

Soy protein for the prevention and treatment of children with cow-milk allergy^{1,2}

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ABSTRACT Soy-protein formulas are widely used for feeding babies with cow-milk allergy. When they first were marketed, these formulas were the only available cow-milk substitute and they ensured a normal life for many children who were affected by the large spectrum of clinical manifestations of cow-milk allergy. Soy-protein formulas were also given to allergy-prone infants for the prevention of atopic diseases when breast milk was not available. Several researchers studied the prevalence of soy sensitization in allergic disease. Few studies used a challenge test for the diagnosis of soy allergy, even those in patients in whom soy allergy was suspected. In most studies the diagnosis of soy allergy was based on anecdotal case histories reported by parents and was not substantiated by scientific diagnostic criteria: no challenge test to soy was made nor were data available on specific immunoglobulin E to soy. In this paper we critically reviewed literature on the safety of feeding soy-protein formulas to babies with cow-milk allergy as well as on the prevention of cow-milk allergy. *Am J Clin Nutr* 1998;68(suppl):1447S–52S.

KEY WORDS Soy-protein formula, cow-milk allergy, prevention of atopic disease, allergenicity of soy

INTRODUCTION

Cow-milk allergy (CMA) induces a large spectrum of clinical manifestations in infants and children. These manifestations mainly affect the gastrointestinal tract, skin, and, more rarely, the respiratory tract (1–4). The severity of the disease varies with a patient's age, atopic status, and clinical presentation (4). It was estimated that CMA occurs in $\leq 2\%$ of all children in the first 3 y of life (5). In this paper we reviewed the literature on the safety of soy-protein formulas (SPFs) for feeding babies with CMA as well as for the prevention of CMA.

BASIC DEFINITIONS OF FOOD ALLERGY-RELATED TERMS

The incorrect criteria used by many investigators to diagnose soy allergy as well as the inexact definition of food allergy has led to confusion about the prevalence of soy allergy in children and the lack of safety of feeding SPFs to babies with CMA. As a consequence, a variety of nonspecific symptoms such as vomiting, colic, diarrhea, and irritability were incorrectly identified as

resulting from soy allergy without any objective confirmation. The correct definition of food allergy is necessary to establish the prevalence of allergy to a given food and to investigate the natural history of food allergies.

Food allergy is defined as an adverse reaction to food that is due to an immunologic mechanism. Several immunologic mechanisms have been suggested as being involved in the phenotypic expression of food allergy; however, only immunoglobulin E (IgE)-mediated reactions can be routinely investigated (6). No reliable laboratory test is available for diagnosing CMA or allergies to other foods. Skin-test responses to cow milk or to other offending foods and detection of food-specific IgE antibodies are usually positive in children with IgE-mediated food allergy. Skin-prick tests for foods have a good negative-predictive value but a rather poor positive-predictive value (7), and tests for detecting food-specific IgE antibodies have the same limits as do other skin tests (7–9). A double-blind, placebo-controlled, oral food challenge is considered the ideal method for definitively confirming histories of adverse reactions to foods. Although in clinical practice and in young children an open food challenge is useful, a double-blind, placebo-controlled, oral food challenge is imperative for the diagnosis of food allergy both for research purposes and in clinical trials (7, 10).

To avoid confusion and misunderstanding, the following terms are defined.

- *Allergen* is the antigenic molecule that takes part in the immune reaction that results in allergy.
- *Allergenicity* is the ability of a given molecule to trigger an allergic reaction in already sensitized individuals.
- *Antigenicity* is the ability of a given molecule to promote antibody synthesis in the non-IgE immune system (IgG, IgA, and IgM).
- *Epitope* is the limited part of the molecule to which the antibody (or the lymphocyte receptor) binds.
- *Allergenic determinants* are epitopes in the IgE system.
- *Antigenic determinants* are epitopes in the IgG, IgA, and IgM systems. Antigenic determinants are usually conformational

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and can easily be destroyed, whereas allergenic determinants are sequential and therefore more resistant.

- *Cross-reactivity* is the possible interaction between the binding site of an antibody and the same allergenic determinant present in different molecules. All the molecules trigger allergic reactions in patients sensitized to one of these molecules, even without previous exposure.

- *Immunogenicity* is the ability of a given molecule to stimulate the IgE system.

- *Sensitization* is the first induction of an IgE response to an allergen.

Because of the peculiarity of the atopic status, a minute dose of allergen may induce IgE antibody responses in atopic babies prone to allergic responses, and this dose is effective for secondary IgE-antibody responses and can trigger severe reactions in sensitized infants. B and T cells appear to bind conformational epitopes associated with shapes found on exposed regions of the folded molecule. However, primary sequences of a few amino acids comprising a sequential epitope may persist in being recognizable for T lymphocyte receptors when specific fragments are presented with appropriate major histocompatibility complex markers on the surface of antigen-presenting cells (11). This mechanism may have clinical relevance when hydrolysate formulas are used both for the prevention and the treatment of CMA. Finally, because primary and secondary prevention of food allergy is antigen specific, for primary prevention (avoiding sensitization) or secondary prevention (treatment) of CMA, a formula without any cow-milk proteins should be given.

NUTRITIONAL ADEQUACY OF SOY-PROTEIN FORMULAS

The distribution of nutrients in SPFs is quite similar to that in cow-milk formulas. SPFs and cow-milk formulas contain the same amount of proteins, lipids derived from vegetable oils, and carbohydrates in the form of maltodextrins, cornstarch, or sucrose (12–15). Commercial SPFs differ from one another most markedly in carbohydrate content. Inclusion of 2 different carbohydrates (sucrose and corn syrup hydrolysates) affords the theoretical advantage of maximizing carbohydrate digestion and absorption. All SPFs are lactose free, fortified with L-methionine, and contain added taurine, carnitine, and iron.

Several clinical studies showed that feeding SPFs to full-term infants is associated with normal growth, protein nutritional status, and bone mineralization (12, 13, 16). One study performed in infants exclusively fed SPFs during the first 6 mo of life showed no immunologic abnormality or increase in infection morbidity (17) as was reported previously (18). No differences in the proportion of infants who seroconverted to oral poliovirus immunization were found between the types of feeding (17).

ANTIGENICITY AND ALLERGENICITY OF SOY PROTEIN IN ANIMALS

Animal models have been used to evaluate the antigenicity and allergenicity of dietary proteins, mainly cow-milk proteins. The specificity of the systemic immune response induced orally was determined by screening circulating reaginic antibodies. The experimental conditions established for oral sensitization to

cow-milk proteins were used to evaluate protein allergenicity of soy and egg white. On the basis of the results of reagent titration by passive cutaneous anaphylaxis, egg white was the most sensitizing protein source, followed by whey proteins and cold soy extract (19). Although in this model only raw soy proteins were tested, soy proteins appear to be less sensitizing than cow-milk proteins, according to the passive cutaneous anaphylaxis titers (19).

Eastham et al (20) showed that feeding rabbits with SPF induced a more profound and complete tolerance than that induced by cow milk. The handling of ingested soy proteins by the immune system is speculated to result in a hypoallergenic state caused by either the stimulation of specific suppressor T cells in Peyer's patches, the hapten effect of partially digested protein fragments, or an effector cell blockade resulting from immune complexes present in slight antigen excess (20). No fatal anaphylactic reaction was triggered with soy protein in animals sensitized to SPFs, although anaphylaxis was triggered with cow-milk protein in all animals sensitized to cow milk (21).

SOY-PROTEIN FORMULA FOR TREATMENT OF COW-MILK ALLERGY

SPF was first described as a cow-milk substitute in 1909 (22) but was not used for feeding babies with CMA until 1929 (23). Since then, SPFs have been widely used for feeding babies with CMA. These formulas were the only available cow-milk substitute in 1929, and such products ensured a normal life for many children who were affected by the large spectrum of clinical manifestations of CMA (13, 16, 23–27). In addition, SPFs have been given to genetically atopic, allergy-prone infants for the prevention of atopic diseases when breast milk was not available (28–39).

More recently, other special formulas derived from the hydrolysis of cow-milk proteins (extensively and partially) have become available on the market (40), and a debate on the allergenicity of SPFs has been increasing (41–46). However, in all these studies, the definition of soy allergy was anecdotal and not based on scientific diagnostic criteria: no challenge to soy was made, nor were data on IgE specific to soy available.

Bias is further evident in the use of incorrect quotations from previous studies. Surprisingly, even important position papers by a prestigious society did not support their recommendation on the use of SPFs with citations of appropriate studies. In 1983, the position paper of the Committee on Nutrition of the American Academy of Pediatrics on the use of SPFs concluded that "Instances when soy-protein formula should not be used included...in the dietary management of documented clinical allergic reactions to cow milk protein" (25). In the same paper the committee stressed that protein hydrolyzed formula is warranted in infants and children with clinical manifestation of CMA. No references were provided showing that such products are superior to SPFs in children with CMA.

In 1990, the Committee on Nutrition of the European Society for Paediatric Gastroenterology and Nutrition reported that available data did not support the use of SPFs in infants with suspected or proven adverse reactions to cow-milk protein (27). To support this recommendation, the committee should have referenced studies on CMA. Surprisingly, the committee referenced studies that were not appropriate (32, 47) because these studies dealt with the use of SPFs for the prevention of atopic diseases and not with the management of adverse reactions to cow milk.

Another common bias is the incorrect quotation of the conclusions of previous studies to support the assumption that SPFs are allergenic. For example, Eastham et al (48) reported that soy proteins are as antigenic and not as allergenic as cow-milk proteins. However, the conclusion of this study is commonly misinterpreted or misunderstood. The authors showed an antibody response (hemoagglutinins that are mainly IgG) to soy proteins in SPF-fed infants that was similar to that found to cow-milk proteins in infants fed cow-milk formula and concluded that soy protein is as antigenic as cow-milk protein (48). IgG antibodies to food antigens are physiologically produced and there is no evidence that they are involved in the development of atopic diseases. Therefore, Eastham et al's (48) conclusion that soy is as allergenic as cow milk is incorrect, as are similar conclusions by other authors.

Several authors have quoted other studies without checking the reliability of the statements. Kahn et al (49), in their work devoted to sleep disturbance and CMA, comment that "soya milk may not be the best choice for replacement of cow milk since up to 5% of allergic infants can also suffer from soya protein intolerance." However, their comment was based on information from a book (50), not on the results of a study double-blind, placebo-controlled, oral food challenge. Pekio et al (51) stated "...when SPFs are used as a substitute for cow-milk allergy, allergy to soy proteins develops in a far higher number of infants." To support this statement, the authors again referenced the studies by Kuitunen et al (41), Jakobsson and Lindberg (42), and Gerrard et al (52), the flaws of which were discussed above.

Eastham (53), in a review on the topic of soy-protein allergy, claimed that this intolerance develops in 15–50% of cases, and quotes findings [in addition to his own (48)] on soy antigenicity; however, the data were not from a double-blind, placebo-controlled, oral food challenge. Wilson and Hamburger (54), in their review article on CMA in the first year of life, state that one of the "primary disadvantages of SPFs is antigenicity. Approximately 25% of patients with CMA are also allergic to soy. In addition, soy proteins are irritating to the gastrointestinal tract of some infants, especially during or after an acute episode of gastroenteritis. Thus, SPFs will not be of value in these two groups of patients." References for this statement were the book by Bahna and Heiner (50) and the study by Gerrard et al (52), which do not support the data and the conclusion of the authors. In the same article, the authors stressed that children with CMA should be fed a partially hydrolyzed formula (54). On the basis of other studies, these products are not recommended in such patients and can trigger severe anaphylaxis (55–57).

Of the studies in which soy allergy was diagnosed, few used a challenge test to make the diagnosis (9, 58, 59). Sampson (58) found that only 5% of 204 patients with atopic dermatitis showed soy sensitivity, as evidenced by double-blind, placebo-controlled challenge tests. Bock and Atkins (59) reported that only 4 children out of 54 (7%) with CMA had symptoms after a double-blind, placebo-controlled food challenge with soy. We found that only 4% of 143 children with atopic dermatitis had a positive challenge test to soy (9). In another study, no child with severe CMA had a positive result after a double-blind, placebo-controlled food challenge to SPF (57).

There is growing evidence that soy proteins can induce enteropathy in young infants with and without cow-milk intolerance, with atrophy of the villi similar to that caused by cow-milk protein intolerance (60–63). Colitis induced by soy protein and

cow-milk protein is clinically and pathologically similar (64). Clinical features of colitis are nonspecific and include fever, leukocytosis, vomiting, blood-tinged mucoid diarrhea, carbohydrate intolerance, dehydration, and metabolic acidosis; shock may occur as a consequence (61). The more chronic reactions may also involve anemia and hypoproteinemia as a result of enteric loss of iron and protein (60). These symptoms usually are described in infants who experience intestinal difficulties after ingestion of cow milk. Histologically, colitis-related lesions are indistinguishable from those seen in untreated celiac disease (60).

Freier et al (44) estimated that gastrointestinal symptoms occur in ≈30% of infants fed soymilk in the treatment of gastrointestinal cow-milk hypersensitivity. On the basis of this observation, they do not recommend the use of SPFs in infants <6 mo of age with cow-milk hypersensitivity manifested by gastrointestinal symptoms. They do use SPFs in infants >6 mo of age and have not noticed any adverse effects. Hill et al (65) described several children with intolerance to multiple food proteins. The children with CMA had slowly evolving, adverse, late reactions (irritability, diarrhea, vomiting, and eczema) within several days of consuming not only to cow milk but also soymilk, casein hydrolysate, and other foods. A nutritionally complete infant formula composed of individual amino acids, fat, carbohydrate, minerals, and vitamins (Neocate; Scientific Hospital Supplies, Liverpool, United Kingdom) proved to be an effective substitute formula for these patients.

Other manifestations, such as atopic dermatitis, may occur in some SPF-fed children (66). Anaphylaxis after the ingestion of soy protein appears to be an extremely rare phenomenon. To our knowledge, only 2 cases have been reported (67, 68).

SOY-PROTEIN FORMULAS USED FOR PREVENTION OF COW-MILK ALLERGY

In 1953 it was reported that SPFs given to atopic, allergy-prone babies prevented the onset of allergic disease, mainly eczema (28). However, the results of this study were criticized because of the lack of a control group. A prospective, long-term study that included a control group was then done (29). A large cohort of 292 infants with family histories of atopic disease were randomly assigned to receive either an SPF or a cow-milk formula; 10 y later, 235 of 295 children were followed up by a physician. Allergic disease had occurred in 18% of the soy group and in 50% of the control group, the difference being attributable to asthma and perennial allergic rhinitis. Surprisingly, no significant difference occurred in the prevalence of eczema, which was low in both groups (29). Three years later, Brown et al (30) did not confirm these optimistic results: allergy occurred in 10% of the children assigned to the soy group and in 13% of the control children, but the difference was not significant.

Encouraging results on the preventive effect of SPF were shown in the elegant study in infants of allergic parents by Matthew et al (31); 23 breast-feeding mothers adhered to a dietary regimen in which dairy products, fish, and eggs were excluded for the first 6 mo postpartum. SPF supplements were given to the infants as necessary. Nineteen mothers who declined to follow the prescribed dietary regimen formed the control group. The incidence of eczema was significantly lower in the regimen group at both 6 and 13 mo. However, the diagnosis of eczema was not blind with regard to dietary group (31).



TABLE 1

Properties of soy-protein formulas

No cow-milk protein
No cross-reactivity with cow-milk protein
Lower immunogenicity than cow-milk formulas
Lower allergenicity than cow-milk formulas
Antigenicity similar to that of cow-milk formulas
Nutritional adequacy similar to that of cow-milk formulas
Better palatability than hydrolyzed formulas
Less expensive than hydrolyzed formulas

In a small but intense study in children with a biparental history of atopic disease, 48 children were randomly assigned to receive SPF or cow-milk formula from weaning to age 9 mo (32). Two-thirds of the children developed atopic disease by age 4 y and there was no significant difference between groups.

Of the other studies published, some have recommended the use of SPFs because their subjects showed fewer allergic reactions to them than to cow-milk formulas, whereas others found a similar frequency of allergic manifestations with either formula (33–39, 47, 69, 70). Businco et al (33–37), in prospective studies of at-risk infants, confirmed the efficacy of preventive dietary measures (defined as exclusive breast-feeding for the first 6 mo supplemented as necessary with SPFs and a diet free of cow milk and eggs for breast-feeding mothers) and preventive environmental measures (ie, elimination of dust mites, smoking, and pets in the house). More recently, these authors observed 174 high-risk infants for ≤ 52 mo; the prevalence of atopic disease at the last follow-up was low: 1% food allergy, 0.5% atopic dermatitis, and 9% asthma (37).

Miskelly et al (69) in their study of 487 at-risk infants, concluded that the allergy symptoms manifested by the intervention group (fed breast milk, an SPF, or both) were similar to those of the control group (fed breast milk, cow-milk formula, or both). Bardare et al (38) confirmed the preventive effect of SPF in a large prospective study including 391 atopic, allergy-prone infants. Breast-feeding was recommended for the first 6 mo of life, and SPF was given when breast milk was not available; selected weaning was also advised. At the end of the first year of life, 13% of the infants in the study group and 29% of the children in the control group had atopic disease ($P < 0.01$) (38).

ADVANTAGES OF SOY-PROTEIN FORMULAS COMPARED WITH HYDROLYZED FORMULAS

The properties of SPFs are listed in **Table 1**. Hydrolyzed formulas may contain small amounts of native proteins from which the product is derived (71–74), but no intact cow-milk protein is present in SPFs. Soy proteins are immunogenic, but according to experimental and clinical studies they are less immunogenic and allergenic than cow-milk proteins (9, 21, 58, 75). SPFs do not cross-react with cow-milk proteins, but hydrolyzed formulas do. As we first reported (55), partially hydrolyzed formulas, and more rarely extensively hydrolyzed formulas, can trigger anaphylactic reactions, which may be life threatening in infants and children with IgE-mediated CMA (54, 72, 73, 76, 77) (**Table 2**). Extensively hydrolyzed formulas may be useful in young babies with cow-milk or soy enteropathy (78). Soy proteins are as antigenic as cow-milk proteins (48), but as previously pointed out, this antigenicity should not necessarily be regarded as harmful.

TABLE 2Immunogenicity, antigenicity, and allergenicity of hydrolyzed formulas and soy-protein formulas (SPFs)¹

	Hydrolyzed formulas			SPFs
	High ²		Partial ²	
	Casein	Whey	Whey	
Immunogenicity (IgE system)	–	–	+	+
Antigenicity (IgG system)	–	–	+	+
Allergenicity	+	+	+++	+
Cross-reactivity with cow-milk protein	+/-	+/-	+++	–


¹ –, absent; +, present; +++, very strong; +/-, weak.

² Degree of hydrolysis.

SPFs are nutritionally adequate, palatable by most infants, and less expensive than hydrolyzed formulas (12).

CONCLUSION

The field of soy allergy is fraught with great confusion, mainly because most studies have lacked scientific criteria for diagnosing soy allergy, have incorrectly interpreted the conclusions of previous studies, and have quoted material from previous studies without consulting the original data. It is unfortunate that although it has been recommended that double-blind, placebo-controlled, oral food challenges be used to diagnose food allergies in research studies, few studies of soy allergy have used this procedure (9, 58).

We claim, on the basis of both personal experience and the few studies in which the diagnosis of soy allergy was confirmed with a double-blind, placebo-controlled, oral food challenge, that SPFs are the preferred food for children with IgE-mediated CMA and that extensively hydrolyzed formulas should be used only when there is scientific evidence that a child is allergic to soy. Further studies are necessary to investigate the prevalence of soy allergy both in children with different disorders associated with CMA and in the general pediatric population. In addition, it is imperative to plan clinical trials to compare the efficacy and safety of SPFs and of hydrolyzed formulas in children with IgE-mediated CMA and to determine ways to prevent CMA in atopic, allergy-prone babies. 

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