



**Chestnut Hill Allergy
& Asthma Associates, LLC**

Food Allergy Cross-Reactivity Focus on Relevance to OIT

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Introduction

Cross-reactivity:

Sensitization to conserved homologous proteins;
Needs >70% similarity in protein sequence of allergens

Versus

Co-allergy:

Being sensitized to two or more different allergens

Immunologic CR vs. Clinical Cross-Reactivity

Immunologic CR/Sensitization:

Presence of IgE binding to an allergen
Not necessarily associated with a
clinical or symptomatic allergy

Versus

Clinical CR:

Symptomatic allergy
Molecular genetics have improved ID of
clinically relevant CR
Food-specific and patient-specific
factors also determine clinical relevance

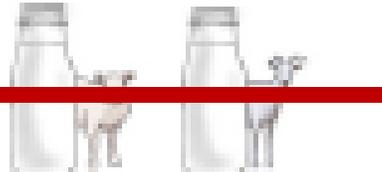
...will positive tests translate to clinical reactions?

Factors Influence Clinical Cross-Reactivity

Immune factors	Protein/food factors	Patient factors
IgE antibody concentration	Degree of homology	Amount eaten
IgE antibody specificity types (proteins, epitopes)	Concentration in edible portion of food (may vary by species or ripening)	Method of preparation (ie, raw, heated)
IgE antibody affinity	Stability to heat/digestion	Augmentation factors (exercise, illness, alcohol, etc.)
Effector cell reactivity		

TABLE 1 from Clinical Relevance of Cross-Reactivity in Food Allergy. Cox AL, Eigenmann PA, Sicherer SH . J Allergy Clin Immunol Pract. 2021;9(1):82-99.

Cow's Milk

Milk (Cow)	Milk (Sheep, Goat)	>90%
		
	Milk (Camel, Mare)	<5%
		
	Beef	~10-20%
		

ORIGINAL ARTICLE

Allergy to goat's and sheep's milk in a population of cow's milk-allergic children treated with oral immunotherapy*

Pablo Rodríguez del Río¹, Silvia Sánchez-García¹, Carmelo Escudero¹, Carlos Pastor-Vargas², José J. Sánchez Hernández³, Inmaculada Pérez-Rangel¹ & María Dolores Ibáñez¹

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- Cow's milk OIT did not necessarily induce desensitization to goat's or sheep's milk
- 25.9% of 58 successfully treated CMA children remained goat's and sheep's milk allergic

Reassuring follow up...

- 396 CM OIT pts bwn 2010-2017
- 110 GM and SM allergic
- 109/110 passed oral challenge with GM
- 105/105 passed oral challenge with SM

Clinical Communications

Cross-desensitization to goat and sheep milk following cow's milk oral immunotherapy



Liat Nachshon, MD^{a,b}, Michael R. Goldberg, MD, PhD^a, Michael B. Levy, MD^a, Naama Epstein-Rigbi, MD^a, Michael Y. Appel, PhD^a, Yitzhak Katz, MD^c, and Arnon Elizur, MD^{a,c}

Clinical Implications

- This study demonstrates that almost all Israeli milk-allergic patients, successfully desensitized to cow's milk could tolerate goat's and sheep's milk as well.

Cow's Milk

- RELEVANCE TO OIT:
- Cow's milk OIT should address co-existing sheep's milk and goat's milk allergy
- This is usually, but not always the case however

Hen's Egg

- Ovomucoid: Gal d 1 is the dominant egg allergen; it is highly allergenic and very stable to heat
- Fifty (96.1%) children with hen's egg allergy showed positive sensitization to at least one of the six avian eggs tested
- The most frequent positive skin tests were related to quail's white (36 = 69.2%) followed by duck's white (34 = 65.5%), and sensitization was the least frequent in pigeon's yolk (23 = 44.2%)

The frequency of cross reactivity with various avian eggs among children with hen's egg allergy using skin prick test results: fewer sensitizations with pigeon and goose egg. Nabavizadh et al. *Allergologia et immunopathologia*. Vol 48 (3); 2022 (265-269).

Hen's Egg

- RELEVANCE TO OIT:
- Clinically relevant avian egg cross-reactivity has not been systematically investigated
- It remains unclear whether an individual successfully treated for hen's egg allergy with OIT could have issue with another avian egg

Wheat



Barley, Rye



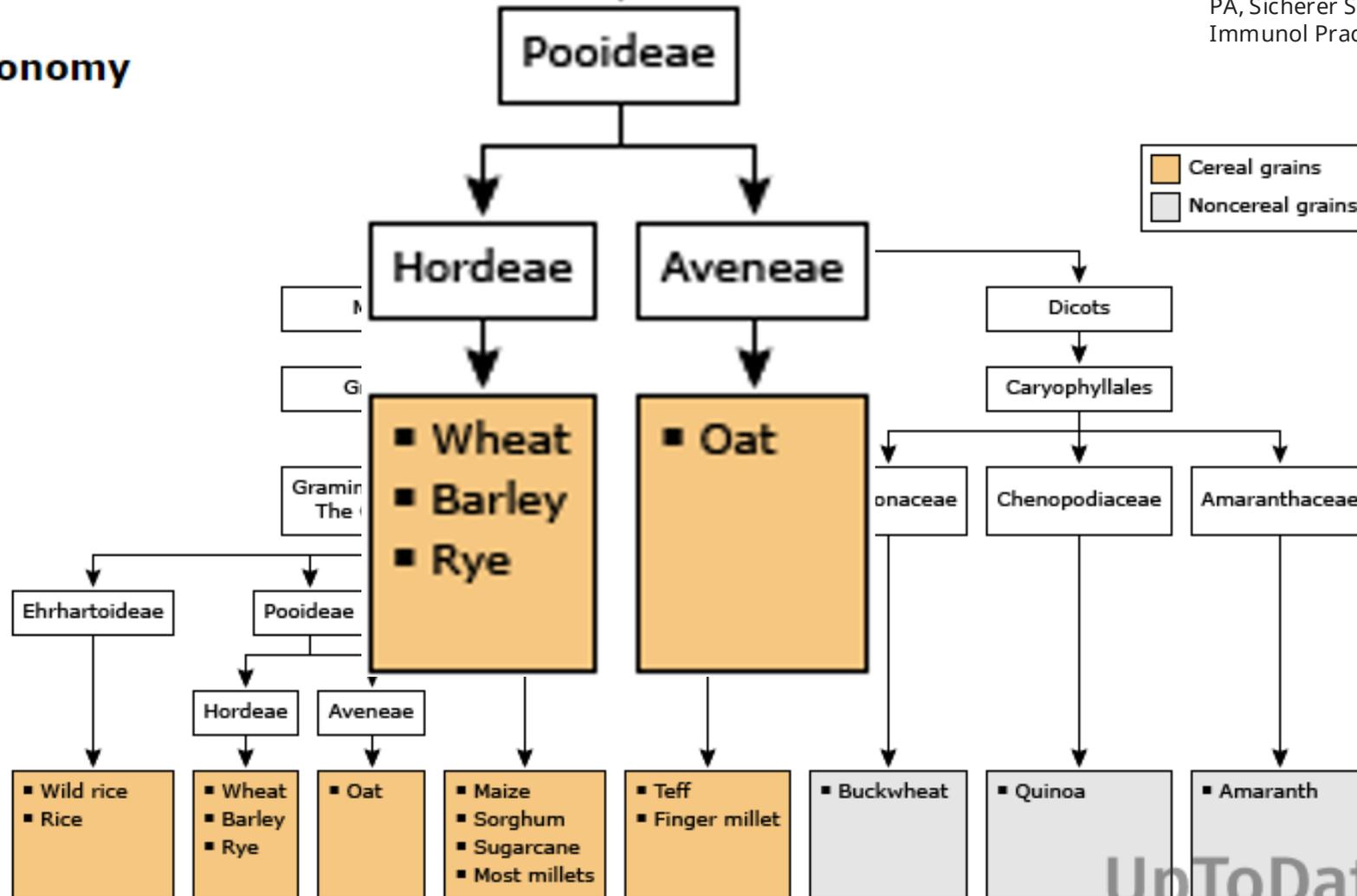
<25%

20-60%

Clinical Relevance of Cross-Reactivity in Food Allergy. Cox AL, Eigenmann PA, Sicherer SH. J Allergy Clin Immunol Pract. 2021;9(1):82.

Grain taxonomy

- Class
- Subclass
- Order
- Family
- Subfamily
- Tribe
- Species



Grains

- Relevant allergens in wheat belong to the gliadin or gluten family
- Immunologic CR: Majority of patients with wheat allergy will have positive SPT and/or IgE to other grains (rye, barley, oat, corn, or rice)
- Clinical CR to wheat, rye, and barley occurs more frequently than to oat, corn, and rice
- Omega-5 gliadin-sIgE predicts cross-reactive barley allergy in children allergic to wheat (Yanagida et al. 2022)

1995: Jones et al. 20% with wheat allergy (n=23) react to rye or barley challenge

2005: Pourpak et al. 18 wheat allergic patients 55.5% react to barley challenge

2020: Srisuwathari et al. (ref 31) in Cox et al. 10 pts with wheat allergy, challenge confirmed to barley 60% and oat 33%

2022: Yanagida et al. 39 wheat allergic patients 50% reacted to barley challenge

Grains

- RELEVANCE TO OIT:
- Nine patients who had positive barley-OFC before wheat OIT were all negative on barley-OFC performed after wheat OIT
- Conclusion of study: Barley allergy is caused by cross-reactivity to wheat
- **OIT for wheat is one option for barley allergy**
- Separate study: 5 patients passed oral challenges to rye after wheat OIT

The clinical cross-reactivity and immunological cross-antigenicity of wheat and barley. Kubota et al. Allergology International. 2022(71);505-511.

Oral Immunotherapy in Children With IgE-Mediated Wheat Allergy: Outcome and Molecular changes. J Investig Allergol Clin Immunol. 2014. 24(4):240-48.

Legumes

<p>Peanut</p> 		<p>Tree Nuts (co-allergy) ~33%</p> <p>Lupine ~20%</p> <p>Sesame (co-allergy) 10-15%</p> <p>Green Bean, Pea, Soy 5-20%</p> 	
<p>Other Legumes</p> <p><i>If Soy</i> </p> <p><i>If Chick Pea</i> </p>		<p>Peanut </p> <p>Lentil, Pea </p>	<p>>75%</p> <p>>50%</p>

- The most prevalent legume allergies include peanut, soybean, lupine, chickpea, lentil, and pea

Legumes

- Immunologic cross-sensitization between legume and peanut proteins is common, BUT clinical allergy is not as common
 - 1989: Sampson study: 69 children with peanut allergy with positive testing for multiple legumes, only 2 demonstrated allergy to more than 1 legume by DBPCFC
 - 2009: Peeters et al.: 39 peanut allergic patients:
 - Sensitization: 87% to soy, 82% to lupine, 55% to pea
 - Clinically relevant: 33% to soy, 35% to lupine, 29% to pea

Cross-allergenicity in the legume botanical family in children with food hypersensitivity. Bernhisel-Broadbent and Sampson. JACI 1989;83(2):435-40.

Clinical relevance of sensitization to lupine in peanut-sensitized adults. Peeters et al. Allergy 2009;64:549-555.

Frequency of sensitization between legumes

TABLE 1 The frequency of sensitization between 10 legumes in six different legume-allergic patient groups.

When allergic for		% sensitized									
	<i>n</i>	Peanut	Soybean	Green pea	Chickpea	Blue lupine	White lupine	Black lentil	Green lentil	Faba bean	White bean
Peanut	30	90%	76.7%	46.7%	53.3%	66.7%	56.7%	70%	63.3%	40%	60%
Soybean	30	63.3%	60%	53.3%	43.3%	46.7%	46.7%	50%	43.3%	36.7%	40%
Green pea	30	76.7%	83.3%	90%	86.7%	83.3%	80%	93.3%	90%	80%	66.7%
Lupine	30	83.3%	80%	70%	80%	93.3%	83.3%	93.3%	83.3%	70%	63.3%
Lentil	17	70.6%	82.4%	94.1%	82.4%	94.1%	82.4%	94.1%	88.2%	76.5%	58.8%
Bean	9	88.9%	100%	100%	100%	100%	88.9%	100%	100%	100%	77.8%

Co-sensitization between legumes is frequently seen, but variable and not always clinically relevant. Smits et al. *Frontiers in Allergy*. Published March 16, 2023. [10.3389/falgy.2023.1115022](https://doi.org/10.3389/falgy.2023.1115022).

TABLE 2 Odd ratios (OR) for allergy when sensitized for the 7S/11S globulin and 2S albumin fraction of the respective food.

Allergic group	Co-allergy	Prevalence of co-allergy	OR	
			7S/11S globulin	2S albumin
Peanut	Soybean		20% (n = 6)	
	Lupine	16.7% (n = 5)	6.33 (0.31–127.6)	11.18 (1.41–88.95)
	Lentil	3.3% (n = 1)	1.62 (0.06–43.25)	1.86 (0.07–49.77)
	Bean	0% (n = 0)	-	-
Soybean	Peanut		63.3% (n = 19)	
	Lupine	16.7% (n = 5)	16.24 (0.81–325.88)	11.18 (1.41–88.95)
	Lentil	6.7% (n = 2)	5.74 (0.25–130.37)	8.81 (0.39–201.38)
	Bean	3.3% (n = 1)	4.83 (0.18–128.79)	10.85 (0.39–298.92)
Green pea	Peanut		73.3% (n = 22)	
	Lupine	40% (n = 12)	0.36 (0.04–3.13)	2.62 (0.61–11.2)
	Lentil	46.7% (n = 14)	0.48 (0.06–4.18)	1.55 (0.18–13.4)
	Bean	23.3% (n = 7)	5.57 (0.28–112.01)	2.83 (0.52–15.46)

Legumes

- At a molecular level, peanut and soybean demonstrate a high degree of cross-reactivity
 - Peanut allergens Ara h 1, Ara h 2, and Ara h 3 show similarities to soy allergens Gly m 5, Gly m 8, and Gly m 6 respectively
- Clinical allergy to soybean among peanut allergic individuals ranges from 3% to 20% (depending on the study)
- Conversely, (this gets confusing to explain, but you will get it), **among soy allergic patients, rate of clinical peanut allergy is high**
 - **60->75% (depending on the study)**

Clinical Relevance of Cross-Reactivity in Food Allergy. Cox AL, Eigenmann PA, Sicherer SH. J Allergy Clin Immunol Pract. 2021;9(1):82-99.

The natural history of soy allergy. Savage et al. JACI 2009;126(3):683-86.

Co-sensitization between legumes is frequently seen, but variable and not always clinically relevant. Smits et al. Frontiers in

Allergy. Published March 16, 2023. [10.3389/falgy.2023.1115022](https://doi.org/10.3389/falgy.2023.1115022).

Legumes

- **Lentils, chickpea, and green pea likely represent an allergenic triad**
 - High degree of both immunologic and clinical cross-reactivity
 - Martinez San Ireneo et al. ... Spanish study: 73% of those with legume allergy reacted to both lentil and pea; 69.4% reacted to both lentil and chickpea; 64% reacted to chickpea, pea, and lentil; there were low rates of reaction to white bean, green bean, and soy
 - Quoted in Cox et al. ... Turkish study: 30 children w lentil allergy, only 5 were monosensitized to lentil, 17 (57%) allergic by history to other legumes, including 40% to chickpea, 17% to peanut, and 13% to pea
 - Pea and/or lentil may be “primary”/dominant allergen to chickpea (Bar-El Dadon et al. 2014)

Clinical Relevance of Cross-Reactivity in Food Allergy. Cox AL, Eigenmann PA, Sicherer SH. J Allergy Clin Immunol Pract. 2021;9(1):82-99.
Clinical features of legume allergy in children from a Mediterranean area. Martinez San Ireneo. Ann Allergy Asthma Immunol. 2008;101:179-184.

Food allergy and cross-reactivity-chickpea as a test case. Bar-El Dadon et al. Food Chemistry. 2014;165:483-488. (Spain)

Legumes

- RELEVANCE TO OIT:
- Most patients (Cox et al. “~90%”) with peanut allergy tolerate all other beans, BUT
- If they have reactions to additional legumes:
 - Caution with lupine, chickpea, lentil, soy, and green pea
- Lentils, chickpea, and green pea likely represent an allergenic triad
- If lentil and/or green pea are “primary”/dominant to chickpea, perhaps perform OIT with lentil and/or green pea as opposed to chickpea

Lentils specifically

- Little is known about cross-reactivity among dal proteins to guide clinical management
- Andreae et al. assessed the association between serum IgE binding patterns of lentil allergic patients on lentil-like (dal) proteins and clinical reaction histories to provide advice
- Looked at: Green lentil, toor dal/pigeon pea, mung dal/mung bean, urad dal/black gram, chana dal/chickpea, mooth dal/moth bean, and masoor dal/red lentil
- In this small study a high degree of immunologic CR was observed

High similarity between lentil and other lentil-like proteins (dal) complicates recommendations on avoidance in lentil allergic patients. Andreae et al. . J Allergy Clin Immunol Pract. 2015;3(5):804-6.

Lentils

- Among lentil-like (dal) proteins, the protein sequence most studies have focused on is green lentil (*Lens culinaris*)
- Specific IgE testing is limited to testing of green lentil (*L. culinaris* green) when using commercially available systems
- Prick-prick testing with individual legumes is not standardized
- Oral food challenge testing remains the reliable method for predicting tolerance or reactivity to various lentils

High similarity between lentil and other lentil-like proteins (dal) complicates recommendations on avoidance in lentil allergic patients. Andrae et al. . J Allergy Clin Immunol Pract. 2015;3(5):804-6.

Lentils

- RELEVANCE TO OIT:
- Clinical cross reactivity between lentils and between lentils and chickpeas is likely
- Prioritize lentil OIT to chickpea OIT if we take the Bar-El Dadon 2014 publication into consideration
- Oral challenges will be necessary following a form of lentil OIT to confirm tolerance to other lentils

High similarity between lentil and other lentil-like proteins (dal) complicates recommendations on avoidance in lentil allergic patients. Andrae et al. . J Allergy Clin Immunol Pract. 2015;3(5):804-6.

Food allergy and cross-reactivity-chickpea as a test case. Bar-El Dadon et al. Food Chemistry. 2014;165:483-488.

Peanut and Tree Nuts

- Peanut and tree nut allergenic proteins demonstrate homology, but they are from different taxonomic plant groups
- Rate of co-allergy is likely less than 35%

Peanuts and Tree Nuts

- RELEVANCE TO OIT:
- Treating peanut allergy with OIT is unlikely to address other tree nut allergies

Tree Nuts

- In the Israeli NUT CRACKER study, 83 children underwent DBPCFC to determine correlations between sensitization and clinical allergy to multiple tree nuts
 - The authors found that most patients were sensitized to 5 to 6 tree nuts, but the majority were clinically allergic to only 1 to 2 tree nuts
 - They found no association between almond allergy and other tree nut allergies

Tree Nuts

- Highly cross-reactive tree nut relationships of walnut-pecan and cashew-pistachio have proven to be clinically relevant in several studies where DBPCFCs have been performed to confirm tree nut allergy
 - NUT CRACKER: Two-thirds of walnut-allergic patients were allergic to pecan, whereas 100% of children allergic to pecan were allergic to walnut
 - NUT CRACKER: All pistachio-allergic children found to be reactive to cashew, and 2 out of 3 cashew allergic patients allergic to pistachio

NUT Co Reactivity-ACquiring Knowledge for Elimination Recommendations (NUT CRACKER) study. Elizur et al. Allergy. 2018;73:593-601.

Association of Clinical Reactivity with Sensitization to Allergen Components in Multifood-Allergic Children. Andorf et al. J Allergy Clin Immunol Pract. 2017;5(5);1325-1334.

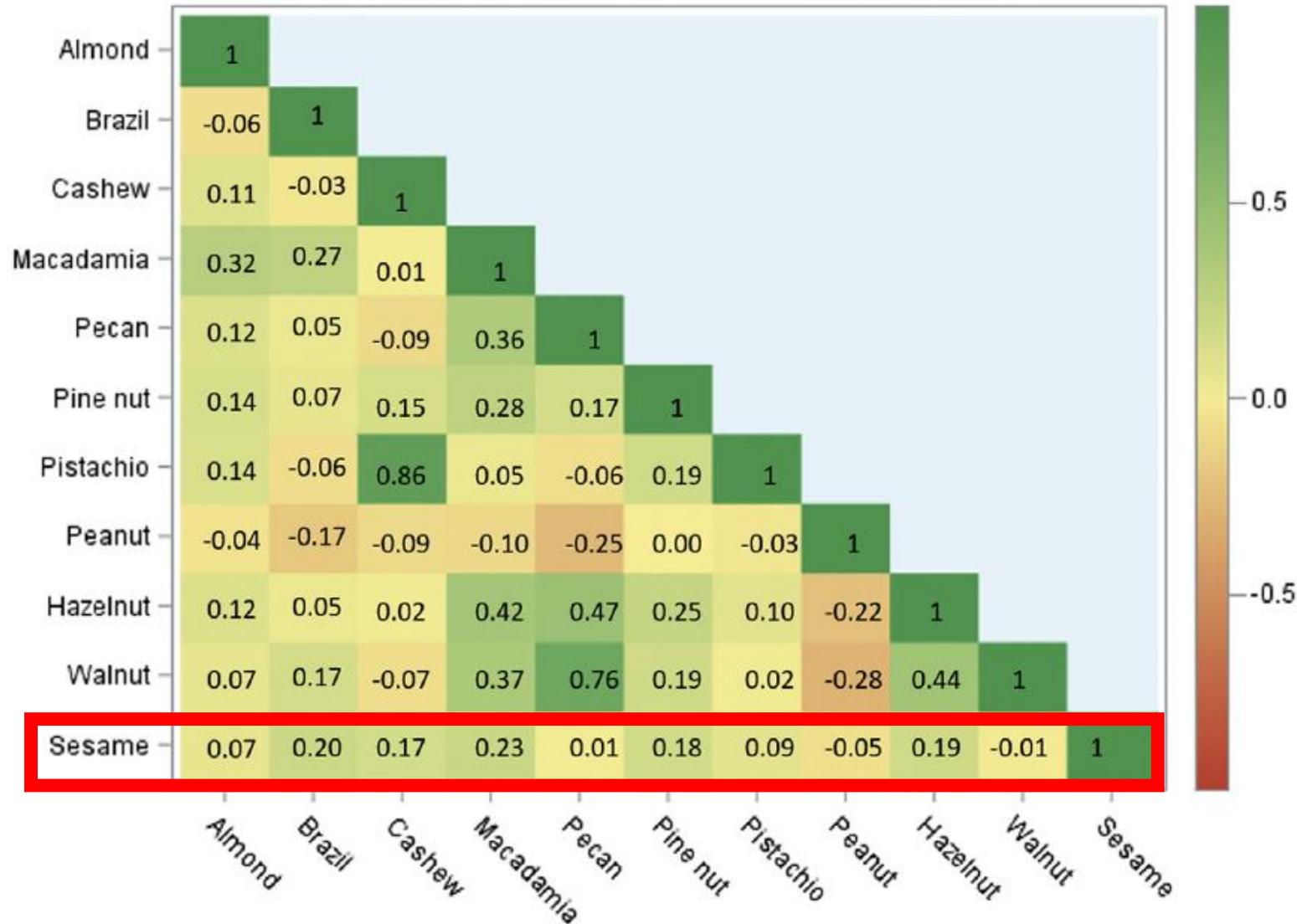
Tree Nuts

- RELEVANCE TO OIT:
- Wasserman and Windom
 - 94% (83 of 88) of cashew-treated patients passed a pistachio challenge
 - 97% (30 of 31) of walnut-treated patients passed pecan challenges
 - Cashew and walnut were selected as the dominant nuts for OIT for those nut diads

Seeds

- Retrospective study of 191 children who underwent food skin testing at Boston Children's Hospital 2006-2008
 - 53% of peanut- and 58% of tree nuts – sensitized children had positive skin testing for sesame
 - BUT, only 13% of peanut-allergic patients and 15% of tree nut – allergic patients reported a history of sesame reaction
 - Children with a history of peanut AND tree nut reactions were more likely to have had sesame reactions (odds ratio 10.2)
 - ***Confirmed sesame allergy was only significantly increased in those children clinically allergic to BOTH peanut AND tree nuts**

Seeds



Clinical Relevance of Cross-Reactivity in Food Allergy. Cox AL, Eigenmann PA, Sicherer SH. *J Allergy Clin Immunol Pract.* 2021;9(1):82.

Defining challenge-proven coexistent nut and sesame seed allergy: A prospective multicenter European study. *JACI.* 2020;145(4):1231-39.

Peanut-sesame co-allergy 10-15%
 Tree nut-sesame co-allergy 10-15%
 Summary drawn by Cox et al. 2021.

FIG 2. Correlation coefficients between nut and sesame seed allergies in all centers.

Other Seeds

- At this time, a diagnosis of 1 seed allergy does not predict multiple seed allergies, and does not necessitate avoidance or performance of allergy testing for all seeds

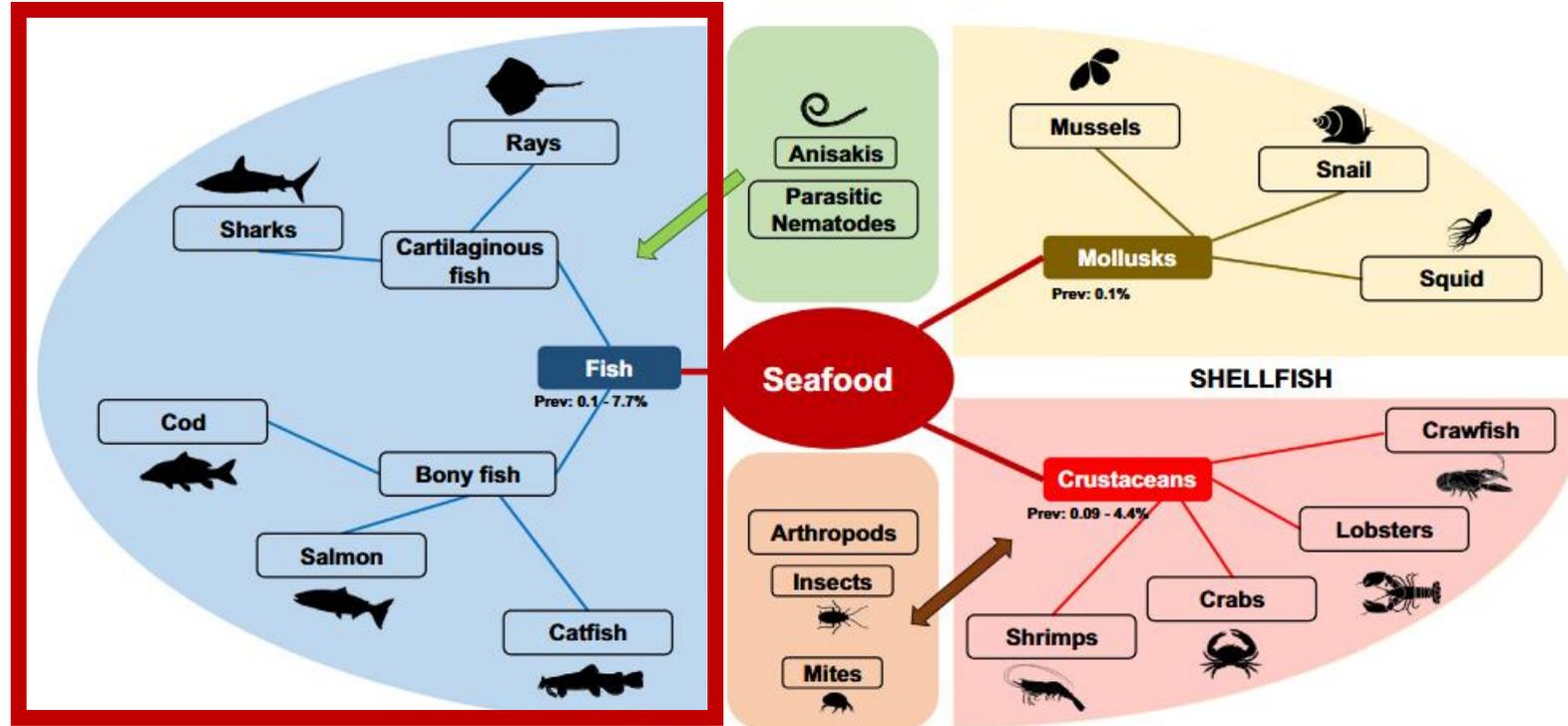
Possible cross-reactivity among seeds and other foods or pollens (Table 4 from Patel and Bahna)

Seed	Foods and pollens that may clinically cross react
Sesame	Kiwi, peanut, poppy seed, rye grain, tree nuts
Sunflower	Brazil nut, mustard, pistachio, mugwort pollen
Poppy	Buckwheat, kiwi, rye grain, sesame seed, tree nuts (particularly hazelnut)
Flax seed	Lupine, peanut, rapeseed, soybean, wheat, rape pollen
Pumpkin	Rosacea family (apple, apricot, cherry, pear, etc.)

Seeds

- RELEVANCE TO OIT:
- On Table 4 by Patel and Banha: Significant cross reactivity between seeds is not observed
- *Treatment will require individual seed OIT
 - We will not be able to depend on cross-reactivity between seeds

Fish



Davis et al.
Clinical
Management of
Seafood Allergy. J
Allergy Clin
Immunol Pract.
Jan 2020

Finned Bony Fish



Other Finned Bony Fish

Cartilaginous Fish
(Dogfish, Ray, Shark)

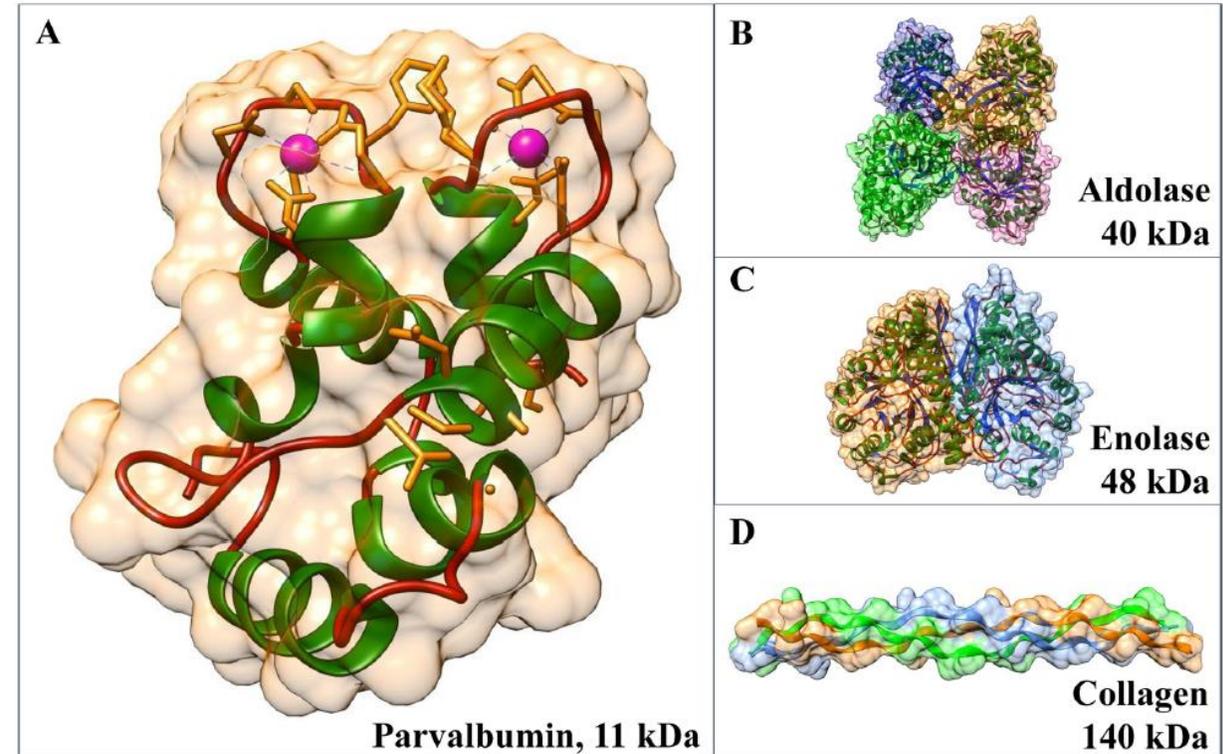


~50%

<5%

Fish

- The major fish allergens are:
 - **Parvalbumins the major fish allergen**
 - Aldolase and enolase are heat labile (present in raw fish)
 - Collagen is found in fish skin

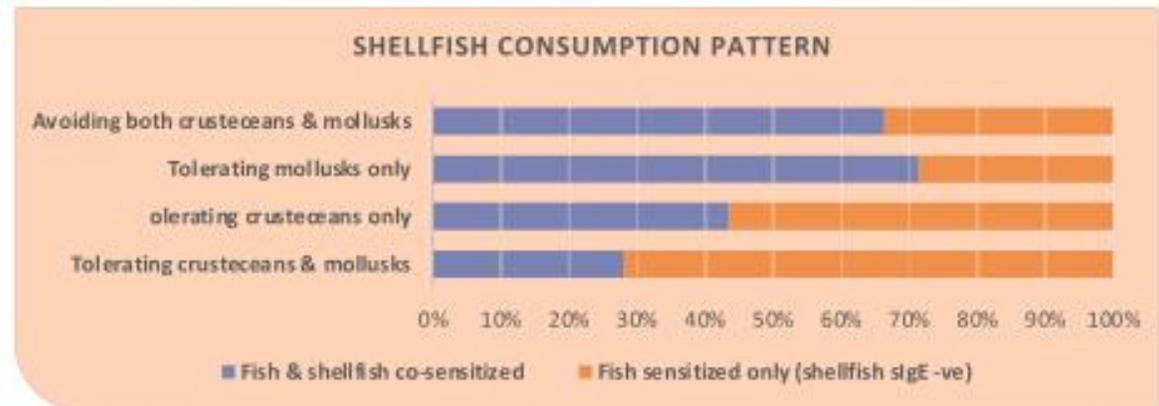
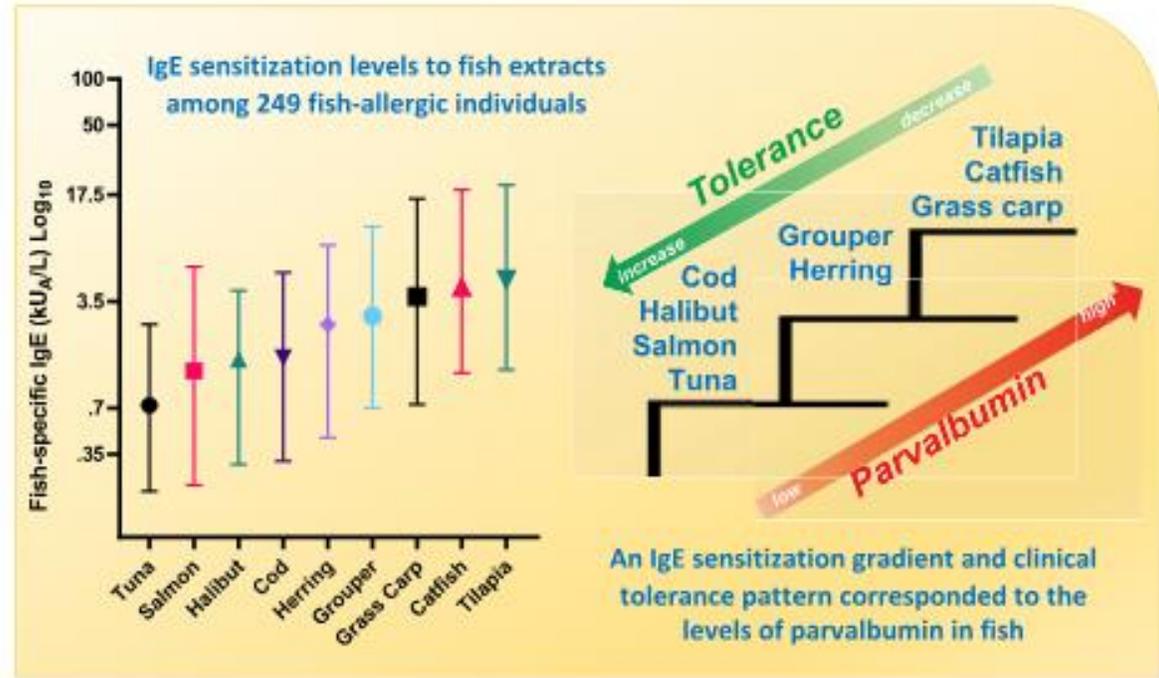
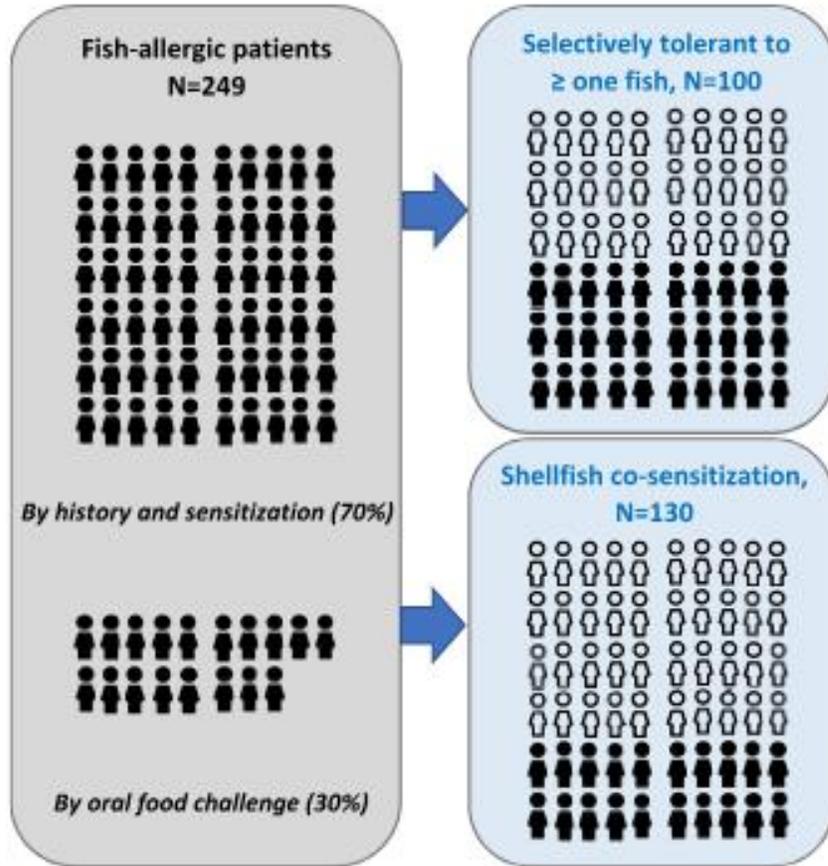


Ruethers et al. Seafood allergy: A comprehensive review of fish and shellfish allergens. *Molecular Immunology*. 100 (2018): 28-57.

Fish

- One may predict higher rates of cross-reactivity with higher degrees of homology
- Beta-parvalbumin content correlates with allergenicity of fish
- Observed clinical cross-reactivity can be affected by many variables:
 - **Heating:** 20-60% reduction in parvalbumin allergenicity
 - **Canning**
 - Different **parts of the fish** have different concentrations of the major proteins
 - Different **species of fish**
 - Immune response to **major and minor fish allergens** can vary among individuals
 - Allergy to isolated types of fish have been reported (observation likely related to allergy to minor proteins)

Real-world Sensitization and Tolerance Pattern to Seafood in Fish-Allergic Individuals



- Cross-reactivity between fish species was common but a considerable proportion of patients were selectively tolerant to fish, typically those with lower levels of β -parvalbumin.
- We should reduce unnecessary shellfish and fish avoidance. There is an unmet need to promote precision medicine for seafood allergies.

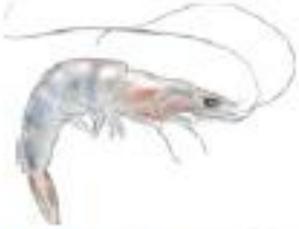
Fish

- From an oral abstract/Ann Allergy Asthma Immunol 133(2024) S2-S100
- Clinical Outcome for Fish and Shellfish OIT, Tran et al, Bellaire, TX
- 3 fish patients treated dehydrated codfish powder to start
 - Maintenance ranged from one fish stick to full-serving size
- 2 shellfish patients treated with dehydrated shrimp
 - Maintenance ranged from one shrimp to full-serving size
- Conclusion: “It is possible to treat seafood allergy using dehydrated shrimp or fish powder for OIT.”

Fish

- RELEVANCE TO OIT:
- OIT success may depend on fish species used for treatment
- Cooking method used
- Identifying and treating appropriate allergens (may be fish species specific)
- May be better to develop OIT protocols with fish species with higher levels of beta-parvalbumin (as opposed to a fish species like tuna that is known to have lower beta-parvalbumin content)
- Oral challenges even after fish OIT to individual fish species may be useful

Shellfish

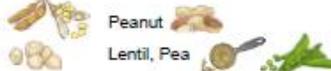
Primary Food Allergy	Cross Reactive Food	Risk (varies with region)
Crustacean Shellfish 	Other Crustaceans Mollusks/Bivalves (Clam, Mussel, Oyster, Squid) 	~75% <50%
Mollusks/Bivalves 	Crustaceans (Crab, Shrimp, Lobster) 	>70%

Shellfish

- In summary, a high rate of clinically relevant cross-reactivity within crustaceans is apparent (approximately 75%), but a substantial number of patients may tolerate non-crustacean mollusk shellfish (approximately 50% or more)
- If mollusk shellfish are not tolerated, it is likely that crustaceans will also be an allergen (>70%)

Shellfish

- RELEVANCE TO OIT:
- High tropomyocin amino acid sequence homology will be advantageous in treating crustacean allergy
- Crustacean OIT using shrimp may not confer protection to all mollusks

Primary Food Allergy	Cross Reactive Food	Risk (varies with region)
Crustacean Shellfish 	Other Crustaceans Mollusks/Bivalves (Clam, Mussel, Oyster, Squid) 	~75% <50%
Mollusks/Bivalves 	Crustaceans (Crab, Shrimp, Lobster) 	>70%
Finned Bony Fish 	Other Finned Bony Fish Cartilaginous Fish (Dogfish, Ray, Shark) 	~50% <5%
Peanut 	Tree Nuts (co-allergy) Lupine Sesame (co-allergy) Green Bean, Pea, Soy 	~33% ~20% 10-15% 5-20%
Other Legumes <i>If Soy</i> <i>If Chick Pea</i>	Peanut Lentil, Pea 	>75% >50%
Tree Nuts <i>If Walnut</i> <i>If Pecan</i> <i>If Cashew</i> <i>If Pistachio</i> <i>If Peanut and Tree Nut</i>	Other Tree Nuts Sesame (co-allergy) Pecan Walnut Pistachio Cashew Sesame (co-allergy) 	15-33% 10-15% ~86-75% >95% ~66-83% >95% 50%
Milk (Cow) 	Milk (Sheep, Goat) Milk (Camel, Mare) Beef 	>80% <5% ~10-20%
Wheat 	Barley, Rye 	<25%

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