Food allergy (FA)⁴ is a relatively rare and sometimes violent reaction of the immune system to food proteins. In its broadest definition, FA includes syndromes involving several immune mechanisms, each causing a variety of symptoms. Although all types of FA must be effectively managed, the most dangerous is immediate-type hypersensitivity (type I) mediated by IgE antibodies to food proteins. Most type I FA appears in the first 2 y of life and occurs in 6–8% of infants (1). As their immune systems mature (by 5 y), ~80% of allergic infants will lose their FAs (2). Symptoms range from mild rashes to life-threatening systemic anaphylaxis and are of 4 main types: dermatological (hives, local swelling, dermatitis, and eczema), gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), respiratory (runny nose, asthma, and tightening of the throat), and systemic (anaphylactic shock, organ failure, cardiac arrhythmia, and death).

Foods vary in clinical allergy significance. Although all food proteins have the potential to be allergenic for some people, 8 foods have been identified as the most frequent human food allergens and account for ~90% of FAs. These foods are milk, eggs, fish, crustacea, wheat, peanuts, tree nuts, and soy (3). This article describes the allergenic potential of soy proteins compared with some of the other major food allergens.

**Immunology of food allergy**

A detailed description of the mechanisms of food allergy is beyond the scope of this article, but several excellent reviews of clinical aspects are available (4–6). Briefly, type I food allergies involve a 3-step process. The first step is sensitization, which begins with transit of relatively intact food antigens across the intestinal barrier. The gut may be unable to effectively exclude intact antigens because of immaturity, injury, or infection. Some intact food antigen uptake is normal, even in adults. Factors affecting whether the antigens stimulate the usual antibody responses (IgG and IgA) and immune tolerance...
Soy allergy characterization

Soy protein is allergenic. The first allergic reactions to soy in humans were described in 1934 (7). Anti-soy IgE antibodies have been identified but allergen specificity patterns are variable and complex. As many as 28 soy proteins bind to IgE from soy-allergic patients (8). Soy is also an Aeroallergen, although the pathologies and allergen reactivity profiles are different for ingestion versus inhalation, where soy hull antigens not present in soy protein isolates seem to dominate (9). A small number of fatal allergic reactions to soy have been reported (10,11), but in all cases victims also had severe peanut allergies and asthma.

What is the relative allergenic reactivity of soy proteins compared with other major food proteins? The answer depends on what clinical and laboratory outcomes are used and which patient populations are studied.

Clinical and laboratory indicators of allergy. Clinical indicators of food allergy include cumulative clinical history of atopic symptoms; history of allergic symptoms soon after specific food ingestion; positive skin prick test (SPT) with food protein extracts; unblinded food challenges; and double-blinded, placebo-controlled, food challenges (DBPCFCs; the gold standard for food allergy diagnosis). Laboratory indicators of food allergy are radioallergosorbent test (RAST), which measures allergen-specific IgE antibodies using radioisotopes; ELISA, which also measures allergen-specific IgE using antibody-conjugated enzymes and chromatic substrates; and immunoblotting of polyacrylamide gel electrophoresis-separated proteins to reveal IgE-allergen binding.

Patient populations. Allergy assessment outcomes can be influenced by the criteria used to define patient enrollment. A variety of clinical populations have been used to study food allergy. Within specific populations, enrollment standards for inclusion and exclusion also vary. When comparing similar studies, it is important to clearly understand the characteristics used to qualify and enroll study subjects. Five clinical populations have been used for most food allergy research: 1) “high-risk” asymptomatic infants (defined variably based on the atopic history status of parents and/or siblings; 2) patients with atopic symptoms (defined variably to include 1 to several allergy-associated symptoms); 3) patients with positive DBPCFCs (a relatively rigorous criterion); 4) patients with cow’s milk allergy (a subset of group 3 that have been rigorously identified using DBPCFCs); and 5) whole-population birth cohorts.

Clinical results

High-risk infants fed cow’s milk protein–based formula (CMF) versus soy protein–based formula (SF). Concern exists about the sensitivity of cumulative atopic symptom scores as indicators of food allergy status, especially for older infants. These subjects may no longer be taking formula and have been exposed to a wide variety of nonfood environmental allergens that may contribute to their atopic symptoms. Some studies show no difference in the cumulative history of atopic symptoms in high-risk infants, food allergy was reduced 3.6 fold with soy. A meta-analysis of allergen reactivity patterns in 17 studies of high-risk infants shows soy allergy occurring in 3–4% of subjects versus 25% for cow’s milk (19).

Patients with atopic symptoms. These studies surveyed the clinical reactivity specificities of infants and children with atopic symptoms; the diagnostic tests used were RAST, SPT, or DBPCFC. Four studies demonstrate the overall incidence of reactivity to soy. Giampietro et al. (20) studied 317 atopic children and found 22% positive to soy by RAST but only 3% were positive by DBPCFC. Magnolli et al. (21) tested 704 atopic children and found 21% soy positive by SPT and only 1.3% soy positive by DBPCFC. Bruno et al. (22) tested 505 atopic children and found 6% soy positive by SPT and 1.2% soy positive by DBPCFC. Burks et al. (23) found 13% soy positive by SPT and 1.8% soy positive by DBPCFC in a study of 165 atopic patients. Overall, these data show a relatively low rate of soy allergy in atopic infants (28 of 1691 patients, 1.7%) and a relatively high rate of false-positive results when SPT and RAST are used to diagnose symptomatic soy food allergy.

Soy reactivity in DBPCFC-positive subjects. Two reports summarized results of DBPCFC patient evaluations performed at major tertiary care allergy centers. Bock and Adkins (24) describe 185 positive food challenges conducted over 16 y, where 31% were positive for cow’s milk proteins and 8% (15 patients) were positive for soy. Sichler et al. (25) reported on 196 positive DBPCFCs completed over 13 y, with 23% positive to soy proteins and 10% (20 patients) positive for soy proteins. With fewer than 35 soy-positive patients identified by DBPCFC over 13 y by 2 of the prominent academic food allergy research groups in the United States, it is apparent that extensive studies of soy-allergic subjects in America would be a daunting task. Patients with soy allergy confirmed by DBPCFC seem very rare.

Soy allergy in patients with cow’s milk allergy. Most often, SF is used clinically to manage intolerance to CMF. A variety of mechanisms are involved in CMF intolerance, which currently affects as many as 36% of infants at some point in y 1 of life. Infants with type I milk protein allergy are estimated to be 6–8% of the total population, so most (~80%) CMF intolerance is not caused by allergy and is effectively managed using SF. Infants with type I allergy to
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CMF are a rigorous test population for evaluating the allergenic reactivity of SF.

Several studies have measured the proportion of infants with documented CMF allergy that will develop soy allergy when SF is substituted for CMF. Bock and Adkins (24) reported 4 of 54 (7%) CMF-allergic infants developed soy allergy when switched to SF. Cantini et al. (26) found 1 of 20 (5%) who developed soy allergy in a similar study. Zeiger et al. (27) observed 13 of 93 (14%) infants allergic to CMF who developed soy allergy. In the study by Kleinola et al. (28), 8 of 80 (10%) developed SF allergy. Together these studies reported that 221 of 247 (89.5%) infants allergic to CMF could be effectively managed with SF. This overall performance approaches the clinical standard for hypoallergenic formula [95% confidence that 90% of allergic infants will not react (29)].

**Frequency of allergy in a whole birth cohort.** Arshad et al. (30) conducted an interesting study on the Isle of Wight, where a whole birth cohort of 981 infants (64% of total births agreed to participate during the 14-mo enrollment period) was followed to age 4 y. The study recorded histories of allergic disorders and assessed the correlation between these data and results of SPT to a variety of common allergens. Data were not adjusted for relative allergen exposure rates and, as mentioned earlier, SPT is known to overestimate the true incidence of food allergy. SPT results for the various allergens were as follows: house dust mite, 11.9%; grass, 7.9%; Alternaria, 4.8%; milk, 1.4%; and peanut, 1.2%. The lowest sensitization rate was for soy at 0.25%.

**Food allergen reaction thresholds.** Another method for ranking the potency of food allergens determines the minimum oral allergen dose required to initiate allergic symptoms. This dose will vary across a population of allergic patients, so the best comparator becomes the dose-response distribution within the allergic population. These data are difficult to obtain because patients with severe allergies must be challenged with increasing allergen doses until a positive reaction occurs. These types of experiments have been reported for only 5 food allergens (Fig. 1). The most important evidence concerns threshold doses for the most sensitive patients. No standards have been set for acceptable minimum allergen doses. However, for comparative purposes, we can apply the “safe for 90% of allergic patients” rule (the hypoallergenic infant formula standard) to the data in Figure 1 to estimate the following “safe” protein doses: peanut, 0.1 mg; hazelnut, 1 mg; egg and milk, ~3 mg; and soy, ~400 mg. Although the number of patients in these studies is relatively low, the >100-fold difference between the safe protein dose for soy and other allergens is striking. If confirmed, this difference should be considered when setting standards and selecting analytical methods appropriate for measuring soy allergens in food products and food production environments. A partial confirmation of this approach is found in a recent statistical analysis of published data by Blindslev-Jensen et al. (34). This report presented estimates of allergen doses causing reactions at rates of 1 per 1,000,000 and 1 per 100 of population. These data, summarized in Table 1, seem to be consistent with the 90% reactivity threshold numbers predicted for soy protein (1 in 10 at 400 mg protein vs. 1 in 100 at 40 mg protein).

**Allergic reaction severity.** In addition to specific allergen frequency, Sicherer et al. (25) reported the severity of allergic reactions that occurred during the positive DBPCFC challenges (Fig. 2). In 13 y of experience with DBPCFCs, these investigators did not observe any severe allergic reactions to soy challenge.

In summary, SFs have been widely studied for the management of food allergy, mainly in infants and young children. In a variety of clinical study designs, soy protein has consistently been shown to be significantly less reactive than cow’s milk protein (an observation without explanation at this point).

![FIGURE 1](https://academic.oup.com/jn/article-abstract/134/5/1213S/4688705)

**FIGURE 1** Food allergen reaction thresholds. Ingested allergen dose (mg protein) vs. % allergic responses in challenged patients. Allergens: ▲ peanut (31), ● hazelnut (32), X egg (33), ● milk (27), ■ soy (27).

![FIGURE 2](https://academic.oup.com/jn/article-abstract/134/5/1213S/4688705)

**FIGURE 2** Allergic reaction severity. Percentage of challenge-positive patients vs. severity of elicited allergic reaction (number of food challenges). Adapted from Sicherer et al. (25).
Although extremely rare, severe soy allergies, including fatal reactions, have been reported.

**Animal data**

The basis for diminished immunological reactivity for soy protein in humans is unexplained. Is this a general property of soy or is low soy reactivity species specific? Data from 2 animal models of food allergy have been used to address these questions.

**Oral sensitization model.** The model using oral sensitization of guinea pigs, best described by Devey et al. (35), involves feeding an experimental protein for 33 d and then administering a rapid systemic antigen challenge on day 35. If sensitization has occurred, IgE and IgG1 antibodies will be produced. Both antibody classes will trigger anaphylactic reactions if activated by the presence of a cross-linking antigen. Antigen is injected and the animals are observed for anaphylactic symptoms, scoring for severity on a 0–5 scale (0 = no symptoms, 5 = death). The advantage of this model is that sensitization simulates antigen digestion and intestinal uptake. Disadvantages are that the model is not very sensitive, it does not include an oral challenge, and the anaphylactic response is usually dominated by an IgG1 response rather than an IgE response.

Results of feeding and challenge trials with CMF and SF are shown in **Table 2**. Two intact cow’s milk-based formulas (Similac and Enfamil) stimulated strong immune responses that caused fatal anaphylactic reactions in all animals fed these products. A formula based on partially hydrolyzed cow’s milk whey protein (Good Start) stimulated weaker but still significant reactions. Animals fed a hypoallergenic formula based on extensively hydrolyzed cow’s milk casein (Alimentum) did not become sensitized as indicated by the absence of allergic symptoms. Interestingly, animals challenged after being fed a formula based on intact soy proteins demonstrated the lowest measurable symptoms of allergy, indicating very low relative reactivity. The significance of this result was confirmed with an important positive control: Guinea pigs were immunized by injection with soy formula mixed with an alum adjuvant on day 0 and challenged as before on day 35. These animals responded with severe allergic symptoms (4 deaths and 1 near death per 5 challenges), indicating that the lack of response to oral soy sensitization was not due to the inability of guinea pigs to produce antibodies to soy.

**TABLE 2**

<table>
<thead>
<tr>
<th>Product/protein</th>
<th>Anaphylaxis score</th>
<th>Statistical group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similac/cow milk</td>
<td>5.00</td>
<td>A</td>
</tr>
<tr>
<td>Enfamil/cow milk</td>
<td>5.00</td>
<td>A</td>
</tr>
<tr>
<td>Good Start/partially hydrolyzed cow milk</td>
<td>3.11</td>
<td>B</td>
</tr>
<tr>
<td>Isomil/soy</td>
<td>1.00</td>
<td>C</td>
</tr>
<tr>
<td>Alimentum/extensively hydrolyzed cow milk</td>
<td>0.07</td>
<td>D</td>
</tr>
<tr>
<td>Isomil/soy—hyperimmunized</td>
<td>4.80</td>
<td>A</td>
</tr>
</tbody>
</table>


2 Anaphylaxis score scale from no reaction = 0 to death = 5.

3 Products with the same letter are not different (t-test, P = 0.05).

4 Hyperimmunized using alum instead of oral sensitization.

**Hyperimmunization model.** Rabbit hyperimmunization is a sensitive model for assessing immunological reactivity (36). This model uses relatively high doses of immunogen formulated with complete Freund’s adjuvant and an aggressive immunization protocol with measurement of antibody responses using quantitative ELISA methods. The model has been used successfully to predict clinical performance of hypoallergenic formulas based on protein hydrolysates (37,38). **Figure 3** shows a comparison of the immunogenicity of various protein systems plus a clinically hypoallergenic casein hydrolysate as a low-end calibrator. Of the 6 intact protein systems tested at equal immunizing doses, soy was the least immunologically reactive (186-fold less reactive than cow’s milk casein). This difference in ingredient reactivity is mirrored in infant formulas based on these proteins. **Figure 4** shows the relative immunogenicity of 3 CMFs compared with 4 SFs. The low-end calibrators in this figure are 2 hypoallergenic formulas based on extensively hydrolyzed casein (Alimentum and Nutramigen) and an essentially nonimmunogenic amino acid formula (Ele-Care). As a group, the SFs are 100 times less immunogenic than the CMFs. These data are surprising because all products contain intact proteins with similar molecular weight profiles. Taken together, the animal data support the clinical findings of relatively low immunological reactivity for soy.

**Biochemistry and immunochemistry of soy allergens**

Food allergens are always complex mixtures of many potentially immunoreactive proteins. Within a food allergen system, individual allergens will also be affected differently by various processing methods. Therefore, the identity and the processing history of food proteins will determine their allergenic potentials and both must be considered in assessing allergen specificity and potency. Individual protein allergens are also complex, with several to many antibody recognition sites (epitopes) per protein. Epitopes can be either sequential (a particular linear amino acid sequence) or conformational (a group of nonlinear amino acids that are in proximity because of protein folding or assembly) and, for glycoproteins, may
FIGURE 4 Immunogenicity of infant formula based on various food protein systems using the hyperimmunized rabbit model. Day 35 adjusted log titer (L) = Log (day 35 IgG antibody titer / day 0 IgG antibody titer). Titer = reciprocal of antiserum dilution yielding an ELISA absorbance value of 0.3 after 10 min of substrate incubation. GdSt = partially hydrolyzed whey-based Good Start (Nestlé), Enml = intact CM-based Enfamil (Mead Johnson), Smlc = intact CM-based Similac (Ross/Abbott), Nrsy = intact soy-based Nursoy (Wyeth-Ayerst), GbSy = intact soy-based Gerber Soy (Mead Johnson), Prsy = intact soy-based Prosobee (Mead Johnson), Isom = intact soy-based Isomil (Ross/Abbott), Ntrm = hypoallergenic extensively hydrolyzed casein-based Nutramigen (Mead Johnson), Alim = hypoallergenic extensively hydrolyzed casein-based Alimentum (Ross/Abbott), ECr = nonallergenic amino acid-based EleCare (Ross/Abbott). Data from Cordle et al. (unpublished, 1995) and Duska-McEwen et al. (45).
Weaknesses in immunoblot data must be remembered: individual studies contain relatively few patients and different patients give different results. Protein separation is accomplished under denaturing conditions that prevent detection of IgE binding to conformational epitopes that may play a significant or even dominant role. The presence and/or intensity of bands do not correlate with clinical reactivity. Cross-reactivity studies show many false-negative reactions. On the positive side, it is likely that immunoblot and ELISA data overestimate the number of clinically significant allergens. Elimination of a few high-affinity triggers of clinical allergy may substantially lower the overall allergenicity of soy.

Conclusions and future directions

A substantial and consistent body of human clinical and animal model data indicates that soy proteins tend to be less immunologically reactive than many other food proteins. The biochemical and immunological basis for these differences is currently unknown. Improved biochemical methods and immunochemo reagents will be required to better characterize and understand soy protein’s unique immunological properties. In vitro methods that correlate better with DBPCFCs are needed, and these methods should be quantitative. Techniques must also allow for detection of conformational allergen epitopes. Finally, DBPCFC-positive patient antiserum sample numbers available for study must be increased substantially and standardized antiserum pools must be assembled and characterized.

LITERATURE CITED

Termine the threshold level for allergenic foods by statistical analysis of published data in the literature? Allergy 57: 741–746.


