
CME review article

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Sesame allergy: a growing food allergy of global proportions?

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Objective: To present an up-to-date synopsis on the global prevalence, natural history, nature of allergens, and immune mechanisms of sesame allergy.

Data Sources: We performed a literature search using the PubMed database. We obtained information on regulatory issues from the Web pages of respective agencies.

Study Selection: The PubMed search was performed using the algorithm *sesame AND allergy*. Date restriction was not used, and only articles in English were considered. The articles obtained were screened for additional references to work not obtained in the initial search. Each article was analyzed, and a pooled source of published information was generated.

Results: Evidence was found for increased reporting of sesame allergy during the past 5 decades, with reports mostly from developed countries. Clinically, most sesame allergy was presented in at least 2 major forms: (1) immediate hypersensitivity, often expressed as systemic anaphylaxis, associated with positive skin prick test and/or IgE antibody test results to sesame proteins with some cross-reactivity with other foods, and (2) delayed hypersensitivity to lignin-like compounds in sesame oil clinically expressed as contact allergic dermatitis. There were a few cases of immediate hypersensitivity to sesame with negative skin prick test and/or IgE antibody test results that were confirmed by oral challenge tests.

Conclusions: Sesame allergy is a significant, serious, and growing problem. Evidence exists of the ability of protein and oil components of sesame to trigger immediate hypersensitivity via IgE antibody and delayed hypersensitivity via cell-mediated immune responses, respectively.

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INTRODUCTION

Food allergies are immune-mediated adverse reactions that have been increasing in prevalence in recent years, especially among infants and children.^{1–3} The range of clinical reactions to food allergens varies from rashes, vomiting, diarrhea, and asthma attacks to systemic anaphylaxis. Among different allergenic foods, peanuts and tree nuts have been identified as

major food types that cause fatal or near-fatal systemic reactions.²

Although any food has the potential to cause a hypersensitivity reaction in a sensitized individual, most food allergies (approximately 90%) are caused by 8 major food types.⁴ Accordingly, the US Food and Drug Administration (FDA) initiative on the food allergen awareness efforts currently focus on the 8 foods that are most frequently implicated in serious allergic reactions: milk, eggs, fish, wheat, tree nuts, legumes (particularly, peanuts and soybeans), crustaceans, and mollusks.⁵ However, in November 2003, a new directive passed into European Commission (EC) law (2003/89 EC) includes 11 foods in addition to sulfites in the EC allergen labeling list: celery, crustaceans, egg, fish, gluten, milk, mus-

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tard, peanuts, sesame, soya, and tree nuts.⁶ Health Canada and the Canadian Food Inspection Agency have jointly identified 10 food products in addition to sulfites that are primarily responsible for approximately 90% of severe adverse food reactions among the Canadian population. These products are peanuts, tree nuts, soy, milk, eggs, fish, crustaceans and shellfish, sesame seeds, sulfites, and wheat.⁷ Thus, sesame is included in the allergen list of both the EC and Canadian Food Inspection Agency but not in the allergen list of the FDA.

Recent years have seen tremendous progress in the research and public awareness on peanut allergy.² In contrast, both research and public awareness on sesame allergy have been limited.^{2,8–10} This review of the literature is intended to generate an up-to-date critical synopsis on sesame allergy focused on addressing the following questions: Is sesame allergy globally prevalent? What is the spectrum of clinical symptoms and available clinical immunology data? Does it encompass more than one type of immune-mediated disease? What is the chemical nature of sesame allergens and their immune cross-reactivity with other foods? We performed a literature search of the PubMed database, and information on regulatory issues was obtained from the Web pages of respective agencies. The PubMed search was performed using the algorithm *sesame AND allergy*. Date restriction was not used, and only articles in English were considered. The articles obtained were screened for additional references to work not obtained in the initial search. Each article was analyzed, and a pooled source of published information was generated.

SESAME SEED AND OIL: GROWING USE IN FOOD, PHARMACEUTICAL, AND COSMETIC INDUSTRIES

It has been reported that sesame cultivation for human use is traceable to 2450 BC in Babylon.¹¹ The family Pedaliaceae to which sesame belongs contains at least 18 species, most of which are indigenous to Africa and Asia.¹¹ Among them, *Sesamum indicum*, with an origin of India, is widely cultivated in many countries, including India, the Middle East, the United States, China, and other Asian and Latin American countries. It is a perennial herbaceous plant that grows up to 1 m in height with pink or bluish white flowers.¹¹

Sesame seeds are available in 3 different colors—white, brown, and black. They are used either directly, as crushed seed, or as a paste. They are used in food either directly or after hulling. Use of sesame seed paste (tahini) is common in the Mediterranean diet.^{11,12} In India, sesame seed is mixed with jaggery or sugar and rolled into cakes or balls and eaten as a confectionary. Sesame seed is becoming a favorite garnishing item in Western fast food industries. It is widely used in the baking industry, where there are reports of occupational allergy (asthma and urticaria) to sesame involving bakers^{13,14} (Table 1).

Sesame seeds contain approximately 50% to 60% oil. Although sesame seeds are most used in the food industries, sesame oil is used in the food (eg, in salad dressings in Oriental, Chinese, and South American cuisines), pharmaceutical, and cosmetic industries. Sesame oil is used in pharmaceutical and cosmetic industries because it is thought to have many desirable properties, such as being stable, neutral, inert, nonirritating, not too viscous, heat resistant, and nonsweating effects.¹¹ There is a report claiming that sesame oil is less antigenic compared with cottonseed or peanut oil.¹⁵ Thus, it has been used in the preparation of intramuscular injections, plasters, liniments, ointments, capsules, soaps, lipsticks, and emulsions and in the formulation of suspensions and ophthalmic preparations. Liniment that contains sesame oil (linimentum zinci oxydi oleosum) has been used in the treatment of eczema and leg ulcers. A Chinese ointment for burn wounds that contains 60% sesame oil (shiunkoh) has been used for centuries in Japan and China.¹⁶ Notably, sesame oil in injections, ointments, and cosmetics has been reported to cause contact allergic dermatitis.^{10,13,17–19}

SESAME ALLERGY: AN EMERGING GLOBAL EPIDEMIC?

The prevalence of sesame allergy in the general global population is unknown. However, there has been a significant increase in the number of reports of hypersensitivity to sesame since the first report from the United States in 1950 (Fig 1). Subsequent reports are mostly from developed countries, including the United States, Australia, many European countries, and Asia (Israel and Japan) (Table 2).^{11,13–44}

A prevalence study of immediate hypersensitivity (IHS) to foods among Australian children found that sesame was in

Table 1. Uses of Sesame Seed and Oil in Food, Pharmaceutical, and Cosmetic Industries

Type of application	Examples
Food industry	Bakery foods: falafel burger, hamburger buns, pizza, wafers, bread sticks, bread crumbs, pastries, pretzels, Italian bread, bagels, biscuits, crackers, biscuits, bread, sandwich, cookies Other foods: halvah, tahini (sesame seed paste), salad dressing, simit (Turkish pretzel), candy, soups, dressed chicken, sauce, gluten free foods (for celiac patients), ground seed (almond paste substitute), sesame paste noodles, chocolate, protein bars, ice cream cones coated with sesame, margarine
Pharmaceutical industry	Ointments (eg, shiunkoh, linimentum zinci oxydi oleosum), intramuscular injections (eg, progesterone), plasters, liniments, capsules, emulsions, ophthalmic preparations
Cosmetic industry	Lipstick (eg, L'Oreal), body oil (eg, Laboratoire, Vichy, France), moisturizing cream (eg, L'Oreal), soaps

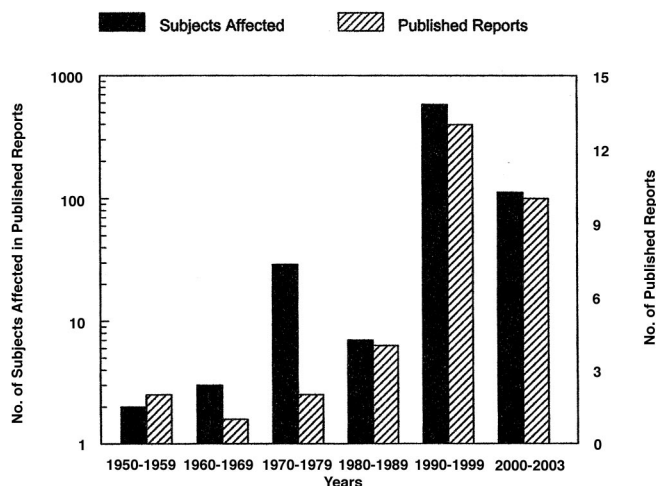


Figure 1. Global trend of sesame allergy between 1950 and 2003.

fourth place (0.42% prevalence), following egg (3.2%), milk (2%), and peanut (1.9%). Sensitivity to sesame was more common than that to any single tree nut studied.²⁵ In the United Kingdom, report of a completed government research project in 1996 estimated an overall prevalence of severe allergic reactions to sesame in the general population of 1 (0.05%) in 2,000.⁴⁵

A recent study on food allergy among Israeli children (n = 9,070) found food allergy prevalence to be 1.7%, with sesame the third most common food causing sensitization (0.18% prevalence), following egg (0.5%) and cow's milk (0.3%) and more than that of peanut sensitization (0.04%).¹² Furthermore, sesame was second only to cow's milk as a leading cause of anaphylaxis.^{12,20} Based on the finding that sesame is a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel, these authors suggest that sesame allergy is a matter of geography after all¹² because of the widespread use of sesame paste in the Middle Eastern diet, with consequent high levels of allergen exposure. Interestingly, although the use of sesame in food is common in India, no published reports exist of sesame allergy from this country. This observation parallels the situation of peanut allergy in Southeast Asia and China. Whether this pattern is due to lack of reporting or true absence of disease due to difference in the method of food preparation or late introduction of sesame in the diet of infants remains unclear.

While studying the prevalence of sesame allergy, it may be useful to distinguish *sesame allergy* from *sesame sensitization*. Most of the articles reviewed herein studied *sesame allergy* based on immediate clinical reactions following exposure to sesame. One study examined only *sesame sensitization* based on skin prick test (SPT) but did not study *sesame disease*.²⁵ Available published data on sesame allergy suggest a potential trend of global epidemic of sesame allergy, although formal evidence from studies on global prevalence is lacking.

HYPERSENSITIVITY TO SESAME: CLINICAL AND IMMUNOLOGIC FEATURES

Analysis of pooled clinical data on sesame allergy from all published reports is presented in Tables 2 and 3.^{11,13-44} As evident, sesame allergy occurs in individuals of all ages from infancy to adulthood. Interestingly, sesame allergy appears to be relatively less frequent in the pubertal age group (ages, 15–20 years). It is unclear from the literature whether the allergy reported among adults is simply due to the persistence of the condition or newer sensitization when the individual became an adult. However, given the age distribution (Table 2), it seems likely that adult patients are newly sensitized. There is only 1 report of 3 children outgrowing sesame allergy in Israel.^{12,20} Since shellfish, tree nut, and most peanut allergies are rarely outgrown and are common among adults, it is possible that sesame allergy might belong to the same category as these.²

Analyses of clinical presentation of sesame allergy revealed that clinical symptoms varied from subject to subject, and they included erythema, conjunctivitis, atopic dermatitis, contact dermatitis, allergic asthma, rhinitis, systemic anaphylaxis, urticaria, gastrointestinal symptoms, angioedema, dyspnea, pruritus, and oral allergy syndrome (Table 3). Notably, systemic anaphylaxis was commonly reported, suggesting the serious nature of the allergic reaction. Contact dermatitis to sesame has been predominantly attributed to the use of sesame seed oil.^{16,23,24,35,38} These studies confirmed contact hypersensitivity by patch testing (read at 48 to 72 hours) with sesame oil or its components. There is one report of contact allergy associated with a positive SPT result, although this study did not use patch testing. Conjunctivitis was less often reported. The type of symptom was independent of the age group of patients or country of reporting (data not shown). Due to incomplete information on sex in the studies, it was not possible to test the role of sex in reported sesame allergy.

In most cases, sesame allergy was elicited following exposure to sesame in food or therapeutics or cosmetics or due to occupation (among bakers). There was an unusual case of hypersensitivity to sesame oil following daily intramuscular injection of progesterone in sesame oil to a patient following in vitro fertilization and embryo transfer.¹⁹ This patient exhibited IHS, as evidenced by a positive SPT result to sesame oil, in addition to pulmonary compromise and marked eosinophilia.

Analyses of clinical immunology data on sesame allergy reports provided a clear pattern of underlying immune basis for sesame allergy (Table 3). Thus, most reported sesame allergy may be classified into at least 2 major categories: (1) IHS associated with a positive SPT result and/or specific IgE antibodies in the blood and (2) delayed hypersensitivity (DHS) associated with positive patch test results with sesame oil. In this group, no data were available for SPT or IgE, except in 1 case IgE was tested and found negative. In addition to these 2 major groups, there was a minor group

Table 2. Global Distribution of Reported Sesame Allergy

Continent (countries)	Age of patients, y				Total No. of affected patients*	References
	0-4	5-14	15-20	≥21		
Asia (Israel and Japan)	47	8	3	6	64	16, 20-24
Australia	531			1	532	25, 26
Europe (England, Finland, France, Germany, Italy, Netherlands, Spain, Switzerland)	4	10	4	56	107	11, 13, 14, 17, 18, 27-38
North America (United States)	6	12	2	12	32	15, 19, 39-44
Total No. of affected patients	57†	30†	9	75	735	

* Total may be larger than the sum of age groups, since it also includes patients with unspecified age.

† Excludes 531 patients from Australia (age range, 0-14 years).

Table 3. Pattern of Clinical Symptoms of Sesame Allergy

No. of patients	Clinical symptoms									Reference
	CD	AD	D	A	N	SA	U	G	AE	
Positive SPT and/or IgE results										
2		+						+	+	37
1			+	+					+	39
23		+	+		+	+	+	+	+	20
1			+	+	+		+			14
1			+		+		+			13
8	+			+	+	+	+	+		34
531			+				+		+	25
1			+			+	+		+	40
9			+		+	+	+	+	+	11
10		+	+				+	+	+	21
12					+	+	+	+	+	33
3				+		+	+		+	41
1			+			+	+	+		17
2			+					+		26
12		+		+		+	+		+	29
10				+		+	+	+	+	28
6		+		+		+				30
1						+	+	+	+	42
28		+	+		+	+	+	+	+	22
20		+	+		+		+	+	+	43
3			+					+	+	15
1			+			+		+		44
2							+			18
Negative SPT and IgE results										
1						+		+		36
1†			+							19
1			+			+	+	+		32
1							+		+	31
Positive patch test (oil) result‡										
1	+								+	24
15	+									35
1	+								+	16
1	+								+	23
14	+									38

Abbreviations: A, allergic asthma; AD, atopic dermatitis or eczema; AE, angioedema; CD, contact dermatitis; D, dyspnea; G, gastrointestinal symptoms; N, nasal symptoms such as rhinitis; plus sign, positive; SA, systemic anaphylaxis; SPT, skin prick test; U, urticaria.

† No data for IgE.

‡ No data for SPT and IgE, except in Kubo et al,¹⁶ where IgE tested negative.

with only 4 cases of IHS associated with negative SPT results and negative specific IgE antibodies in the blood. Many symptoms in this category overlapped with the first category. The underlying mechanisms in this category are unclear.

In summary, most reported sesame allergies belong to either IHS to sesame proteins linked to an underlying IgE antibody response (classic Gell and Coombs type I hypersensitivity reaction) or DHS to sesame oil caused by the classic cell-mediated immune response (Gell and Coombs type IV hypersensitivity reaction).

SESAME ALLERGENS: CHEMICAL AND IMMUNE PROPERTIES

Analyses of the reports suggest that sesame allergens belong to 2 broad categories based on their chemical nature and the type of hypersensitivity they elicit. The first category is proteins or glycoproteins, which have a wide range of molecular mass (7–78 kDa); this suggests that sesame seed contains multiple allergens and sesame proteins are linked to mainly IHS reactions mediated by IgE antibodies. The second category is lignin-like molecules in sesame oil; the 3 chemical allergens identified are sesamol, sesamin, and sesamol, which are all reported to be unsaponifiable fractions of sesame oil (Table 4).^{13,16,17,23,24,28–30,37,43,46,47} Although sesame seeds are available in 3 colors (white, brown, and black) and show quantitative differences in protein content (eg, white seeds have more protein than black seeds, 182 vs 28 mg/g), all 3 varieties have been reported to trigger allergic reactions.³⁰

Although an international nomenclature committee on allergens has designated 3 proteins in sesame as allergens (*Ses i 1* [9 kDa, 2S albumin], *Ses i 2* [7 kDa, 2S albumin], and

Ses i 3 [45 kDa, 7S vicilin]), available evidence suggests the existence of many more IgE-binding proteins in sesame seed (Table 4). Both *Ses i 2* and *Ses i 3* are seed storage proteins, and *Ses i 2* is the major soluble protein (constitutes approximately 25% of total protein content). *Ses i 3*, a 7S vicilin-type globulin of *S indicum*, shows 80% homology with a major peanut allergen (*Ara h 1*) and shares IgE-binding epitope with this peanut allergen. There are reports of cross-reactivity among allergens in sesame and allergens in other foods, including hazelnut, rye, kiwi, poppy seed, black walnut, cashew, macadamia, pistachio, and peanuts^{17,37,43,46} (Table 4). Given the general suggestion in the field of cross-reactivity between nuts,⁴⁸ it might be prudent for sesame allergic patients to avoid these cross-reacting foods in addition to sesame, although clinical relevance of such cross-reactivity remains to be established. Furthermore, the general rule for food allergy is to expose children to a food challenge to avoid unusual elimination diets.

All reported contact allergic dermatitis to sesame has been shown to be caused by 3 sesame oil components: sesamol, sesamin, and sesamol (Table 4 and Fig 2). Sesame oil used for pharmaceutical purposes contains approximately 0.002% of sesamol and sesamol and 0.27% of sesamin.⁴⁹ It is reported that the relatively stable nature of sesame oil is due to sesamol, an antioxidant.⁴⁷ However, others dispute the presence of sesamol in sesame oil.²⁴ These authors also report that the key allergenic structure of sesame oil is present only in sesamol and sesamin. The following structure was suggested to be responsible for allergenicity: tetrahydro-1-(3, 4 (methylenedioxy) phenyl) 1H, 3H-furo (3, 4–C) furan (Figure 2).²⁴

Table 4. Chemical Nature of Sesame Seed Allergens

Allergen name and molecular weight, kDa	Shares IgE epitope with	Reference
Protein		
~20, ~50	H, R, K, PS	37
	BW, BN, C, H, M, P	46
14, 25, 30		29
14		13
9 (2S albumin: major allergen; <i>Ses i 1</i>), 30, 14.4, 38.7, 43, 18, 53		28
7 (2S albumin major soluble protein; <i>Ses i 2</i>), 9, 20, 25, 29, 32, 34, 45 (7S vicilin-type globulin; <i>Ses i 3</i>), 52, 78	PN (<i>Ara h 1</i>)	43
14 (2S albumin precursor; major allergen), 20–25, 30–35, 40		22
12, 13, 22, 23.5, 32, 34, 36, 47, 53, 57.5		30
10, 12, 15–20, 25, 30–67	PS (10–12 kDa)	17
Oil (unsaponifiable lignin-like molecule)		
Sesamin, sesamol, sesamol		47
Sesamin, sesamol		24
Sesamin, sesamol		16
Sesamin, sesamol		23

Abbreviations: BN, brazil nut; BW, black walnut; C, cashew; H, hazelnut; K, kiwi; M, macadamia; P, pistachio; PN, peanut; PS, poppy seed; R, rye.

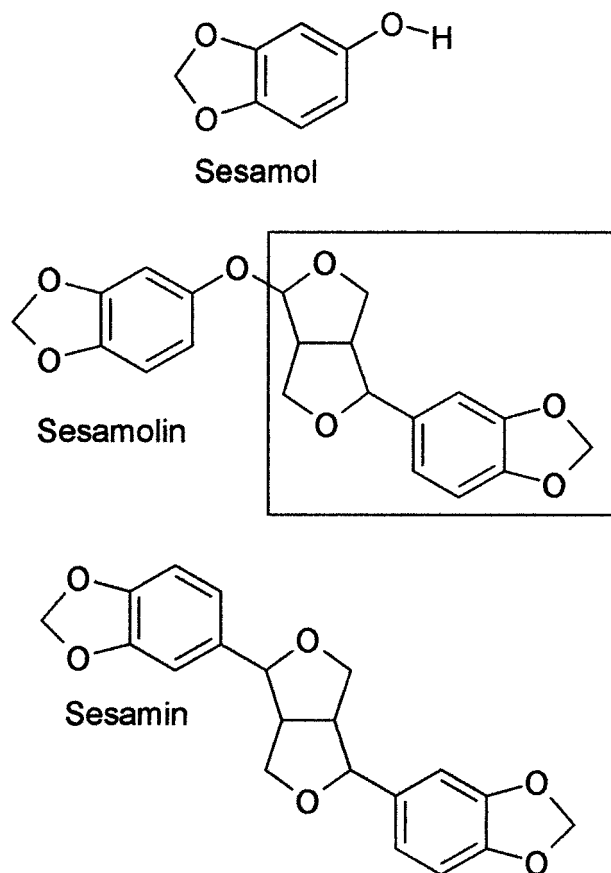


Figure 2. The small chemicals implicated in sesame oil-induced contact allergic dermatitis. Boxed area corresponds to the allergenic structure shared by both sesamolin and sesamin: [tetrahydro-1-(3, 4 (methylenedioxy) phenyl) 1H, 3H-furo (3, 4-C) furan].

SUMMARY AND FUTURE DIRECTIONS

Compelling evidence exists in the literature that sesame allergy is becoming a serious public health problem in many countries around the globe. Whereas IHS to sesame has a strong potential to trigger systemic anaphylaxis, DHS is predominantly expressed as contact dermatitis with angioedema. Clinical immunology data provide a basis to classify sesame allergy into at least 2 distinct categories that might be useful in future research to further understand disease mechanisms and develop relevant therapeutics. To our knowledge, this is the first example of a food allergy with evidence of protein and oil components of a single food that trigger IHS via IgE antibody and DHS via cell-mediated immune responses, respectively.

Only one report in the literature states that 3 children outgrew their sesame allergy within 1 to 2 years in Israel, suggesting that sesame allergy may be rarely outgrown similar to tree nuts and peanuts, although recent reports suggest that peanut allergy may be outgrown in approximately 25% of cases.^{2,12} A recent study on determining threshold doses of

food allergens to trigger clinical reactivity reports that the lowest observed adverse effect level for sesame was at 30 mg for sesame seed and 1 to 5 mL for sesame oil to trigger anaphylaxis by double-blind placebo-controlled food challenge test, suggesting the strong allergenic potency of sesame.³³ The authors of this study state that asthma induced by sesame could be even more severe than peanut, milk, or egg. Thus, the present literature review further supports the concerns raised by others that widespread use of sesame in food “may eventually cause sesame to share the same ‘notoriety and fate’ as the peanut—a major cause of severe food allergic reactions.”^{10,20}

Although it is currently unclear why sesame allergy is growing, many issues need to be considered: (1) Is this problem part of the global trend of increased allergies and asthma in general?^{1,50} (2) What is the role of the environment in the context of the hygiene hypothesis or the reduced microbial exposure hypothesis?^{51–53} (3) Is there a role for food processing on sesame allergenicity, since most exposure to sesame occurs following use in food and dry roasting (as opposed to frying or boiling) has been shown to increase peanut allergenicity?⁵⁴ (4) Has increased use of sesame in fast food and other commodities resulted in increased disease outcome due to widespread exposure to sesame allergens? Clearly, more basic and applied research is warranted.

We were unable to find any reported efforts to develop preventive and therapeutic methods for sesame allergy other than total avoidance of this food. Further research in this direction would be desirable to meet the challenge faced by this emerging food allergy with features similar to peanut and tree nut allergies (eg, potential for systemic anaphylaxis).

Sesame has been added to the list of major food allergens for use in food labeling in EC and Canada. Unfortunately, it is not yet included in the FDA listing of allergenic foods. We hope that the present article provides an overview of the seriousness of sesame allergy that might help the FDA consider including this food in the major allergen listing for labeling purpose in the United States. Inclusion of sesame in the allergen listing would be of great benefit for labeling-based prevention of life-threatening sesame allergy among US children and adults.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

CME Examination

1–5, Gangur V et al. 2005;95:4–11.

CME Test Questions

- Which of the following foods does the US Food and Drug Administration *not* consider a major “red-flag” allergenic food” for regulatory purposes?
 - legumes (peanut, soy)
 - tree nuts
 - milk
 - egg
 - wheat
 - fish
 - crustaceans and mollusks
 - sesame
- Sesame allergy has been reported to affect which of the following patient groups?
 - those younger than 4 years
 - 5- to 14-year-olds
 - 15- to 20-year-olds
 - those older than 21 years
 - all these age groups
- Which of the following foods appear to exhibit cross-reactivity with sesame?
 - hazelnut
 - kiwi
 - poppy seed
 - black walnut
 - brazil nut
 - a, b, d, and e only
 - all these foods
- Clinical presentation of sesame allergy may include which of the following symptoms?
 - anaphylaxis
 - angioedema
 - atopic dermatitis
 - contact dermatitis
 - any of these symptoms are possible
 - a and d only
- Based on the evidence reviewed in this article, sesame appears to trigger hypersensitivity reactions via at least which of the 2 following mechanisms?
 - IgE- and IgG-mediated hypersensitivity
 - IgE- and cell-mediated hypersensitivity
 - IgG- and cell-mediated hypersensitivity
 - Arthus-type reaction and cell-mediated hypersensitivity
 - IgE and Arthus-type reactions

Answers found on page 44.