hill et al. 1997
UK 16420 randomly selected adults (age of >15 years)	tree nuts 0.4% (interview survey, questionnaire)	Emmett et al. 1999
UK, Isle of White 1218 children of general population	tree nuts 0.7% hazelnut 0.1% (SPT, Clinical history)	Tariq et al. 1996
USA a) adults and b) children of general population	peanut and/or tree nuts a) 1.6% b) 0.6% (telephone survey, estimated corrected prevalence: 1.1% in general population)	Sicherer et al. 1999

1.2 Subjects with Atopic or Other Diseases

Country / Subjects	Allergy / Sensitivity	References
Croatia, Zagreb 71 confectionary workers	hazelnut 6% (SPT)	Zuskin et al. 1994
Denmark, Copenhagen 101 birch pollen and/or hazelnut sensitive patients	hazelnut 72% (SPT)	Andersen & Lowenstein 1978
France 20 latex allergic or at risk patients	hazelnut 15% (RAST)	Leonard et al. 1996
France 80 cases of food- related anaphylaxis (study period 1993-97)	hazelnut, cashew nut, pistachio 7.5% (reported to CICBAA databank)	European Commission 1998
France, Nancy and Toulouse 544 food allergic children	hazelnut 2.7% (food challenge)	Rance et al. 1999
France, Paris 19 patients with exercise-induced anaphylaxis	tree nuts 32% (SPT, RAST)	Guinnepain et al. 1996
France, Pierre Benite 580 patients with adverse reactions to food	hazelnut 22% (RAST)	Andre et al. 1994
France, Toulouse 142 food allergic children	hazelnut 1.4 % (labial food challenge)	Rance & Dutau 1997

Germany, Berlin 167 pollen and food sensitive patients	hazelnut 90% and 78% (SPT and case history)	Jankiewicz et al. 1996
Germany, Cologne 225 hazel pollen allergic patients	hazelnut 92% (scratch test)	Herkenrath et al. 1982
Germany, Ulm 80 patients with pollen associated food allergy	hazelnut 71% (clinical history, SPT)	Boehncke et al. 1998
Italy, Florence 54 episodes of food-dependent anaphylaxis in 44 children (age of 1 month to 16 years) (from 1994-1996)	hazelnut 1.9%	Novembre et al. 1998
Italy, Genoa 132 pollen and food sensitive patients	hazelnut 22% (incidents of hypersensitivity)	Troise et al. 1992
Italy, Milan 262 fruit and/or vegetable allergic patients	hazelnut 37 % (clinical history)	Ortolani et al. 1988
Italy, Milan 100 fruit and/or vegetable allergic patients	hazelnut 32 % (clinical history)	Ortolani et al. 1989
Netherlands 131 cases of food- induced anaphylaxis (from 1993-1997)	tree nuts 18% (survey, reported to the TNO Nutrition and Food Research Institute)	European Commission 1998
Netherlands, Rotterdam 79 tree-pollen allergic patients	hazelnut 90%, 40%, and 44% (SPT, RAST, and case history)	de Groot et al. 1996
Poland 163 food allergic infants	hazelnut 42% (RAST)	Hofman 1994
Spain, Barcelona 102 patients allergic to dried fruits	hazelnut 76%, 58%, and 69% (SPT, HR, and RAST)	Amat Par et al. 1990
Spain, Madrid 355 food allergic children	hazelnut 5.4% (SPT, RAST)	Crespo et al. 1995
Spain, Madrid 29 plant-derived food allergic patients	hazelnut 10% (SPT)	Diez-Gomez et al. 1999
Spain, Pamplona 74 patients with atopic dermatitis	nuts 6.8%(SPT, RAST, Histamine Release)	Resano et al. 1998
Spain, Salamanca a) 84 mugwort sensitive patients without other pollen sensitizations b) 57 fruit allergic patients (age of 6-56 years, mean 21.5)	a) hazelnut 2.4% (RAST) b) hazelnut 8.8%(clinical history)	a) Garcia-Ortiz et al. 1996 b) Garcia Ortiz et al. 1998
Sweden 60 severe allergic reactions caused by food	soybean, nuts and almonds >70%	Foucard et al. 1997
Sweden a) 61 cases of food- induced anaphylaxis (from 1994-1996) b) 55 cases of food- induced anaphylaxis (from 1994-1996)	a) tree nuts 18% (reported to the National Food Administration) b) tree nuts 16%(Hospital Reports)	European Commission 1998
Sweden, Halmstad / Malmö a) 380 birch pollen allergic patients b) 103 patients without birch pollen allergy	a) hazelnut 53% b) hazelnut 7% (questionaire)	Eriksson et al. 1982
Sweden, Skövde 47 birch pollen allergic patients	nuts and apples 68% (Clinical history)	Fogle-Hansson & Bende 1993

Switzerland, Bern 22 patients with severe food-induced anaphylaxis (study period 1994-96)	nuts 14%	Rohrer et al. 1998
Switzerland, Zurich a) 402 food allergic adults (study period 1978-87) b) 383 food allergic patients (study period 1990-94)	a) hazelnut 2.5% b) hazelnut 37% (anamnesis, clinical relevance, diagnostic tests)	a) Wüthrich 1993 b) Etesamifar & Wüthrich 1998
UK, Cambridge 62 peanut and/or nut allergic patients	hazelnut 21% (SPT)	Ewan 1996
UK, London 100 patients with food intolerance	nuts/peanuts 22% (repeated challenge)	Lessof et al. 1980
UK, Manchester 90 patients expierenced anaphylactic reactions to foods (from 1994-1996)	hazelnut 4.4% (suspected cause of patients' worst reaction)	Pumphrey & Stanworth 1996
USA, Denver, CO a) 180 food allergic children b) 32 peanut allergic children	a) nuts 10% (DBPCFC) b) nuts 0% (DBPCFC)	Bock & Atkins 1990
USA, Little Rock, AR 54 tree nut allergic patients	hazelnut 13% (acute allergic reactions)	Sicherer et al. 1998

1.3 Associated Allergies

Country / Subjects	Allergy / Sensitivity	References
Multicenter *(Copenhagen, Milan, Zurich)* 67 patients with positive DBPCFC to hazelnut	birch pollen 87% (SPT)	Ortolani et al. 2000
Switzerland, Zurich 19 patients with positive DBPCFC to hazelnut	hazel pollen 100% birch pollen 100% alder pollen 100% ash pollen 68% grass pollen 53% rye pollen 53% mugwort pollen 16% (SPT)	Ballmer-Weber et al. 2000

2 Symptoms of Hazelnut Allergy

Symptoms & Case Reports	References
systemic reactions anaphylaxis (3, 5, 11, 13), exercise-induced anaphylaxis (8, 10) cutaneous symptoms angioedema (1, 7, 13), atopic dermatitis (7), eyelid angioedema (2, 7), eczema (9), seasonal rhinoconjunctivitis (13), urticaria (1, 3, 4, 7, 13) gastrointestinal symptoms angioedema of lips and tongue (7), diarrhea (7), glottis edema (7), laryngeal edema (3, 9), oral itching (2, 4, 5, 9), swelling of lips, tongue, and throat (4), vomiting (7, 9), oral allergy syndrome (2, 12, 13), perioral erythema and itching (4), in general (4) respiratory symptoms allergic rhinitis (9), asthma (3, 7, 9), bronchial obstruction (1), dyspnoea (9) other symptoms migraine (intolerance reaction) (6)	(1) Aas 1978 (2) Ortolani et al. 1989 (3) Gluck 1990 (4) Hirschwehr et al. 1992 (5) Fogle-Hansson & Bende 1993 (6) Guariso et al. 1993 (7) Vocks et al. 1993 (8) Martin-Munoz et al. 1994 (9) Ewan 1996 (10) Guinnepain et al. 1996 (11) Pumphrey & Stanworth 1996 (12) Asero 1997 (13) Diez-Gomez et al. 1999
Onset of Symptoms Symptoms occurred immediately or within a few minutes in all patients after ingestion of hazelnut, 1 patient had additional reactions of conjunctivitis and rhinitis after 4 hours (67 DBPCFC positive patients)	(1) Ortolani et al. 2000
Percentage of reactions Asthma 65%, atopic dermatits 80%, allergic rhinitis 55%, and food hypersensitivity 90% in 20 tree nut allergic patients without peanut allergy (1) Symptoms of first acute allergic reactions to tree nuts in 54 patients: skin only 28%, respiratory only 11%, gastrointestinal only 3%, skin and respiratory 31%, skin and gastrointestinal 5%, gastrointestinal and respiratory 1%, all 3 systems 21% (1) Symptoms after DBPCFC with hazelnut in 67 patients: oral allergy syndrome in 88%, oral and gastrointestinal symptoms in 4.5%, and oral and systemic symptoms in 7.5% (2)	(1) Sicherer et al. 1998 (2) Ortolani et al. 2000
Threshold for Elicitation of Symptoms A dose of 500 mg filbert *(Corylus maxima)* induced symptoms of asthma, conjunctivitis, and urticaria in a hazelnut allergic patient (DBPCFC) (1) The mean provocative doses were 1.4 g, 2.7 g, and 15.3 g hazelnut in hazelnut allergic patients from Copenhagen, Zurich, and Milan, respectively (DBPCFC) (2)	(1) Bock 1978 (2) Ortolani et al. 2000

3 Diagnostic Features of Hazelnut Allergy

Parameters / Subjects	Outcome	References
Age and Onset of Symptoms 54 tree nut allergic patients	Age of patients at first reactions: 62 months (10 to 264 months) Time of onset after ingestion: 2 min (0.3 to 30 min) (median / range)	Sicherer et al. 1998
Age and Gender 731 tree nut allergic patients (age 7 months to 65 years, median 6.6 years)	Similar sensitization pattern to peanut, hazelnut, and brazil nut at all ages and gender (RAST)	Pumphrey et al. 1999
IgE patients who believed they never ingested tree nuts	Hazelnut specific serum IgE (RAST): 2.7 kIU/L (median)	Sicherer et al. 1998
IgE birch pollen allergic patients: a) responding and b) non-responding to DBPCFC with birch pollen related foods	Hazelnut specific serum IgE (RAST): a) 17.4 kU/L b) 8.6 kU/L (mean values, no significant difference)	Reekers et al. 1999
SPT, IgE and Clinical Relevance nut allergic patients	SPT and RAST were found to be reliable for the diagnosis of allergy to nuts	Aas 1978
SPT, IgE and Clinical Relevance 43 to 67 hazelnut allergic patients	positive reactions in 51% and 12% of patients with clinical hazelnut allergy tested with fresh hazelnuts and commercial extracts, respectively (SPT) hazelnut specific IgE in 55% of patients with clinical hazelnut allergy (RAST)	Ortolani et al. 1988
a) ***RAST and Clinical Relevance*** **b)** ***SPT and Clinical Relevance*** 27 patients with clinical history of hazelnut allergy	a) RAST (specific IgE > 0.7 kU/L): positive results in 48% positive preditive value 72% negative preditive value 52% b) SPT with commercial extracts and fresh food: positive results in 22% and 41% positive preditive value 66% and 73% negative preditive value 45% and 51%	Ortolani et al. 1989
RAST and Clinical Relevance 46 patients with clinical history and positive SPT to hazelnut	Hazelnut specific RAST: positive 87% negative 13%	Boehncke et al. 1998
SPT, RAST, Histamine Release and Clinical Relevance 102 patients allergic to dried fruits	Correlation of tests to clinical history of hazelnut allergy: 87% for SPT 80% for HR 89% for RAST	Amat Par et al. 1990
SPT, RAST and Histamine Release 30 birch pollen allergic patients with clinical symptoms of hazelnut allergy	Positive results to hazelnut in: 50% by SPT 43% by RAST 80% by Histamine Release	Bindslev-Jensen et al. 1991
RAST and Open Challenge children considered on history to be allergic to tree nuts	Children with positive IgE tree nut titres: >50% negative challenge test	Armstrong & Rylance 1999

SPT, RAST, and DBPCFC 86 patients with history of hazelnut allergy (from Copenhagen, Milan, Zurich)	Positivity in DBPCFC: 78% (8 placebo responders; 11 non-responders of which 4 had positive open-challenge) Tests in DBPCFC-positive subjects: a) RAST (specific IgE > 0.7 kU/L): positive preditive value 92% negative preditive value 5% b) SPT with commercial extracts and fresh food: positive preditive value 92% and 94% negative preditive value 5% and 15%	Ortolani et al. 2000
Open Challenge 17 children with perceived peanut or tree nut allergy	Open challenge procedure, where negative tests (SPT, RAST) indicate tolerance of nuts: 15 showed no reactions, all of them continued to ingest foods containing nuts without incidents.	Baker et al. 1999
HLA Genotypes Birch pollen and hazelnut allergic patients	HLA-alleles DRB1*01, DQA1*0101, and DQB1*0501 were significantly decreased as compared to pollen allergic patients in general; insignificant differences as compared to birch pollen allergic individuals without hazelnut allergy	Boehncke et al. 1998
Birch Pollen spec. IgE 103 birch pollen- hypersensitive patients free of oral allergy syndrome (at begin of the followed-up study)	Birch pollen specific serum IgE- levels in patients: a) who developed Apiaceae (carrot, celery, fennel) sensitivity 15.5 AU/mL b) who developed apple/hazelnut allergy only 8.5 AU/mL c) who remained free of oral allergy syndrome 5 AU/mL (median values, P < 0.05)	Asero 1997
Birch Pollen spec. IgE 19 patients with positive DBPCFC to hazelnut	All patients had Bet v 1-specific IgE and 5 patients had Bet v 2-specific IgE (RAST)	Ballmer-Weber et al. 2000

4 Therapy of Hazelnut Allergy

<table>
<tr><th>Treatment*</th><th>Outcome</th><th>References</th></tr>
<tr><td>Treatment with Astemizole
30 birch pollen allergic patients with clinical symptoms of hazelnut allergy</td><td>Treatment with astemizole significantly reduced the symptoms after oral provocation with hazelnuts compared with placebo (P = 0.004) without completely abolishing symptoms</td><td>Bindslev-Jensen et al. 1991</td></tr>
<tr><td>Tree Pollen Immunotherapy
72 children with birch pollinosis (age of 6-16 years), prevalence of adverse reactions to nuts before immunotherapy 79%
I. subcutaneous immunotherapy for 3 years with a) birch pollen preparation or b) a mixture of birch, alder, and hazel pollen
II. oral immunotherapy for 10 months with c) birch pollen preparation or d) placebo capsules</td><td>Assessment of food allergy after treatment (self-reported):
<table>
<tr><th></th><th>improved</th><th>unchanged</th><th>worse</th></tr>
<tr><td>a) (n=19)</td><td>37%</td><td>42%</td><td>21%</td></tr>
<tr><td>b) (n=20)</td><td>55%</td><td>30%</td><td>15%</td></tr>
<tr><td>c) (n=14)</td><td>21%</td><td>64%</td><td>14%</td></tr>
<tr><td>d) (n=14)</td><td>14%</td><td>86%</td><td>0%</td></tr>
</table>
no significant more decrease in birch pollen immunotherapies as compared to placebo oral immunotherapy</td><td>Möller 1989</td></tr>
</table>

* Studies may be experimental, unproved, or controversial. Please notice the disclaimer !

5 Composition of Hazelnuts

5.1 Distribution of Nutrients

For other hazelnut products see: USDA Nutrient Database

Nutrients: Content per 100 g		
Energy 2739 kJ (648 kcal) Water 5.2 g Protein 12.0 g Lipids 61.6 g Carbohydrate 11.4 g Minerals 2.4 g **Minerals** Sodium 2 mg Potassium 635 mg Magnesium 155 mg Calcium 225 mg Manganese 6 mg Iron 3800 µg Copper 1280 µg Zinc 1870 µg Phosphorus 335 mg Chloride 10 mg Fluoride 17 µg Iodine 2 µg Selenium 2 µg	**Vitamins** Carotene 30 µg Vitamin E 25 mg Vitamin B1 390 µg Vitamin B2 210 µg Nicotinamide 1350 µg Pantothenic acid 1150 µg Vitamin B6 450 µg Folic acid 70 µg Vitamin C 3 mg **Amino Acids** Arg 2030 mg His 280 mg Ile 770 mg Leu 890 mg Lys 380 mg Met 140 mg Phe 510 mg Thr 400 mg Trp 200 mg	Tyr 470 mg Val 870 mg **Lipids** Palmitic acid 3000 mg Stearic acid 1100 mg Oleic acid 47.4 g Linolic acid 6300 mg Linoleic acid 150 mg **Other** Salicylic acid 140 µg Purines 25 mg

Reference: Deutsche Forschungsanstalt für Lebensmittelchemie, Garching bei München (ed), **Der kleine "Souci-Fachmann-Kraut" Lebensmitteltabelle für die Praxis**, WVG, Stuttgart 1991

6 Allergens of Hazelnut and Pollen

Nut Proteins / Glycoproteins	Allergen Nomenclature	References
Major Hazelnut Allergen [18 kDa]	Cor a 1.0401	Hirschwehr et al. 1992, Lüttkopf et al. 1999 [GenBank]
Hazelnut Profilin		van Ree et al. 1992, 1995
Lipid-transfer protein [9 kDa]		Akkerdaas et al. 2000
Allergens: 14, 18, 37, 40, 46, and 69 kDa		Hirschwehr et al. 1992
Allergens: 2 allergens <16 kD, 17 kDa, and 42 kDa		Caballero et al. 1997
Allergens: 7, 9, 38, 42, and 50 kDa		Schocker et al. 1999
Allergens: 25, 37, and 55 kDa, and 14, 18, 22, and 69 kDa		Koppelman et al. 1999
4.8 kDa Allergen		Hird et al. 2000

Pollen Proteins / Glycoproteins	Allergen Nomenclature	References
Major Pollen Allergen [17 kDa]	Cor a 1	Rohac et al. 1991, Breiteneder et al. 1993, Hoffmann-Sommergruber et al. 1997
Allergens: 14, 17, 37, 44, 60, and 69 kDa		Hirschwehr et al. 1992

6.1 Sensitization to Hazelnut Allergens

Country / Subjects	Sensitivity to	References
Austria, Vienna a) 25 hazel pollen and hazelnut allergic patients b) 18 hazel pollen allergic patients without sensitivity to hazelnuts	Hazel pollen: **Allergen** — **in a)** — **in b)** 14 kDa profilin — 8% — - 17 kDa (Cor a 1) — 100% — 100% 30 kDa allergen — - — 6% 37 kDa allergen — 4% — 6% 44 kDa allergen — 12% — - 60 kDa allergen — 24% — - 69 kDa allergen — 12% — 17% Hazelnut: **Allergen** — **in a)** — **in b)** 14 kDa allergen — 8% — - 18 kDa allergen — 100% — 22% 37 kDa allergen — 20% — - 40 kDa allergen — 8% — - 46 kDa allergen — 4% — - 69 kDa allergen — 16% — - (SDS-PAGE immunoblot)	Hirschwehr et al. 1992
Germany, Berlin / Borstel / Langen a) 27 hazelnut allergic patients b) 28 hazelnut and birch pollen sensitive children	Hazelnut: **Allergen** — **in a)** — **in b)** 17-18 kDa allergen — 93% — 79% 48 kDa glycoprotein — 41% — 61% (SDS-PAGE / immunoblot)	Müller et al. 2000
Germany, Munich 7 hazelnut allergic patients	Hazelnut: 20 kDa allergen in 71% 14 - 67 kDa allergens (SDS-PAGE / immunoblot)	Vocks et al. 1993
UK, Manchester / York 4 hazelnut-peanut sensitized patients	Hazelnut: 4.8 kDa allergen (2D-PAGE / immunoblot, MALDI-TOF)	Hird et al. 2000

6.2 Major Hazelnut Allergen (Cor a 1.0401)

6.2.1 Molecular Biological Properties

Major Hazelnut Allergen		References
Allergen Nomenclature Cor a 1.0401		(1) Larsen & Lowenstein 2000
Isoallergens and Variants 3 different isoforms by IEF-PAGE (1)		(1) Hirschwehr et al. 1992
Molecular Mass 18 kDa (1), (SDS-PAGE)		(1) Hirschwehr et al. 1992
Isoelectric Point 3 isoforms: pI 5.7, 6.1, and 6.3 (1) pI 5.2-5.8 (2)		(1) Hirschwehr et al. 1992 (2) Caballero et al. 1997
Cor a 1 Isoform	**Cor a 1.0401**	(1) Lüttkopf et al. 1999 [GenBank]
SWISS-PROT:		
GenBank:	AAD48405	
PIR:		
Amino Acids	161 aa	
mRNA		
cDNA		
Biological Function Bet v 1 family of pathogenisis-related proteins (1)		(1) SWISS-PROT
Sequence Homology of Cor a 1.0401 to: Birch pollen allergen Bet v 1 isoforms: aa 63-78% identity, aa 85% similarity (1) Hazel pollen Cor a 1.01 isoforms: aa 58-60% identity, aa 69-71% similarity (1) Hazel pollen Cor a 1.02 isoform: aa 70% identity (1) Hazel pollen Cor a 1.03 isoform: aa 71% identity (1) Apple allergen Mal d 1 isoforms: aa 55-57% identity, aa 66-69% similarity (1) Celery allergen Api g 1: aa 35% identity, aa 55% similarity (1) Carrot allergen Dau c 1 isoforms: aa 34-35% identity, aa 52% similarity (1)		(1) BLAST at PIR

6.2.2 Allergenic Properties

Major Hazelnut Allergen	References
Frequency of Sensitization IgE-binding to 18 kDa allergen in 100% of patients (1)	(1) see 5.1 Sensitization to Hazel Allergens
Histamine Release Histamine releasing capacity of 18 kDa allergen was demonstrated using blood basophils from 1 hazelnut allergic patient (1)	(1) Hirschwehr et al. 1992
Allergenic Potencies IgE- binding capacities of 18-kDa allergen isoforms: pI 6.3 = pI 6.1 > pI 5.7 (2D-PAGE immunoblot of purified 18-kDa allergen) (1)	(1) Hirschwehr et al. 1992
Cross-reactivity IgE- cross- reactive to rBet v 1 (1)	(1) see 7 Cross-Reactivities

6.3 Major Pollen Allergen (Cor a 1)

6.3.1 Molecular Biological Properties

<table>
<tr><th>Major Pollen Allergen</th><th>References</th></tr>
<tr><td>Allergen Nomenclature Cor a 1.01 - Cor a 1.03</td><td>(1) Larsen & Lowenstein 2000</td></tr>
<tr><td>Isoallergens and Variants
4 isoallergens or variants by SDS/IEF-PAGE (1)
4 recombinant variants of Cor a 1.01 with aa identities of 96-99% (2)
2 additional isoallergens Cor a 1.02 and Cor a 1.03 (3)</td><td>(1) Rohac et al. 1991
(2) Breiteneder et al. 1993
(3) Hoffmann-Sommergruber et al. 1997</td></tr>
<tr><td>Molecular Mass
17 kDa (1), (SDS-PAGE)</td><td>(1) Rohac et al. 1991</td></tr>
<tr><td>Isoelectric Point pI 5.0-5.8 (1)</td><td>(1) Rohac et al. 1991</td></tr>
<tr><td>Amino Acid Sequence, mRNA, and cDNA
<table>
<tr><th>Protein</th><th>Cor a 1.0101</th><th>Cor a 1.0102</th><th>Cor a 1.0103</th><th>Cor a 1.0104</th></tr>
<tr><th>formerly</th><th>Cor a 1/5</th><th>Cor a 1/6</th><th>Cor a 1/11</th><th>Cor a 1/16</th></tr>
<tr><td>SWISS-PROT:</td><td>Q08407</td><td>Q08407</td><td>Q08407</td><td>Q08407</td></tr>
<tr><td>GenBank:</td><td>X70999</td><td>X71000</td><td>X70997</td><td>X70998</td></tr>
<tr><td>PIR:</td><td>S30053</td><td>S30054</td><td>S30055</td><td>S30056</td></tr>
<tr><td>Amino Acids</td><td>159 aa</td><td>159 aa</td><td>159 aa</td><td>159 aa</td></tr>
<tr><td>mRNA</td><td>619 bp</td><td>742 bp</td><td>655 bp</td><td>860 bp</td></tr>
<tr><td>cDNA</td><td></td><td></td><td></td><td></td></tr>
</table>
<table>
<tr><th>Protein</th><th>Cor a 1.0201</th><th>Cor a 1.0301</th></tr>
<tr><td>SWISS-PROT:</td><td></td><td></td></tr>
<tr><td>GenBank:</td><td>Z72439</td><td>Z72440</td></tr>
<tr><td>PIR:</td><td></td><td></td></tr>
<tr><td>Amino Acids</td><td>160 aa</td><td>160 aa</td></tr>
<tr><td>mRNA</td><td></td><td></td></tr>
<tr><td>cDNA</td><td>564 bp</td><td>577 bp</td></tr>
</table></td><td>(1) Breiteneder et al. 1993
(2) Hoffmann-Sommergruber et al. 1997</td></tr>
<tr><td>recombinant Protein
Expression in Escherichia coli:
4 recombinant isoforms (1, 2)</td><td>(1) Breiteneder et al. 1993
(2) Schenk et al. 1994</td></tr>
<tr><td>Biological Function
Bet v 1 family of pathogenisis-related proteins (1)</td><td>(1) SWISS-PROT</td></tr>
</table>

Sequence Homology a) of Cor a 1.01 isoforms to: Birch pollen allergen Bet v 1: aa 71-73% identity, 80.5-83% similarity (1) Alder pollen allergen Aln g 1: aa 75.5-76.7% identity, 83.6-85% similarity (1) Hornbeam pollen allergen Car b 1: aa 83.6-89.9% identity, 89.3-95% similarity (1) Apple allergen Mal d 1: aa 54% identity (2) b) of Cor a 1.02 isoform to: Cor a 1.01 isoforms: aa 73-75% identity, aa 85-87% similarity (3) Birch pollen allergen Bet v 1: aa 80-85% identity, 89-93% similarity (3) Apple allergen Mal d 1 isoforms: aa 56-66% identity, aa 72-81% similarity (3) Celery allergen Api g 1: aa 40% identity, aa 61% similarity (3) Carrot allergen Dau c 1 isoforms: aa 40% identity, aa 58% similarity (3) c) of Cor a 1.03 isoform to: Cor a 1.01 isoforms: aa 63-65% identity, aa 74-78% similarity (3) Cor a 1.02 isoform: aa 71% identity (3) Birch pollen allergen Bet v 1: aa 67-73% identity, 78-82% similarity (3) Apple allergen Mal d 1 isoforms: aa 61-71% identity, aa 77-83% similarity (3) Celery allergen Api g 1: aa 39% identity, aa 62% similarity (3) Carrot allergen Dau c 1 isoforms: aa 37% identity, aa 58-60% similarity (3)	(1) Breiteneder et al. 1993 (2) Vieths et al. 1996 (3) BLAST at PIR

6.3.2 Allergenic Properties

Major Pollen Allergen	References
Frequency of Sensitization IgE-binding to Cor a 1 in 100% of patients (1)	(1) see 5.1 Sensitization to Hazel Allergens
Allergenic Potencies Differential IgE reactivity to 4 rCor a 1 isoforms by samples of 5 hazelpollen allergic patients (immunoblot) (1, 2)	(1) Breiteneder et al. 1993 (2) Schenk et al. 1994
Cross-reactivity IgE- cross- reactive to rBet v 1 (1)	(1) see 7 Cross-Reactivities

T-Cell Proliferation / Epitopes

Stimulation of Bet v 1 specific T-cell clones with natural Cor a 1 (1)

Stimulation of Bet v1 specific T-cell clones from birch pollen and hazelpollen allergic patients with natural and recombinant Cor a 1 isoforms (2):

Isoform	**Positive Stimulation:**
nCor a 1	in 4/6 clones
rCor a 1/5	in 3/6 clones
rCor a 1/6	in 5/6 clones
rCor a 1/11	in 3/6 clones
rCor a 1/16	in 4/6 clones

Stimulation of Bet v1 specific T-cell clones from birch pollen and hazelpollen allergic patients with synthetic peptides according to internal sequences of rCor a 1 isoforms and rBet v 1 (2):

rCor a 1	**5**	**6**	**11**	**16**	**rBet v 1**
aa 12-23	+	+	+	-	+
aa 63-74 * (1)	+	+	+	+	+
aa 77-88	-	+	+	-	+
aa 97-108	-	+/-	-	+/-	+/-
aa 111-122	+	+	+	+	+
aa 144-155	+	+	+	+	+

* same sequence in all Cor a 1 isoforms

Amino acids critical for T-cell proliferation with synthetic peptides (2):
aa 12-23 position 14 (substitution Pro / Ser)
aa 77-88 position 80 (substitution Lys / Thr)
aa 97-108 position 100 (substitution Ser / His)

(1) Ebner et al. 1993
(2) Schenk et al. 1994

7 Isolation & Preparation

Extract / Purified Allergens	**Methods**	**References**
Protein extract from nuts	Nuts grounded under liquid nitrogen, extraction overnight at 4°C with potassium phosphate buffer (pH 7.0) containing PVPP, EDTA, sodium diethyldithiocarbamate and sodium azide, centrifugation, filtration, dialysis, and lyophylization, storage -20°C	Hirschwehr et al. 1992
Protein extract from nuts	Comparison of different extraction conditions (3 buffer systems, 3 temperatures for 4h): no differences in IgE-binding, maximum yield of soluble proteins with tris/tricine buffer at 45°C	Vieths et al. 1998
Protein extract from nuts	Nuts were peeled, chopped, and ground; extraction with ammonium carbonate buffer (pH 8.0) at 4°C for 4h; filtration, defatted extract centrifued, supernatant dialyzed and lyophylized, storage -20°C	Caballero et al. 1997
Protein extract from nuts	Nuts blended and added to ammonium bicarbonate buffer (pH 7.8), placed on ice, blended and rocked for 48 h at 4°C, centrifugation, storage at -70°C	Teuber et al. 1997

Protein extract from nuts	Hazelnuts were shelled, skinned, and ground; extraction with bicarbonate buffer (pH 9.2) containing tetramethylen sulphone; homogenization and stirring for 1 h at RT; centrifugation and protein precipitation with acetone at -20°C for 30 min; after centrifugation protein solids washed with butanol and dried	Hird et al. 2000
Protein extract from oil	Oil added to ammonium bicarbonate buffer (pH 7.8), rocked for 48 h at 4°C, centrifugation, and aqueous layer ultracentrifuged, storage at -70°C	Teuber et al. 1997
18-kDa allergen from hazelnut	Hazelnut protein extract treated 3 times with Bioacryl BPA-1000 (precipitation of nucleic acid and major proteins other than 18-kDa allergen), centrifugation, dialysis of supernatant, further purification with IEC and RP-HPLC	Hirschwehr et al. 1992 Schenk et al. 1994
Hazelpollen allergen Cor a 1	Aqueous extract of hazelpollen followed by preparative RP-HPLC	Ebner et al. 1993

8 Cross-Reactivities

Cross-Reacting Allergens	Subjects / Methods	References
Hazelnut *(Pollen)* birch pollen *	Partial identity between birch pollen and hazelnut antigens (CLIE using rabbit anti- birch Ab)	Andersen & Lowenstein 1978
Hazelnut *(Pollen)* birch pollen *	Correlation between birch pollen allergy and hazelnut hypersensitivity (1129 adults with bronchial asthma and/or allergic rhinitis, questionaire)	Eriksson 1978
Hazelnut *(Pollen)* alder, hazel, aspen, and bog-myrde pollen *	Correlation between sensitization to hazelnut and pollen in birch pollen allergic patients (SPT)	Eriksson et al. 1982
Hazelnut *(Pollen)* tree (elm, olive, birch, plane, ash), weed (parietaria, mugwort), and grass pollen *	Sensitization to pollens in 63 hazelnut allergic patients: tree pollen 67%, weeds 40%, grasses 11% (2 positive results from SPT, HR, and RAST)	Amat Par et al. 1990
Hazel pollen *(Pollen)* birch pollen, Cor a 1	Inhibition of IgE- binding to Cor a 1 by birch pollen extract	Rohac et al. 1991
Hazelnut, Hazel pollen *(Pollen)* birch pollen allergens: a) rBet v 1 b) rBet v 2 (profilin)	3 patients with hazel pollen and hazelnut allergy (pooled serum): a) IgE- binding to 18 kDa hazelnut allergen and Cor a 1 was abolished by rBet v 1 b) IgE- binding to 14 kDa hazelnut and hazel pollen allergens was abolished by rBet v 2 (immunoblot inhibition)	Hirschwehr et al. 1992
Hazel pollen *(Pollen)* birch pollen allergens: rBet v 1 and rBet v 2 (profilin)	102 patients from Austria, France, Sweden, and Switzerland: 75 to 84% inhibition of IgE- binding to hazel pollen extract by a combination of recombinant Bet v 1 and Bet v 2 (mean percentages, RAST inhibition) 11 tree pollen allergic patients: inhibition of IgE- binding to 2 hazel pollen allergens of 12 to 17 kDa by Bet v 1 and Bet v 2 (immunoblot inhibition)	Niederberger et al. 1998
Hazelnut *(Pollen)* mugwort pollen	Serum pool from 28 patients with specific IgE to mugwort pollen and hazelnut: 63% inhibition of IgE- binding to hazelnut by mugwort; 36% inhibition of IgE- binding to mugwort by hazelnut (RAST inhibition)	Caballero et al. 1997

Hazelnut *(Pollen)* mugwort pollen allergens (33-, 65-kDa), hazelnut allergens (17-, 42-, <16-kDa)	Hazelnut extract inhibits IgE- binding to 33- and 65-kDa mugwort allergens; mugwort extract inhibits IgE-binding to all hazelnut allergens (SDS-PAGE and IEF-PAGE immunoblot inhibition)	Caballero et al. 1997
Hazelnut *(Pollen)* hazel pollen	5 patients with hazel pollen and hazelnut allergy (pooled serum): IgE- binding to hazelnut allergens was reduced by hazel pollen extract; IgE- binding to hazel pollen allergens was not reduced by hazelnut extract (immunoblot inhibition)	Hirschwehr et al. 1992
Hazelnut: *(Pollen)* birch pollen, rBet v 1, rBet v 2 profilin, timothy grass pollen extract; 21 patients with clinical relevant allergy to pollen and plant-derived food	Mixture of rBet v 1 and rBet v 2 inhibited IgE-binding to 10-14 kDa (profilin related) and 17-21 kDa (Bet v 1 related) hazelnut allergens, timothy grass pollen inhibited IgE-binding to 30-100 kDa allergens from hazelnut (immunoblot inhibition); 83% (4-100%) inhibition of IgE-binding to hazelnut extract by mixture of rBet v 1 and rBet v 2 and 94% (17-100%) by mixture of rBet v1, rBet v 2, and timothy pollen extract (26 sera) (RAST inhibition)	Kazemi-Shirazi et al. 2000
Hazelnut *(Nuts)* walnut, cashewnut, pecannut, almond	6 hazelnut allergic adults: Inhibition of IgE binding to hazelnut proteins by walnut (30-35%), cashewnut and pecannut (appr. 15%), and almond (appr. 8%) (RAST inhibition)	Koppelman et al. 1999
Hazelnut *(Nuts, Peanuts)* significant associations: peanut, walnut, almond *	262 fruit and/or vegetable allergic patients (clinical history, SPT, RAST)	Ortolani et al. 1988
Hazelnut *(Nuts, Peanuts, Seeds)* walnut, brazil nut, almond, pecan, pistatio, pine nut, peanut, sesame seeds *	111 peanut and/or tree nut allergic patients: strong correlation (r >0.7) between hazelnut and walnut, brazil nut, almond, and sesame; moderate correlation (r >0.6) between hazelnut and peanut, pecan, pistachio, and pine nut (RAST)	Sicherer et al. 1998
Hazelnut *(Fruits, Seeds)* kiwi fruit, poppy seeds, sesame seeds	8 Patients with food / pollen allergy (immunoblot inhibition)	Vocks et al. 1993
Hazelnut *(Fruits)* kiwi fruit	3 kiwi allergic patients: moderate inhibition of IgE-binding to kiwi extract by hazelnut extract (RAST inhibition)	Gall et al. 1994
Hazelnut *(Rye)* rye flour *	Correlation between specific IgE to rye flour and nuts (peanut, almond, brazil nut, coconut, hazelnut) (3310 atopic patients, RAST, r = 0.5 to 0.8)	Seifert et al. 1988
Hazelnut *(Various Foods)* kiwi fruit, poppy seeds, sesame seeds, rye flour	5 patients: 50 to 100% inhibition of IgE- binding to poppy seed by hazelnut; 2 patients each: 56 and 84% inhibiton to kiwi by hazelnut, 78 and 91% inhibition to sesame seed by hazelnut; 1 patient: 77 and 84% inhibition to rye flour by hazelnut and vice versa (RAST inhibition)	Seifert et al. 1988

* multiple sensitization (not proved by inhibition-tests)

9 Allergenicity of Different Hazelnut Varieties

Varieties / Subjects	Differences	References
6 Hazelnut Varieties hazelnut allergic patients	No significant differences in relative amounts of allergens (SDS-PAGE / immunoblot)	Vieths et al. 1998
5 Hazelnut Varieties 8 hazelnut allergic patients	Similar IgE binding patterns to all varieties, slight differences as regards intensity of detection (SDS-PAGE / immunoblot) Minor differences in IgE-binding potencies of varieties: Contorta (Germany) > Barcelona (USA) > Levantiner (Turkey) and Neapler (Sicily) > Römer (Italy) (EAST inhibition)	Wigotzki et al. 2000b

10 Stability of Hazelnut Allergens

Treatment	Effects	References
Hazelnuts *(Storage)* storage (1 to 19 weeks at room temperature)	No significant differences as compared to native hazelnuts (SDS-PAGE immunoblot, EAST inhibition)	Wigotzki et al. 2000b
Hazelnuts *(Heat)* heating to 100°C for 30 min	Heating of the food reduced allergenic activity in anti-birch pollen IgE system, while considerable activity was retained in anti- hazelnut IgE system (RBL cell mediator release assay)	Vieths et al. 1998
Hazelnuts *(Heat)* roasting to 140°C for a) 20 min and b) 40 min	Positivity in SPT with: raw hazelnuts 95% roasted hazelnuts a) 47% roasted hazelnuts b) 11% (19 patients with positive DBPCFC to hazelnut)	Ballmer-Weber et al. 2000
Hazelnuts *(Heat)* heating of ground hazelnuts at 100-185°C for 15-90 min (dry heating oven) or microwave heating (630 W, 10 min)	No reduction of IgE binding after heating 100°C for 90 min or after microwave treatment; decrease of IgE binding after heating to >100°C for 15 min; after heating to >170°C the major allergens abolished in immunoblotting; a minor allergen with <14 kDa detectable after heating up to 185°C for 15 min (19 hazelnut allergic patients, SDS-PAGE immunoblot, EAST inhibition)	Wigotzki et al. 2000b
Hazelnuts *(Hydrolysis)* 2 step digestion with a) pepsin (2 h) and b) pancreatic enzymes (45 min) (extract from hazelnuts)	IgE-binding after combined hydrolysis (a + b) of hazelnut proteins reduced to <10% as compared to native protein extract (EAST, hazelnut allergic patients)	Vieths et al. 1999
Hazelnuts *(Enzymic Hydrolysis)* hydrolysis of hazelnut proteins up to 240 min with a) pepsin b) trypsin, elastase, and protease (from Tritirachium album) c) pancreatin	a) only slightly decrease in IgE-binding after peptic hydrolysis for 60 min (maximum EAST inhibition appr. 65%); after 240 min maximum EAST inhibition was about 40% as compared to native hazelnut extract and 2/7 sera still showed IgE-binding in SDS-PAGE immunoblot b) hydrolysis with trypsin, elastase, and protease (from Tritirachium album) significantly decreased IgE-binding after 30 min of treatment to a maximum EAST inhibition <30% c). Hydrolysis with pancreatin for 60 min reduced IgE-binding to < 30% maximum inhibition (15 hazelnut allergic patients)	Wigotzki et al. 2000a

11 Allergen Sources

Reported Adverse Reactions	References
Food / Food additives After ingestion of hazelnuts (1) Ingestion of hazelnut fragment in muesli (2) Accidental ingestion of tree nuts by 30% of tree nut allergic patients over a period of 5.5 years (3)	(1) see 2 Symptoms of Hazelnut Allergy (2) Ewan 1996 (3) Sicherer et al. 1998
Chocolate Asthma after ingestion of 3-6 g of chocolate containing 0.2% of hazelnut proteins (1)	(1) Malmheden Yman et al. 1994

Potential Adverse Reactions	References
Food compounds Nickel allergy: Consumption of hazelnuts in larger amounts may increase the nickel intake, which potentially could elicit nickel allergic reactions (2) Salicylic acid intolerance: Correlation between acetylsalicylic acid intolerance and hazelnut hypersensitivity maybe due to natural content of salicylic acid (1129 adults with bronchial asthma and/or allergic rhinitis, questionaire) (1)	(1) Eriksson 1978 (2) Flyvholm et al. 1984

Allergens in Hazelnut Products	Content / Products	References
Hazelnut Allergens hazelnut oil (blend of refined and unrefined oils) and pool serum from 17 nut or peanut allergic patients	Protein content in hazelnut oil: 62 µg/ml; IgE- binding to protein extract in dot immunoblot	Teuber et al. 1997
Hazelnut Proteins commercial food products without labeling of hazelnut	a) Amounts of hazelnut between 1.8 and 421 mg/kg in 14 of 27 samples (ELISA, polyclonal antibodies, limit of detection 0.002%) b) Qualitative detection of hazelnut in the same samples as a), no false positive results (hazelnut specific PCR detection of 182bp product from cDNA of Cor a 1.0401, limit of detection 0.001%)	a) Holzhauser & Vieths 1999 b) Holzhauser et al. 2000
Hazelnut Proteins samples assumed to be free of hazelnuts: chocolate spread, chocolate bar, chocolate cookie, muesli cookie, and cake	Amounts of hazelnut between 3.4 and 752 mg/kg in 15 of 26 samples; a complaint sample of chocolate spread contained 4 g/kg of undecleared hazelnut (ELISA, rabbit-antibodies)	Koppelman et al. 1999

12 Food Allergen Labeling

Food Allergen	Labeling / Regulation Status	References
International Regulations Tree nuts* and products of these	mandatory labeling of prepackaged food / advisary status (1)	(1) Codex Alimentarius Commission 1999
European Regulations Tree nuts* and products of these	labeling appropriate / recommendation (1)	(1) Bousquet et al. 1998

* including almond, brazil nut, cashew nut, hazelnut, pecannut, pistachio, and walnut

13 References

- Aas K (1978) **The diagnosis of hypersensitivity to ingested foods. Reliability of skin prick testing and the radioallergosorbent test with different materials** *Clin Allergy 8:39-50*
- Akkerdaas J, Hefle S, Aalberse R, van Ree R (2000) **Characterization of non-pollen-related hazelnut allergens** *J Allergy Clin Immunol 105(1Pt2):Abstract No.410*
- Amat Par P, Sanosa Valls J, Lluch Perez M, Malet Casajuana A, Garcia Calderon PA (1990) **Dried fruit hypersensitivity and its correlation with pollen allergy** *Allergol Immunopathol Madr 18:27-34*
- Andersen KE, Lowenstein H (1978) **An investigation of the possible immunological relationship between allergen extracts from birch pollen, hazelnut, potato and apple** *Contact Dermatitis 4(2):73-9*
- Andre F, Andre C, Colin L, Cacaraci F, Cavagna S (1994) **Role of new allergens and of allergens consumption in the increased incidence of food sensitizations in France** *Toxicology 93(1):77-83*
- Armstrong D, Rylance G (1999) **Definitive diagnosis of nut allergy** *Arch Dis Child 80:175-7*
- Asero R (1997) **Relevance of pollen-specific IgE levels to the development of Apiaceae hypersensitivity in patients with birch pollen allergy** *Allergy 52(5):560-4*
- Baker H, Luyt D, Stern M (1999) **Open challenge to nuts in children** *Allergy 54(1):79-80*
- Ballmer-Weber BK, Vieths S, Bucher C, Lüttkopf D, Wüthrich B (2000) **Hazelnut allergy: Validation of diagnostic procedures on the basis of double-blind placebo-controlled food challenges** *Allergologie 23:285-91* [in German]
- Bindslev-Jensen C, Vibits A, Stahl-Skov P, Weeke B (1991) **Oral allergy syndrome: the effect of astemizole** *Allergy 46:610-3*
- Bock SA, Lee WY, Remigio LK, May CD (1978) **Studies of hypersensitivity reactions to foods in infants and children** *J Allergy Clin Immunol 62:327-34*
- Bock SA, Atkins FM (1990) **Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges** *J Pediatr 117(4):561-7*
- Boehncke WH, Loeliger C, Kuehnl P, Kalbacher H, Bohm BO, Gall H (1998) **Identification of HLA-DR and -DQ alleles conferring susceptibility to pollen allergy and pollen associated food allergy** *Clin Exp Allergy 28(4):434-41*
- Bousquet J, Björkstén B, Bruijnzeel-Koomen CAFM, Huggett A, Ortolani C, Warner JO, Smith M (1998) **Scientific criteria and the selection of allergenic foods for product labelling** *Allergy 53:3-21*
- Breiteneder H, Ferreira F, Hoffman-Sommergruber K, Ebner C, Breitenbach M, Rumpold H, Kraft D, Scheiner O (1993) **Four recombinant isoforms of Cor a I, the major allergen of hazel pollen** *Europ J Biochem 212:355-62*
- Caballero T, Pascual C, Garcia-Ara MC, Ojeda JA, Martin-Esteban M (1997) **IgE crossreactivity between mugwort pollen (Artemisia vulgaris) and hazelnut (Abellana nux) in sera from patients with sensitivity to both extracts** *Clin Exp Allergy 27:1203-11*
- Codex Alimentarius Commission (1999) **Food labelling - complete texts** *Joint FAO/WHO Food Standards Programme, FAO/WHO, Rome*
- Crespo JF, Pascual C, Burks AW, Helm RM, Esteban MM (1995) **Frequency of food allergy in a pediatric population from Spain** *Pediatr Allergy Immunol 6:39-43*
- de Groot H, de Jong NW, Vuijk MH, Gerth van Wijk R (1996) **Birch pollinosis and atopy caused by apple, peach, and hazelnut; comparison of three extraction procedures with two apple strains** *Allergy 51(10):712-8*
- Diez-Gomez ML, Quirce S, Cuevas M, Sánchez-Fernández C, Baz G, Moradiellos FJ, Martinez A (1999) **Fruit-pollen-latex cross-reactivity: implication of profilin (Bet v 2)** *Allergy 54:951-61*
- Ebner C, Ferreira F, Hoffmann K, Hirschwehr R, Schenk S, Szepfalusi Z, Breiteneder H, Parronchi P, Romagnani S, Scheiner O, Kraft D (1993) **T cell clones specific for Bet v I, the major birch pollen allergen, crossreact with the major allergens of hazel, Cor a I, and alder, Aln g I** *Mol Immunol 30:1323-9*
- Emmett SE, Angus FJ, Fry JS, Lee PN (1999) **Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members** *Allergy 54:380-5 (erratum 54:891)*
- Eriksson NE (1978) **Food sensitivity reported by patients with asthma and hay fever. A relationship between food sensitivity and birch pollen-allergy and between food sensitivity and acetylsalicylic acid intolerance** *Allergy 33:189-96*
- Eriksson NE, Formgren H, Svenonius E (1982) **Food hypersensitivity in patients with pollen allergy** *Allergy 37:437-43*
- Etesamifar M, Wüthrich B (1998) **IgE- mediated food allergies including oral allergy syndrome in 383 patients** *Allergologie 21:451-7* (in German)
- European Commission (1998) **Reports on tasks for scientific cooperation. The occurrence of severe food allergies in the EU** *European Commission, Directorate-General III, SCOOP/NUTR/REPORT/2, Brussels*
- Ewan PW (1996) **Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations** *BMJ 312:1074-8*

- Flyvholm MA, Nielsen GD, Andersen A (1984) **Nickel content of food and estimation of dietary intake** *Z Lebensm Unters Forsch 179:427-31*
- Fogle-Hansson M, Bende M (1993) **The significance of hypersensitivity to nuts in patients with birch pollen allergy** *Allergy 48:282-4*
- Foucard T, Edberg U, Malmheden-Yman I (1997) **Fatal and severe food hypersensitivity. Peanut and soya underestimated allergens** *Lakartidningen 94(30-31):2635-8*
- Gall H, Kalveram KJ, Forck G, Sterry W (1994) **Kiwi fruit allergy: a new birch pollen-associated food allergy** *J Allergy Clin Immunol 94(1):70-6*
- Garcia-Ortiz JC, Cosmes PM, Lopez-Asunsolo A (1996) **Allergy to foods in patients monosensitized to Artemisia pollen** *Allergy 51(12):927-31*
- Gluck U (1990) **Pollinosis and oral allergy syndrome** *HNO 38:188-90* (in German)
- Guariso G, Bertoli S, Cernetti R, Battistella PA, Setari M, Zacchello F (1993) **Migraine and food intolerance: a controlled study in pediatric patients** *Pediatr Med Chir 15:57-61* (in Italian)
- Guinnepain MT, Eloit C, Raffard M, Brunet-Moret MJ, Rassemont R, Laurent J (1996) **Exercise-induced anaphylaxis: useful screening of food sensitization** *Ann Allergy Asthma Immunol 77:491-6*
- Herkenrath C, Gottmann-Luckerath I, Steigleder GK (1982) **Combined allergy against hazel pollen and hazel nuts** *Z Hautkr 57:1399-405* (in German)
- Hill DJ, Hosking CS, Zhie CY, Leung R, Baratwidjaja K, Iikura Y, Iyngkaran N, Gonzalez-Andaya A, Wah LB, Hsieh KH (1997) **The frequency of food allergy in Australia and Asia** *Environ Toxicol Pharmacol 4:101-10*
- Hird H, Pumphrey R, Wilson P, Sunderland J, Reece P (2000) **Identification of peanut and hazelnut allergens by native two- dimensional gel electrophoresis** *Electrophoresis 21:2678-83*
- Hirschwehr R, Valenta R, Ebner C, Ferreira F, Sperr WR, Valent P, Rohac M, Rumpold H, Scheiner O, Kraft D (1992) **Identification of common allergenic structures in hazel pollen and hazelnuts: a possible explanation for sensitivity to hazelnuts in patients allergic to tree pollen** *J Allergy Clin Immunol 90(6 Pt 1):927-36*
- Hoffmann-Sommergruber K, Vanek-Krebitz M, Radauer C, Wen J, Ferreira F, Scheiner O, Breiteneder H (1997) **Genomic characterization of members of the Bet v 1 family: genes coding for allergens and pathogenesis-related proteins share intron positions** *Gene 197:91-100*
- Hofman T (1994) **Specific IgE antibodies for nuts in infants** *Pol Tyg Lek 49:328-9* (in Polish)
- Holzhauser T, Stefan Vieths S (1999) **Quantitative sandwich ELISA for determination of traces of hazelnut *(Corylus avellana)* protein in complex food matrixes** *J Agric Food Chem 47:4209-18*
- Holzhauser T, Wangorsch A, Vieths S (2000) **Polymerase chain reaction (PCR) for detection of potentially allergenic hazelnut residues in complex food matrixes***Eur Food Res Technol 211:360-5*
- Jankiewicz A, Aulepp H, Baltes W, Bogl KW, Dehne LI, Zuberbier T, Vieths S (1996) **Allergic sensitization to native and heated celery root in pollen-sensitive patients investigated by skin test and IgE binding** *Int Arch Allergy Immunol 111(3):268-78*
- Kazemi-Shirazi L, Pauli G, Purohit A, Spitzauer S, Fröschl R, Hoffmann-Sommergruber K, Breiteneder H, Scheiner O, Kraft D, Valenta R (2000) **Quantitative IgE inhibition experiments with purified recombinant allergens indicate pollen-derived allergens as the sensitizing agents responsible for many forms of plant food allergy** *J Allergy Clin Immunol 105:116-125*
- Koppelman SJ, Knulst AC, Koers WJ, Penninks AH, Peppelman H, Vlooswijk R, Pigmans I, van Duijn G, Hessing M (1999) **Comparison of different immunochemical methods for the detection and quantification of hazelnut proteins in food products** *J Immunological Methods 229:107-20*
- Larsen JN, Lowenstein H (2000) **Official list of allergens: IUIS Allergen Nomenclature Subcommittee** *ftp://biobase.dk / pub / who-iuis / allergen.list*
- Leonard JC, Morin C, Albecq JF (1996) **Latex allergy and orthopedic surgery** *Rev Chir Orthop Reparatrice Appar Mot 82:321-6* (in French)
- Lessof MH, Wraith DG, Merrett TG, Merrett J, Buisseret PD (1980) **Food allergy and intolerance in 100 patients - local and systemic effects** *Q J Med 49(195):259-71*
- Malmheden Yman I, Eriksson A, Everitt G, Yman L, Karlsson T (1994) **Analysis of food proteins for verification of contamination or mislabelling** *Food Agric Immunol 6:167-72*
- Martin-Munoz F, Lopez-Cazana JM, Villas F, Contreras JF, Diaz JM, Ojeda JA (1994) **Exercise-induced anaphylactic reaction to hazelnut** *Allergy 49:314-6*
- Moller C (1989) **Effect of pollen immunotherapy on food hypersensitivity in children with birch pollinosis** *Ann Allergy 62:343-5*
- Müller U, Lüttkopf D, Hoffmann A, Petersen A, Becker WM, Schocker F, Niggemann B, Altmann F, Kolarich D, Haustein D, Vieths S (2000) **Allergens in raw and roasted hazelnuts (*Corylus avellana*) and their cross-reactivity to pollen** *Eur Food Res Technol 212(1):2-12*

- Niederberger V, Pauli G, Gronlund H, Froschl R, Rumpold H, Kraft D, Valenta R, Spitzauer S (1998) **Recombinant birch pollen allergens (rBet v 1 and rBet v 2) contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen: a quantitative IgE inhibition study with sera from different populations** *J Allergy Clin Immunol 102(4 Pt 1):579-91*
- Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagna G, Giovane A, Vierucci A (1998) **Anaphylaxis in children: clinical and allergological features** *Pediatrics 101(4):e8*
- Ortolani C, Ispano M, Pastorello E, Bigi A, Ansaloni R (1988) **The oral allergy syndrome** *Ann Allergy 61(6 Pt 2): 47-52*
- Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC (1989) **Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome** *J Allergy Clin Immunol 83(3):683-90*
- Ortolani C, Ballmer-Weber BK, Hansen KS, Ispano M, Wüthrich B, Bindslev-Jensen C, Ansaloni R, Vannucci L, Pravettoni V, Scibilia J, Poulsen LK, Pastorello EA (2000) **Hazelnut allergy: A double- blind, placebo- controlled food challenge multicenter study** *J Allergy Clin Immunol 105:577-81*
- Pumphrey RS, Stanworth SJ (1996) **The clinical spectrum of anaphylaxis in north-west England** *Clin Exp Allergy 26:1364-70*
- Pumphrey RS, Wilson PB, Faragher EB, Edwards SR (1999) **Specific immunoglobulin E to peanut, hazelnut and brazil nut in 731 patients: similar patterns found at all ages** *Clin Exp Allergy 29:1256-9*
- Rance F, Dutau G (1997) **Labial food challenge in children with food allergy** *Pediatr Allergy Immunol 8(1):41-4*
- Rance F, Kanny G, Dutau G, Moneret-Vautrin DA (1999) **Food hypersensitivity in children: Clinical aspects and distribution of allergens** *Pediatr Allergy Immunol 10:33-8*
- Reekers R, Busche M, Wittmann M, Kapp A, Werfel T (1999) **Birch pollen- related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens** *J Allergy Clin Immunol 104:466-72*
- Resano A, Crespo E, Fernandez Benitez M, Sanz ML, Oehling A (1998) **Atopic dermatitis and food allergy** *J Investig Allergol Clin Immunol 8(5):271-6*
- Rohac M, Birkner T, Reimitzer I, Bohle B, Steiner R, Breitenbach M, Kraft D, Scheiner O, Gabl F, Rumpold H (1991) **The immunological relationship of epitopes on major tree pollen allergens** *Mol Immunol 28:897-906*
- Rohrer CL, Pichler WJ, Helbling A (1998) **Anaphylaxie: Klinik, Ätiologie und Verlauf bei 118 Patienten** *Schweiz Med Wochenschr 128:53-63* (in German)
- Schenk S, Hoffmann-Sommergruber K, Breiteneder H, Ferreira F, Fischer G, Scheiner O, Kraft D, Ebner C (1994)**Four recombinant isoforms of Cor a 1, the major allergen of hazel pollen, show different reactivities with allergen-specific T-lymphocyte clones** *Eur J Biochem 224:717-22*
- Schocker F, Luttkopf D, Muller U, Thomas P, Vieths S, Becker WM (2000) **IgE binding to unique hazelnut allergens: identification of non pollen-related and heat-stable hazelnut allergens eliciting severe allergic reactions** *Eur J Nutr 39(4):172-80*
- Seifert HU, Seifert B, Düngemann H, Vocks E, Borelli S, Gugger A (1988) **Immunologische Kreuzreaktionen bei Nüssen, Roggenmehl, Kiwi, Sesam und Mohnsamen** *Allergologie 11(5):169-72* (in German)
- Sicherer SH, Burks AW, Sampson HA (1998) **Clinical features of acute allergic reactions to peanut and tree nuts in children** *Pediatrics 102(1):e6*
- Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA (1999) **Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey** *J Allergy Clin Immunol 103:559-62*
- Straumann F, Wüthrich B (2000) **Food allergies associated with birch pollen: comparison of Allergodip and Pharmacia CAP for detection of specific IgE antibodies to birch pollen related foods***J Investig Allergol Clin Immunol 10:135-41*
- Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW (1996) **Cohort study of peanut and tree nut sensitisation by age of 4 years** *BMJ 313:514-7*
- Teuber SS, Brown RL, Haapanen LA (1997) **Allergenicity of gourmet nut oils processed by different methods** *J Allergy Clin Immunol 99:502-7*
- Troise C, Voltolini S, Delbono G, Negrini AC (1992) **Allergy to pollens from Betulaceae and Corylaceae in a Mediterranean area (Genoa, Italy) - a ten-year retrospective** *J Investig Allergol Clin Immunol 2:313-7*
- Vieths S, Aulepp H, Becker WM, Buschmann L (1996) **Characterization of labile and stable allergens in foods of plant origin** in: *Food Allergies and Intolerances: Symposium (Eisenbrand G, Dayan AD, Ring J, Aulepp H, Elias PS, Grunow W, Schlatter J, eds) pp 130-49 VCH Weinheim*
- Vieths S, Hoffmann A, Holzhauser T, Muller U, Reindl J, Haustein D (1998) **Factors influencing the quality of food extracts for in vitro and in vivo diagnosis** *Allergy 53(46 Suppl):65-71*
- Vieths S, Reindl J, Müller U, Hoffmann A, Haustein D (1999) **Digestibility of peanut and hazelnut allergens investigated by a simple in vitro procedure** *Eur Food Res Technol 209:379-88*

- Vocks E, Borga A, Szliska C, Seifert HU, Seifert B, Burow G, Borelli S (1993) **Common allergenic structures in hazelnut, rye grain, sesame seeds, kiwi, and poppy seeds** *Allergy 48(3):168-72*
- Wigotzki M, Schubert S, Steinhart H, Paschke A (2000a) **Effects of in vitro digestion on the IgE-binding activity of proteins from hazelnuts *(Corylus avellana)*** *Internet Symposium on Food Allergens 2:1-8*
- Wigotzki M, Steinhart H, Paschke A (2000b) **Influence of varieties, storage and heat treatment on IgE-binding proteins in hazelnuts *(Corylus avellana)*** *Food Agric Immunol 12:217-29*
- Wüthrich B (1993) **Nahrungsmittelallergie** *Allergologie16:280-7* (in German)
- Zuskin E, Kanceljak B, Mustajbegovic J, Schachter EN (1994) **Immunologic findings in confectionary workers** *Ann Allergy 73:521-6*

Common Abbreviations

2D	two-dimensional
3D	three-dimensional
aa	amino acid(s)
Ab	antibody
Act c 1, 2	nomenclature of kiwi fruit allergens *(Actinidia chinensis)*
Api g 1-5	nomenclature of celery allergens *(Apium graveolens)*
Ara h 1-7	nomenclature of peanut allergens *(Arachis hypogaea)*
Bos d 4, 5, 6, 7, 8	nomenclature of cow's milk allergens *(Bos domesticus)*
C	concentration of N,N'-methylenbisacrylamide (crosslinker)
Cas s 1, 5	nomenclature of chestnut allergens *(Castanea sativa)*
CAST	cellular antigen stimulation test
CCD	cross-reactive carbohydrate determinants
CICBAA	Cercle d'Investigations Cliniques et Biologiques en Allergologie Alimentaire (France)
CIE	crossed immunoelectrophoresis
CNBr	cyanogen bromide
cIEF	capillary isoelectric focussing
CLA	cutaneous lymphocyte antigen
CLIE	crossed line immunoelectrophoresis
CMA	cow's milk allergy
CRIE	crossed radioimmunoelectrophoresis
Cor a 1	nomenclature of hazel pollen allergens *(Corylus avellana)*
Cyn d 1	nomenclature of bermuda grass pollen allergens *(Cynodus dactylus)*
DBPCFC	double-blind, placebo-controlled food challenge
DEAE	diethylaminoethyl (cellulose) (anion exchanger)
DNA	deoxyribonucleic acid
DTT	dithiothreitol
EAST	enzyme allergosorbent test
EC	enzyme classification system
EDTA	ethylenediaminetetraacetic acid, disodium salt
ELISA	enzyme linked immunosorbent assay
EW	egg white
FEIA	fluorescence enzyme immunosorbent assay
Fuc	fucose
Gad c 1	nomenclature of baltic cod allergen *(Gadus callarias)*
Gal	galactose
Gal d 1-5	nomenclature of egg allergens *(Gallus domesticus)*
GlcN	glucosamine
GlcNAc	N-acetylglucosamine
Gly m 1, 2, 3	nomenclature of soybean allergens *(Glycine max)*
GST	glutathione-S-transferase
Hev b 1-10	nomenclature of latex allergens *(Hevea brasiliensis)*
HLA	human leucocyte antigen
Hol l 1	nomenclature of sweet velvet grass allergens *(Holcus lanatus)*

HPLC	high performance liquid chromatography
HPS	hydrophobic protein of soybean
HR	Histamine Release
IEC	ion exchange chromatography
IEF	isoelectric focussing
Ig	immunoglobulin
IL	interleukin
INF-gamma	interferon-gamma
Lol p 1	nomenclature of rye grass allergens *(Lolium perenne)*
LTA4	leukotriene A4
LTB4	leukotriene B4
LTC4	leukotriene C4
LTP	lipid transfer protein
LY	lysozyme
Man	mannose
Mal d 1, 2, 3	nomenclature of apple fruit allergens *(Malus domestica)*
MALDI-MS	matrix-assisted laser-induced desorption/ionization mass spectrometry
MAST	multiple allergen sorbent test
MHC	major histocompatibility complex
Mr	molecular mass
Mus a 1	nomenclature of banana allergens *(Musa* spp.*)*
NeuNAc	N-acetylneuraminic acid
NMR	nuclear magnetic resonance (spectroscopy)
NPV	negative predictive value
NRL	natural rubber latex
OA	ovalbumin
OAS	oral allergy syndrome
OM	ovomucoid
Ory s 1	nomenclature of rice allergens *(Oryza sativa)*
OT	ovotransferrin
PAGE	polyacrylamide gel electrophoresis
PBMC	peripheral blood mononuclear cells
PBS	phosphate buffered saline
Phl p 1	nomenclature of timothy grass allergens *(Phleum pratense)*
pI	isoelectric point
PCA	passive cutaneous anaphylaxis (test)
PCR	polymerase chain reaction
PPT	prick to prick test (skin test with fresh foods)
PPV	positive predictive value
Prs a 1 (Pers a 1)	nomenclature of avocado allergens *(Persea americana)*
Pru av 1, 2, 4	nomenclature of sweet cherry allergens *(Prunus avium)*
Pru p 3	nomenclature of peach allergens *(Prunus persica)*
PVDF	polyvinyliden difluoride
PVPP	polyvinyl polypyrrolidone
RAST	radioallergosorbent test

RBL cells	rat basophil leukaemia cells
RIEP	radioimmunoelectrophoresis
RNA	ribonucleic acid
RT	room temperature
SAFT	skin application food test
SDS	sodium dodecylsulfate
SEC	size exclusion chromatography
SPT	skin prick test
T	total acrylamide concentration
TCC	T-cell clone
TCL	T-cell line
TGF-beta-1	transforming growth factor beta-1
TH	thermolysin
TNF-alpha	tumor necrosis factor alpha
TR	trypsin
Tris	tris-(hydroxymethyl)aminomethane
WgA	wheat germ agglutinin
Xyl	xylose

Abbreveations of DNA-encoded Amino Acids

Alanine	Ala	A	Leucine	Leu	L
Arginine	Arg	R	Lysine	Lys	K
Asparagine	Asn	N	Methionine	Met	M
Aspartic acid	Asp	D	Phenylalanine	Phe	F
Cysteine	Cys	C	Proline	Pro	P
Glutamine	Gln	Q	Serine	Ser	S
Glutamic acid	Glu	E	Threonine	Thr	T
Glycine	Gly	G	Tryptophan	Trp	W
Histidine	His	H	Tyrosine	Tyr	Y
Isoleucine	Ile	I	Valine	Val	V