

# Allergenicity and nutritional adequacy of soy protein formulas

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**Soy protein formulas are used for different conditions, including cow milk protein allergy, lactose and galactose intolerance, and severe gastroenteritis. Feeding soy protein formulas to normal term infants is associated with normal growth, normal protein nutritional status, and normal bone mineralization. Recent studies of infants fed soy protein formulas exclusively during the first months of life revealed no immunologic abnormality; however, the use of such formulas for management of cow milk protein allergy and for prevention of atopy is controversial. Although in the past decade many studies have stressed soy allergenicity, soy allergenicity has been confirmed by the challenge test in only a few studies. In this article we review the studies dealing with the allergenicity of soy protein formulas. We also present our own data on their use in the prevention and management of cow milk protein allergy. (J PEDIATR 1992;121:S21-S28)**

Soy, like the lentil and the pea, belongs to the family Leguminosae, and it has been used for infant nutrition by the Chinese and Japanese for many centuries. However, in Western countries the first description of the use of a soy product as a cow milk substitute was made in 1909.<sup>1</sup> A soy protein formula was used for the first time to feed infants with cow milk protein allergy in 1929.<sup>2</sup> Subsequently, soy protein formulas have been widely used to feed infants with this disorder. These formulas were the only available cow milk substitute, and they ensured not only survival but also a normal life for many children who were affected by the wide spectrum of clinical manifestations of CMP allergy.<sup>2-8</sup> More recently, other products, such as CMP hydrolyzed formulas, have become available; as a result, the safety of soy formula for the treatment of children with CMP allergy has been debated. This article reviews commonly cited works on the allergenicity of soy protein formulas and pre-

sents additional data on the use of these formulas for the prevention and management of CMP allergy.

## NUTRITIONAL ADEQUACY OF SOY PROTEIN FORMULAS

Soy protein formulas contain purified soy proteins. The fat is a mixture of vegetable oils, and carbohydrates are represented by maltodextrins, corn starch, or sucrose. Commercial soy formulas differ from each other most markedly in carbohydrate content. Feeding soy formulas to

|      |                          |
|------|--------------------------|
| CMP  | Cow milk protein         |
| RAST | Radioallergosorbent test |

normal term infants is associated with normal growth, normal protein nutritional status, and normal bone mineralization.<sup>4, 5, 9, 10</sup> All soy protein formulas are lactose free, are fortified with L-methionine, and contain added taurine, carnitine, and iron. Recent studies of infants fed a soy formula exclusively during the first 6 months of life revealed no immunologic abnormality or increase in morbidity because of infection as previously reported.<sup>11, 12</sup> No differences in the proportion of infants who developed serum an-

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tibodies to oral poliovirus immunization were found by type of feeding.<sup>12</sup>

Rickets has been reported only in premature infants weighing less than 1.5 kg at birth and fed a soy protein formula exclusively beginning on day 13 of life.<sup>13</sup> Because daily recommended vitamin requirements, including vitamin D, are added to soy formulas, problems similar to those found in premature infants have not been found in term infants. Soy formulas, in contrast to human milk and cow milk formulas, contain no intrinsic L-carnitine, the function of which is to transfer fatty acids into the mitochondria. Consequently, L-carnitine has recently been added to some soy formulas in the same amount as that found in human milk.<sup>14</sup>

## INDICATIONS

Soy protein formulas are used for different conditions, including CMP allergy, lactose and galactose intolerance, and severe gastroenteritis in infants.<sup>6</sup> Many foods such as cakes, biscuits, ice cream, desserts, and beverages can be made with soy formulas, thus offering children with CMP allergy a varied diet.

The use of these formulas to prevent atopy is controversial. Some studies have shown that soy formulas for the first 6 months of life significantly reduced the prevalence of atopic diseases in high-risk infants.<sup>15,16</sup> Matthew et al.<sup>17</sup> showed that prolonged breast-feeding supplemented with soy protein formula significantly reduced the prevalence of atopic dermatitis in high-risk infants. Our prospective studies in at-risk infants confirmed the efficacy of both dietary preventive measures (exclusive breast-feeding for the first 6 months, supplemented, when necessary, with a soy protein formula; cow milk-free and egg-free diet for nursing mothers) and environmental preventive measures (elimination of house dust mites, smoking, and pets in the house) in selected high-risk infants.<sup>18-22</sup> In a multicenter study of 2291 infants, those for whom these dietary and environmental measures were undertaken had a 5% prevalence of atopic diseases at 1 year of age, compared with 13% in bottle-fed infants.<sup>22</sup> More recently, we followed 174 high-risk infants for up to 52 months (Figs. 1 and 2). The prevalence rates of atopic diseases at 52 months of age were as follows: 1% food allergy, 0.5% atopic dermatitis, and 9% asthma (unpublished observations). In our studies of at-risk infants given soy protein formula when breast-feeding was not available, we did not see an increased prevalence of soy allergy.

Several studies have failed to show any preventive effect of feeding soy formulas on the onset of atopic diseases.<sup>23-25</sup> The contradictory results may be explained by different factors. Kjellman and Johansson<sup>23</sup> studied 23 infants for only 1 year; these authors allowed the mothers to consume cow milk while breast-feeding, and they failed to specify

how long or whether feeding of solid foods was delayed. In addition, an incidence of atopic disease at age 1 year of 66.7% among infants fed either soy or cow milk formulas is unusually high. In a 12-month prospective study, Merrett et al.<sup>24</sup> reported on 500 "at risk" infants and concluded that the allergy symptoms manifested in the two groups of infants (soy protein and cow milk) were similar, but all symptoms were less in the breast-fed infants; these nursing mothers were on a restricted diet, contrary to those studied by Kjellman and Johansson.<sup>23</sup> Chandra et al.<sup>25</sup> reported that the feeding of a milk-whey partially hydrolyzed formula to infants with a family history of allergy significantly reduced the prevalence of atopy in these infants compared with that achieved in breast-fed, soy formula-fed, or cow milk formula-fed infants. However, the infants in this study seemed to belong to a very select population of atopic infants; many had unusually high specific IgE and total cord blood IgE values.<sup>25</sup> In addition, several symptoms such as colic, otitis, and wheezing, which cannot always be defined as allergy symptoms, were classified as atopic disease, and the connection between these symptoms and food allergy was not confirmed. Moreover, it would be expected that gastrointestinal symptoms caused by soy allergy would be more frequent in the soy-fed infants, but that was not the case. Of the five infants in whom atopic symptoms developed while they were receiving partial hydrolyzed formula, four had a positive skin test reaction to CMPs; these findings indicate hypersensitivity to CMPs and suggest that sensitization to milk proteins may occur in infants receiving this formula.<sup>25</sup>

## BASIC DEFINITIONS OF FOOD ALLERGY

The issue of soy allergenicity is surrounded by confusion mainly because of the incorrect use or the misunderstanding of the definition of key words describing the biologic activity of allergens. Correct definitions are a prerequisite for effective communication in scientific circles, and for comparison of the results of different studies.

The appropriate definition of food allergy is mandatory to establish the prevalence of hypersensitivity to a given food. There is a general agreement that *food allergy* is defined as a group of symptoms occurring locally, in the gastrointestinal tract, or in remote organs as a result of an immunologic reaction. Different immunologic reactions may be involved in the clinical manifestations of food allergy, but the immunologic reaction easiest to demonstrate routinely is the IgE-mediated reaction. No reliable laboratory test is available for the diagnosis of food allergy; therefore, the double-blind food challenge test is considered the "gold standard" for the diagnosis of food allergy in patients enrolled in research studies or in clinical trials.

*Immunogenicity* is the ability of a given molecule to sen-

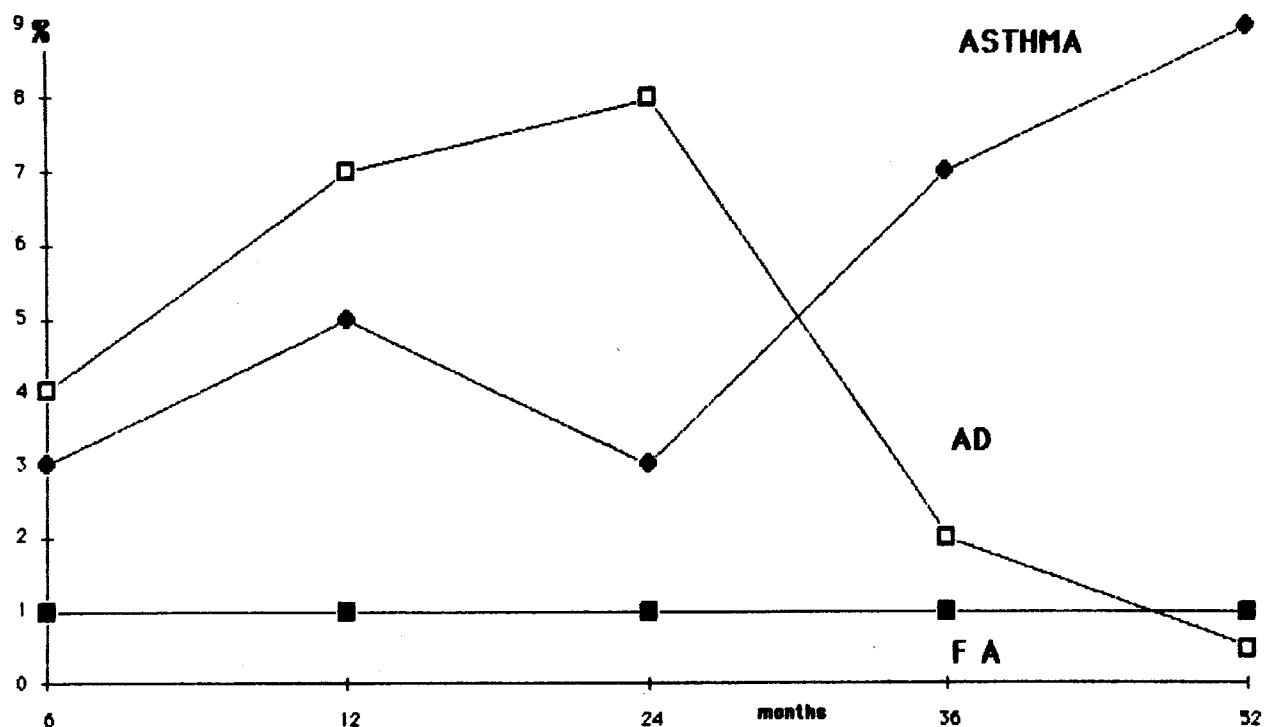


Fig. 1. Prevalence of atopic diseases in high-risk children (%) followed for 52 months. AD, Atopic dermatitis; FA, food allergy.

sitize the human IgE system. An *allergen* is an antigenic molecule that takes part in the immune reaction that results in allergy. *Allergenicity* is the ability of a given molecule to elicit an allergic reaction in sensitized individuals. *Antigenicity* is the ability of a given molecule to promote antibody synthesis in the non-IgE immune system (IgG, IgA, IgM). The antibody (or the lymphocyte's receptor) binds to a very limited part of the molecule, which is called an epitope. *Allergenic determinants* are epitopes in the IgE system; *antigenic determinants* are epitopes in the IgG, IgA, or IgM systems. Usually, antigenic determinants are conformational and can easily be destroyed, whereas allergenic determinants are sequential and more resistant. *Cross-reactivity* is the possible interaction between the binding site of an antibody and the same allergenic determinant present in different molecules.

#### ANTIGENICITY OF SOY PROTEINS

The antigenicity of soy proteins has recently been studied. The globulin fraction of the seed represents the major protein component (90%) and is principally composed of  $\beta$ -conglycin and glycine.  $\beta$ -Conglycin is a glycoprotein with a molecular weight of approximately 180,000. It is a trimer composed of three major subunits,  $\alpha$ -1,  $\alpha$ , and  $\beta$ , which have a molecular weight of 76,000, 72,000, and 53,000, respec-

tively. Glycine has a molecular weight of 320,000 to 360,000 and is made up of six subunits; polypeptides are heterogeneous and have a molecular weight ranging from 19,000 to 45,000. The globulins comprise a broad range of molecular sizes and display four major sedimentation components in the ultracentrifuge, designated 2S, 7S, 11S, and 15S, respectively.<sup>26-28</sup> However, soybean proteins of soy formulas are processed and denatured by heat; therefore the processed proteins of soy formulas are less antigenic than the crude ones. Eastham et al.<sup>29</sup> reported that soy proteins are as antigenic as CMPs. However, this study is frequently quoted incorrectly or misunderstood. These authors demonstrated that an increase in the titer of antibody to soy proteins occurred in all infants fed this formula, which was comparable with that found in cow milk formula-fed children. They concluded that soy protein is as antigenic as CMP.<sup>29</sup> However, only soy antigenicity was studied; the authors measured the production of hemagglutinins to cow milk and soy proteins, which mainly belong to the IgG class, not IgE. IgG antibodies to food antigens are physiologically produced by healthy subjects; these antibodies are not harmful, and they are not involved in the development of atopic diseases. These antibodies are probably involved in the induction of tolerance to oral food antigens. Consequently they should not be regarded as dangerous but per-

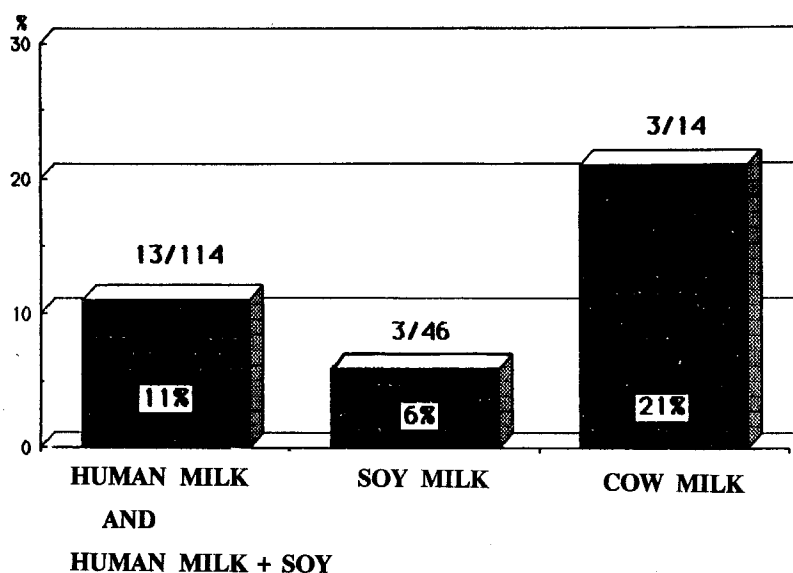


Fig. 2. Prevalence of atopic disease in high-risk children (%) according to type of feeding.

haps as even protective in certain conditions. In light of these data, to draw from the study of Eastham et al.<sup>29</sup> the conclusion that soy is as allergenic as cow milk is incorrect. Although soy protein is naturally antigenic, the degree and the sort of sensitization appear to be such that the prevalence of clinically significant, symptomatic immunologic reactions among infants fed soy may be considerably less than that among infants consuming cow milk.<sup>30</sup>

Feeding experimental rabbits with soy formula induced a more profound and complete tolerance than that induced by cow milk.<sup>31</sup> Thus soy protein was significantly more effective than CMP in inducing a specific and systemic tolerance. More recently, it has been reported that no fatal anaphylactic reaction could be triggered with soy proteins in animals sensitized to soy protein formulas, whereas anaphylaxis could be triggered with CMPs in all animals sensitized to cow milk.<sup>32</sup>

### ALLERGENICITY

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 CMP intolerance.<sup>33-36</sup> This disorder may be due to cellular immune reactions, but the underlying mechanisms are not fully understood. Although atopic dermatitis may occur in some soy protein-fed children, anaphylaxis after the ingestion of soy protein appears to be an extremely rare phenomenon; to our knowledge, only one case has been reported.<sup>37</sup>

In the past few years the allergenicity of soy protein formulas has been emphasized in the medical literature but

with surprisingly few scientific data to substantiate this assumption. In most studies, no challenge to soy was made, nor were data on specific IgE antibodies to soy available. It was reported that 3% to 80% of children with CMP allergy had soy allergy,<sup>38-46</sup> but in all except three studies<sup>41-43</sup> the diagnosis of soy allergy was based on clinical evaluations or on anecdotal case histories reported by parents, without confirmation of the diagnosis with the challenge test.

Kuitunen et al.<sup>38</sup> studied 54 children with malabsorption syndrome and cow milk intolerance, and Jakobsson and Lindberg<sup>39</sup> studied 20 children with cow milk intolerance. A clinical intolerance to soy was noted in 4 (11%) of 35 and in 7 (35%) of 20 children, respectively. However, in both studies no challenge to soy was done, nor were data on specific IgE antibodies to soy available. Freier et al.<sup>40</sup> reported a 30% incidence of soy allergenicity but failed to substantiate these data in any way. Bishop et al.<sup>44</sup> studied 97 children with challenge-proven CMP allergy, not always IgE mediated. A significant incidence of soy hypersensitivity was anecdotally reported in 37 (47%) of 78 children; again, no data on challenge to soy or on specific IgE antibodies to soy were recorded. Gerrard et al.<sup>45</sup> showed that 10 of 50 children with CMP allergy, all of them fed a soy protein formula, had symptoms caused by soy allergy, although 5 of 10 children had undefined symptoms such as rhinorrhea, bronchiolitis, and vomiting; again, no challenge test to soy or skin test to soy was performed. Moreover, five children tolerated another soy protein formula, suggesting that the soy protein had been denatured in one but not the other formula, or that other ingredients in the soy formula caused symptoms.

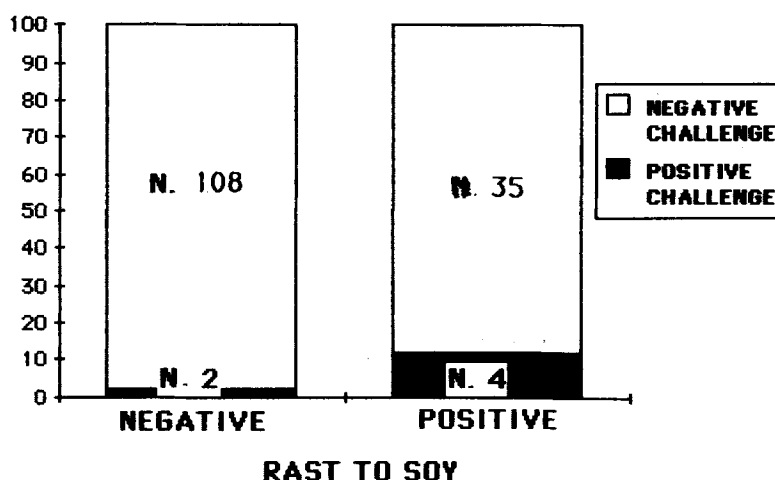


Fig. 3. Response to soy challenge according to RAST results in children with atopic dermatitis.

Another bias of studies dealing with soy allergenicity involves quotations of previous studies to support the theory that soy is allergenic. In fact, several authors quote other studies, apparently without checking the reliability or availability of their quotations. Kahn et al.,<sup>46</sup> in their work devoted to sleep disturbance and cow milk allergy, commented that 5% to 30% of children with CMP allergy also have soy protein intolerance; to support this assumption, they quoted a book and an article not dealing with studies on soy allergenicity. Eastham<sup>47</sup> recently reviewed the topic of soy protein allergy and claimed that intolerance develops in 15% to 50% of cases; he quoted articles, in addition to his own, on soy antigenicity,<sup>29</sup> with data not relying on double-blind food challenges. An unspecified "high rate" of sensitization to soy was extrapolated by Guesry et al.<sup>48</sup> from studies cited by Glaser and Johnstone<sup>15</sup> and by Kjellman and Johansson,<sup>23</sup> which did not discuss soy allergenicity but, rather, discussed the use of soy protein formulas for the prevention of atopy, and from the study by Eastham et al.,<sup>29</sup> which is a study on soy antigenicity. Even the Committee on Nutrition of the European Society of Pediatric Gastroenterology and Nutrition<sup>8</sup> has stated, "The Committee considers that available data do not support the view that soy-protein formulas should be the preferred choice when suspected or proven adverse effects to cow milk protein is the indication." Surprisingly, this committee cited two articles<sup>23, 25</sup> dealing not with the use of soy protein formula for the management of adverse reactions to cow milk but with its use in high-risk infants for the prevention of atopy.

Bias is further evident in the use of incorrect quotations of the conclusions of previous studies to support the theory that "soy is allergenic." The study by Hill et al.<sup>49</sup> does not lend support to the thesis presented above because these authors did not state that 50% of the children with cow milk

intolerance in their study were also reactive to soy. In fact, they specified that the soy formula which they used contained sucrose and that many of the infants studied were intolerant to sucrose. No challenge to soy or to sucrose was done by Hill et al.<sup>49</sup>

To our knowledge, only three studies employed the challenge test for the diagnosis of soy allergy.<sup>41-43</sup> Sampson<sup>41</sup> found that only 5% of 204 patients with atopic dermatitis had soy sensitivity, as demonstrated by double-blind, placebo-controlled challenge tests.<sup>41</sup> Bock and Atkins<sup>42</sup> reported that 4 (7%) of 54 children with CMP allergy had symptoms after double-blind, placebo-controlled challenge tests with soy. We have shown that only 4% of 143 children with atopic dermatitis had a positive reaction to challenge with soy<sup>43</sup> (Fig. 3). In addition, the RAST for soy allergy showed a sensitivity of 0.69, a specificity of 0.83, a positive predictive value of 0.10, and a negative predictive value of 0.77. Aas<sup>50</sup> showed that 21 children with atopic dermatitis and IgE antibodies to soy had a negative reaction to challenge with soy. False-positive RAST results may be caused by several factors, such as impurities in the allergen extract, nonspecific binding of IgE antibodies, high levels of total IgE, or IgE antibodies without clinical significance. Our study<sup>43</sup> showed a significant correlation between total serum IgE levels and RAST class to soy ( $\rho = 0.66$ ). High total IgE levels may interfere with the RAST and cause false-positive results.<sup>50</sup> Johansson<sup>51</sup> suggested that IgG antibodies with the same allergen specificity as that of the IgE antibodies can bind readily to the paper disk and can interfere with the assay, thus giving a false binding of IgE antibodies through IgE-IgG immune complexes.<sup>51</sup> The unreliability of the RAST for soy allergy makes the challenge test mandatory in attempts to establish the diagnosis of soy allergy.

**Table.** Immunogenicity and cross-reactivity of hydrolyzed formulas and soy protein formulas in CMP allergy

|                                             | Hydrolyzed formula |                |         | Soy protein formula |
|---------------------------------------------|--------------------|----------------|---------|---------------------|
|                                             | Casein, extensive  | Whey Extensive | Partial |                     |
| Immunogenicity                              | —                  | +              | +       | +                   |
| Antigenicity                                | —                  | +              | +       | +                   |
| Allergenicity                               | +                  | ++             | +       | —                   |
| Cross-reactivity with IgE antibodies to CMP | +                  | ++             | +++     | —                   |

Fomon<sup>52</sup> recently summed up his 30-year studies on the use of soy protein formulas for infant nutrition by emphasizing that fewer than 1% of the soy formula-fed infants had adverse reactions to soy protein; this finding indicates that, at least in children with CMP allergy and without serious gastrointestinal symptoms, soy protein formulas are safe. According to recent studies, the natural history of soy allergy seems good.<sup>53, 54</sup>

#### PROPERTIES OF SOY PROTEIN FORMULAS

The main properties of soy protein formulas are as follows:

- No minute amount of CMPs
- No cross-reactivity with CMPs
- Lower immunogenicity (IgE antibodies) than CMPs
- Lower allergenicity than CMPs
- Similar antigenicity (IgG antibodies) to CMPs
- Nutritional adequacy similar to that of cow milk formulas
- Better palatability than extensively hydrolyzed formulas
- Less expensive than extensively hydrolyzed formulas

Hydrolyzed formulas may still contain small amounts of native proteins from which the product is derived,<sup>55</sup> but no minute amount of intact CMPs are present in soy protein formulas. Soy proteins are immunogenic, but according to experimental and clinical studies they are less immunogenic and allergenic than CMPs.<sup>30, 32, 41, 43</sup> Soy protein formulas do not cross-react with CMPs, whereas hydrolyzed formulas do. As we reported,<sup>56</sup> whey and partial hydrolyzed formulas can trigger anaphylactic reactions, which may even be life-threatening, in infants and children with IgE-mediated CMP allergy (Table). Because of residual allergenic epitopes and contamination with minute amounts of intact proteins, these products are not safe for children with IgE-

mediated cow milk allergy,<sup>54-59</sup> but they may be useful in young infants with cow milk or soy enteropathy.<sup>60</sup> Soy proteins are as antigenic as CMPs,<sup>29</sup> but, as previously pointed out, this antigenicity should not be regarded as harmful. Soy protein formulas are nutritionally adequate, the taste is well accepted by most infants, and the formulas are less expensive than hydrolyzed formulas.

#### CONCLUSIONS

We believe that soy protein formulas should be the preferred choice for children with IgE-mediated CMP allergy, and that extensively hydrolyzed casein formulas should be tried when there is scientific evidence that the child is allergic to soy. Partially hydrolyzed whey formulas should never be used for infants with IgE-mediated CMP allergy<sup>54-59</sup>, because of the good negative predictive value, a prick-test to hydrolyzed formulas should be performed (Sampson et al.<sup>61</sup>; Ragno V, Giampietro P, Bruno G, Businco L: unpublished observations) before these products are given to infants with CMP allergy. Finally, we believe that the statement of the American Academy of Pediatrics<sup>6</sup> that "soy protein formula should not be used . . . in the dietary management of documented allergic reactions to cow milk proteins" should be reconsidered.

Although it has been established that double-blind food challenge is the gold standard for the diagnosis of food allergy in research studies,<sup>41, 62</sup> soy allergenicity is commonly emphasized by many authors and lecturers who quote studies in which soy allergenicity is not documented with this procedure. In addition, even prestigious authors of articles published in outstanding journals quote studies without consulting the original data. As a consequence, errors are perpetuated and the resulting confusion is deleterious for both patients and science.

Further studies are necessary to establish the prevalence of soy allergy in different disorders associated with CMP allergy, and to evaluate the safety of soy protein formulas and hydrolyzed formulas in children with IgE-mediated CMP allergy.

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