

Natural history of soy allergy and/or intolerance in children, and clinical use of soy-protein formulas

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Atopic diseases of infants and children are common, debilitating, chronic and sometimes even life-threatening. Several well-conducted studies in high risk babies have demonstrated a significant reduction in the prevalence and severity of atopic diseases with dietary and environmental manipulations. The currently available cow's milk (CM) substitutes for infants are soy protein (SP) formulas (SPFs), hydrolyzed formulas (HF), and home-made meat-based formulas. Soybeans have been cultivated in Eastern countries for many centuries and were first used to feed US babies with CM allergy (CMA) in 1929. Since then, SPFs containing purified SP, a mixture of vegetable oils, and purified carbohydrate have been developed. From a nutritional point of view, SPFs are adequate, support normal growth, protein status, bone mineralization, are well accepted, and economical.

SPFs are used for different conditions including CMA, lactose and galactose intolerance and in the management of severe gastroenteritis, and some studies show that feeding SPFs for the first six months of life significantly reduces the prevalence of atopic diseases in high risk babies. Although gastrointestinal symptoms and atopic dermatitis (AD) may occur in some SPF-fed children, anaphylaxis following the ingestion of soybean is extremely rare in children. However, in the past few years the antigenicity/allergenicity of SPFs has been over-emphasized in the medical literature.

In this paper on the natural history of soy antigenicity/allergenicity we discuss all the pros and cons of SPFs, their composition and nutritional value, the basic immune definitions, chemistry and characterization of SPs. We then discuss the antigenicity and allergenicity of SPFs in animals, recent data on the use of SPFs and the incidence of soy allergy in children, clinical reactions to SPFs, and the clinical relevance of skin testing and IgE antibodies to soy, challenge test procedure, clinical indication of SPFs, and their relevance in the prevention of atopy. We have meta-analyzed 17 different studies and conclude that history-based SPF allergy incidence totals 27%, in skin prick tests (SPT) RAST-oral food challenge (OFC)/double-blind food challenge (DBFC)-based epidemiological studies attains 3%, and in challenge test studies 4%. We suggest that double-blind placebo-controlled food challenge (DBPCFC) studies in larger cohorts of babies may establish a more reliable prevalence of SPF allergy in different disorders associated with CMA.

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Background

The availability of reliable infant formulas is a rather recent acquisition, at the point that until the 19th century there was intrinsically no safe and satisfactory equivalent of breast-feeding. Many babies not fed by mothers or wet nurses died before their first

year: more than 80% of infants admitted to the Paris Foundling Hospital between 1771 and 1777 failed to reach their first birthday; in the Dublin Foundling Hospital only 0.4% of babies admitted between 1775 and 1779 survived, with a mortality rate as high as 99.6%; in London in the early 19th century only 10% of babies not breastfed survived their first

birthday (1–4). Subsequent discoveries in the field of biology and medicine provided a more thorough basis for development of substitutes for human milk, and several scientists worked to develop adequate substitutes for breast milk. Von Liebig patented the first preparation consisting of a mixture of wheat flour, CM, and malt flour, which was cooked with a little bit of potassium bicarbonate to reduce acidity (4). Then the Swiss company Nestlé prepared a new CM substitute and Cantani Sr, a strenuous advocate of breastfeeding (5), added the weight of his scientific fame conceding that it might be used when breast-milk was totally unavailable or insufficient and no truly reliable wet nurse was feasible (5).

Although the first description of the use of a soy formula in the Modern World as a CM substitute appeared in 1909 (6), the use of soybean in infant feeding goes back to Eastern countries where it was employed for alimentation as early as in 82 BC. The process started from the whole seeds, subjected to extraction to obtain the separation of the proteic part as a liquid, which was called soy milk for its equivalence to CM. According to the classical Chinese method, the seeds were first washed and then soaked all night long. Then the seeds were ground into a fine powder which was mixed with water and filtered to remove the insoluble residues and finally boiled for 10–20 minutes (7).

Only in 1929 a SPF was employed for feeding babies with CMA (8). Originally, fat-free soy flour was used as the source of protein, but non digestible carbohydrates, among which primarily stachyose and raffinose tended to produce loose, malodorous stools in infants fed these formulas. To overcome these difficulties, preparations containing protein from hydrosoluble soy isolates were marketed, and literally supplanted soy-flour formulas. Subsequently SPFs underwent numerous improvements, also to meet the requirements of the Infant Formula Act (9–12).

For several decades SPFs have been the only available CM substitute, and ensured a normal growth for many children affected by CMA (13–17). Nowadays such products contain purified SPs, the fat is a mixture of vegetable oils, and carbohydrates are represented by maltodextrines, corn, starch, or saccharose. All SPFs are lactose-free, are fortified with L-methionine, and contain added taurine, carnitine and iron. The daily recommended vitamin requirements are added to SPFs, including vitamin D, hence problems similar to those found in premature infants have never been found in fullterm infants (17). Carnitine, the function of which is to transfer fatty acids into the mitochondria, has been added to some SPFs in the same amount as that found in human milk, since SPFs, in contrast to hu-

man breast milk and cow's milk formulas (CMFs), contain no intrinsic L-carnitine (17).

Manufacturers have further improved the susceptibility of minerals to better their delivery to and subsequent absorption by SPF-fed infants. SPFs insure a normal growth in all infants (15), and bone mineral content is similar in infants fed SPFs and human milk (18).

Definitions

There is a general agreement that some basic points require definition prior to their use in a discussion on allergenicity of a given food. An EAACI Position Paper (19) has recently proposed standardized definitions for food reactions. Adverse food reactions are divided into toxic and non-toxic food reactions. Non-toxic reactions depend on an individual susceptibility, they may result from immune mechanisms, food allergy or hypersensitivity, or from non immune mechanisms, food intolerance. FA (food allergy) can be further divided into IgE- and non IgE-mediated reactions (19). In addition, we use in the text the following definition stemming from our personal experience:

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.

Soy allergenicity is the ability of a soy molecule to elicit an IgE-mediated reaction in sensitized patients.

Soy antigenicity is the ability of a soy molecule to promote antibody synthesis in non IgE immune system (IgG, IgA, IgM).

Soy allergy is a term denoting an IgE-mediated reaction resulting from the ingestion of SPFs.

Soy intolerance is a term indicating reactions resulting from SPF ingestion in which non IgE-mediated mechanisms are involved.

In infancy, FA has protean manifestations and is provoked by many different food allergens. In addition to the lack of really useful diagnostic tests, there is the difficulty of easily and reliably conducting DBPCFC, which is considered the "gold standard" for the diagnosis of FA in general pediatric practice (20). Thus it is imperative that a scientific approach be adopted and that doctors attentively record the case history and observe the response to elimination diets and challenges. Symptoms provoked by soy allergy can be diagnosed routinely when an IgE-mediated reaction can be demonstrated (19). Following SPF administration by the oral route, they may occur in the gastrointestinal tract, or in distant organs such as the skin, whereas non IgE-mediated soy intolerance is mainly associated with gastrointestinal symptoms (21).

Chemistry and characterization of soy proteins

SPs are broadly divided into two fractions, globulin and whey fractions, by acid precipitation at pH 4.5 (22). The globulin fraction represents the major protein component comprising 85% of the total protein. It consists of a broad range of molecular weight (MW) and displays four major sedimentation components in the ultracentrifugate, designated 2S, 7S, 11S and 15S, respectively (22). The 7S and 11S are mainly composed of β -conglycin and glycinin (22). β -conglycin is a glycoprotein with a MW of approximately 180 kD. It is a trimer composed of three major subunits, α -1, α -2 and β , with a MW of 76, 72, and 53 kD, respectively, while glycinin has a MW of 320 and 360 kD and is made up of two major subunits with a MW ranging from 18 to 35 kD (23). Two allergens, Gly m 1A and 1B each with a MW of 7.5 kD, have been characterized, and the amino acid sequence of Gly m 1 has been partially identified (24). In addition there is a hydrophobic protein from soybean seed (HPS), a member of a new family of cysteine-rich proteins, which seems essentially the same protein of Gly m 1 (25). The 2S fraction is the most allergenic (22), however in almost all SPFs, the 2S subfraction is virtually absent (23) and no fraction appears to be more antigenic than any other (26). Recently, the immunoblotting approach has been shown to provide more detailed information on the composition of specific endogenous allergens (27). SPs are processed and denatured by heat (28), therefore the processed proteins of SPFs are less antigenic than the crude ones. Heppe et al. (29) tested four infant formulas in animals. They used an ELISA to detect antigenic β -conglycinin and glycinin, and noted considerable differences. A significant correlation was found between the presence of these immunoreactive proteins and the level of allergic reactions. However, the *in vitro* and *in vivo* results did not entirely correspond, thus raising a question about the value of *in vitro* assessments.

Antigenicity and allergenicity

Antigenicity

Animal models provide comparative parameters on the antigenicity and allergenicity of CM proteins (CMPs), therefore a convenient *in vivo* model may be necessary to determine the overall allergenicity contributed by different protein fractions from various sources, including different SPFs. The digestive system of young calves appears to be suitable for studies on the antigenicity leading to the development of gastrointestinal FA, since following the introduction of certain non-milk formulas such as SPFs the animals appear to develop disorders,

which possess many of the features of the human allergic responses (30, 31). The studies in preruminant calves given liquid feeds containing heated soybean flour (HSF) provided evidence of disturbances in digestion and transportation, and in the luminal absorption of water and nutrients. The disorders developed progressively with successive meals and, after brief withdrawal of HSF, could be provoked by subsequent challenge. Studies demonstrated areas of tissue damage to the mucosal lining of the gut wall and concurrent with the development of digestive functional abnormalities. Low levels of IgG even before receiving feeds containing HSF were apparent in their serum (30), and sometimes intradermal tests were positive for HSF (31). Therefore, HSF-fed calves had neither serum reaginic antibodies nor delayed hypersensitivity reactions, demonstrating that systemic immune reactivity was not stimulated by HSF. These findings led to the suggestion that a gastrointestinal allergy ensued, possibly to the antigenic glycinin and β -conglycinin (30, 31), while leading to the development of significant circulating IgG soy-specific antibodies not decreasing after prolonged exposure to dietary HSF (30). These results tally well with studies demonstrating increases of IgG antibodies in SPF-fed children (15).

The guinea pig model has been long considered an appropriate screening procedure for evaluating the sensitizing capacity of infant formulas (28). However, although this is a convenient animal for *in vivo* studies of antigenicity, there is no evidence that sensitization to dietary protein results in any adverse physiological problems in its gastrointestinal tract, therefore this model failed to match the scientists' needs, also in terms of immunogenic sensitivity and allergy mechanisms, for example IgG₁ in guinea pigs and IgE in humans (32). It has been shown that feeding rabbits with SPFs induces a more profound and complete tolerance than CM (33). In other words, SPFs induced an antibody response of IgG type equivalent to the response to CM-protein, but the tolerance resulting with SPFs was more profound and complete than that achieved with CM. Eastham et al. (33) speculated that the handling of ingested SPF by the immune system may result in a hypoallergenic state by stimulation of specific suppressor T cells in Peyer's patches by the hapten effect of partially digested protein fragments or by effector cell blockade due to immune complexes present in slight antigen excess.

Allergenicity

In a subsequent study on the guinea pig model (34), the specificity of the systemic immune response induced orally was determined by a screening of the circulating reaginic antibodies. In this model, sera from animals orally sensitized against whey pro-

teins were tested with pure fractions in the passive cutaneous anaphylaxis (PCA) test (34). The experimental conditions established for oral sensitization to CMP were also applied for the evaluation of protein allergenicity from soy and egg white. Following reagin titration by PCA, egg white was the most sensitizing protein source (PCA titres 1,000–2,000) in comparison with whey proteins (PCA titres 100–500), and with soy cold extract (PCA titres 20–50) (34). It has been reported subsequently that in a guinea pig model no fatal anaphylactic reaction could be triggered with SPs in animals sensitized to SPs (only non-fatal reactions in 30%), while a high degree of sensitizing capability of CM formula was shown when challenged with β -lactoglobulin (80% fatal and 20% nonfatal reactions). No reaction was shown after feeding with a cow collagen or SP hydrolysate formula (35). Recently, Cordle et al. (32) have made a good case for using the rabbit model as screening test for the selection of proteins for human study. To test the immunogenicity of soy (SH) and casein (CH) hydrolysates, they employed a hyperimmunization model, in which the magnitude of the antibody response to intact casein was considerably greater than that of intact SH. Studying the *in vitro* cross-reactivity, they have demonstrated that rabbits immunized with the SH at either 5 or 100 mg protein equivalent/rabbit showed very low cross-reactivity to the intact SH, with peak titers of 76 at day 56 and 89 at day 21, respectively. However, the peak titers of intact CH at day 49 were 59 and 1,500–2,000, respectively. Cross-reactivity titers of intact soy antibody with the SH reached a peak titer of 41 at day 35, whereas that of intact casein antibody with the CH had a peak of 150 at day 49. Cordle et al. showing that soy proteins are 22.5 times less sensitizing than CMP predicted that SP would be less allergenic than casein in humans (32). Although it is not always feasible to extrapolate to human beings the results of experimental studies done in the animal model, the hyperimmunization model in the rabbit (32) appears the ideal model to use in such investigations, also for diagnostic purposes. Burks et al. (26) attempted to determine which components were the most allergenic in SPs. With eight serum samples of SP-allergic children and non-atopic controls, ELISA and immunoblots to crude SPs were performed and found that IgE and IgG specific antibodies to crude soy are elevated in patients with positive DBPCFC to soy, but none of the soy fraction investigated were clearly more antigenic. In a parallel paper (23) they compared the allergenicity of two commercially available infant SPFs, a powdered and a liquid one, and found that IgE and IgG antibodies to the liquid formula were significantly higher than to the powdered soy. Finally, using the immunoblot approach

no qualitative or quantitative differences were shown in the endogenous allergens in transgenic glyphosate-tolerant soybeans compared with the parental soybean variety or with soybeans from commercial varieties (27).

From an immunological point of view, no intact soybean protein is currently employed in SPFs, since they are processed and denatured by heat, even if modified and processed foodstuffs may retain their allergenicity (28, 32). Indeed, it has been suggested that the allergenicity of the protein fractions could be changed in the processing of each isolate or by altering the amount of antigenic sub-fractions (23). Therefore, the peptides or the proteins produced may be partly different according to the method used. Accordingly, some children may be sensitized to one epitope, while others are administered another formula not containing epitopes. This was probably the reason why one SPF was tolerated and a second one not (23), thus suggesting that only in one SPF the SP had been properly denatured. Being soy a totally different protein, unrelated to CM, evidence suggests the significance of the technologies employed in its manufacture.

Clinical aspects

Soy antigenicity in children has been overemphasized in the medical literature, based on the studies of Eastham et al. (36, 37) who reported that "SP is as antigenic as CM" (37). Eastham et al. (37) demonstrated an antibody response to SPs in all SPF-fed infants that was comparable to that found to CMPs in bottle-fed infants. However, only soy antigenicity was studied: as we have demonstrated (15), the authors measured not IgE but hemagglutinins to soy and to CM, which mainly belong to IgG antibodies. IgG antibodies to food antigens are also produced by healthy subjects, and the rate of IgG production is enhanced during infancy. Possibly, IgG may even be involved in the induction of tolerance to food antigens (15). According to May, the conclusion that soy is as allergenic as CM is unfounded (38). Furthermore, the Prosobee powder used by Eastham et al. (37) was particularly antigenic (29). In 1983, the Committee on Nutrition of the American Academy of Pediatrics (AAP) in a Position Paper on the use of SPF (14) stressed that SPFs should not be used in the dietary management of documented clinical allergic reactions to CMPs, while HFs are warranted in infants and children with allergic disease. However, no evidence was given that HFs are superior to SPFs in children with CMA (14). The European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) Committee concluded that SPFs should not be the preferred choice in suspected or proven adverse reac-

tions to CM (16), but supported the thesis with two studies (39, 40) dealing instead with the use of SPFs in the prevention of atopy.

Several papers have stressed that soy allergy is common, mainly in children with CMA, and that even very high proportions of children with CMA had soy allergy (39–70). In several instances the presumed allergenicity of SPFs has been highlighted (14, 16, 62–64, 69). However, in all studies but seven (20, 42–44, 59, 62, 64) the diagnosis of soy allergy was based on clinical history and/or evaluation, SPT, or parental reports without confirming the diagnosis with challenge tests (41, 46, 48–50). Most studies appear to have included heterogeneous cohorts of children in different age groups, some with gastrointestinal and more with cutaneous symptoms. Obviously, a high figure may also depend on the small cohort size (48, 71–74), thus introducing the possibility of a type II error in the data.

The most reported clinical manifestations are gastrointestinal. Anaphylaxis is rare and skin lesions are scarcely known.

A) Gastrointestinal symptoms

The more frequently reported symptoms include diarrhea, vomiting, and failure to thrive (41, 46–49, 73, 74, 77–79), in addition to flat jejunal lesion after challenge test with SP (51, 80, 81).

Two major clinical patterns of disease are seen:

1) Food-induced enterocolitis syndrome

This disorder is most commonly seen in babies between one week and three months of age with symptoms isolated to the gastrointestinal tract, not infrequently resulting in dehydration and acidosis (73). The disease is often induced by SPFs and CM, because SPF(s) are frequently used to treat chronic diarrhea, but have also been associated with intolerance and continued diarrhea (82). Stools contain occult blood, neutrophils, and eosinophils, and jejunal biopsies typically reveal flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells. Food challenges may result in profuse vomiting and diarrhea within minutes to 6 hours and can induce dehydration, hypotension, and, as a consequence, shock (73). Elimination of the offending allergen frequently leads to resolution of symptoms, although secondary disaccharidase deficiency may last longer (73).

2) Food-induced colitis

SP- and CM-induced colitis are clinically and pathologically similar (83, 84). Colitis typically manifests itself in the first few months of life, clinical features are non-specific, including fever, leukocytosis, vomiting, chronic diarrhea, lactose intolerance, dehydration, metabolic acidosis, and eventually shock (73, 77). The more chronic reactions may also involve anemia and/or hypoproteinemia, result-

ing from enteric loss of iron and protein (80). CM- and SPF-induced colitis commonly resolve after 6 months–2 years of allergen avoidance. The colonic lesions consist of mucosal edema with noticeable increases of eosinophils and IgE-containing cells in the epithelium and lamina propria (77, 85).

In both disorders, histologic or ultrastructural examinations show lesions less pronounced than those seen in active celiac disease or untreated CMA with malabsorption (51, 80, 81), with partial or total villous atrophy associated with hyperplasia of the crypts (51). An increment in the number of intraepithelial lymphocytes (51), and a depressed neutrophil chemotaxis and enhanced random migration was also shown in such patients (83).

After the challenge test to soy, the proximal jejunal biopsy shows hemorrhage, edema, absent eosinophils, and PMN infiltration in the lamina propria; villi are absent, the surface epithelium is abnormal with a few microulcerations. Ninety-six hours after the challenge test the proximal jejunal mucosa returns normal morphologically (80). Mucosal biopsies from infants with SP intolerance studied with scanning electron microscope showed more severe lesions (81). Increased numbers of IgA- and IgM-containing plasma cells in the lamina propria at the time of the clinical reaction to soy feeding (85) paralleled increases in serum IgA and IgG levels in infants during a positive CM-challenge in intestinal CMA (51). In addition, localized IgE-mediated gastrointestinal mast cell activation may be involved (86). However, SPT and RAST results matched very poorly (87, 88), thus corroborating the hypothesis that IgE-mediated hypersensitivity does not play a role in soy induced enteropathy (87). Furthermore, there is evidence that infants with chronic diarrhea secondary to acute gastroenteritis and with SPF intolerance fare better with a SPF rich in lactose than with conventional lactose-free SPFs, thus suggesting that soy clinical intolerance may be related to the carbohydrate components (82). Burks et al. (89) have provided evidence for no pathogenic role of serum food-specific antibodies in SP intolerance, thus confirming that serum-specific IgE antibodies are not elevated in this group of patients (73). Evidently, these children are not atopic (90). Diarrhea was the presenting symptom in 19 children (6%), two of whom had positive RAST to soy, however the challenge test was negative (42).

The diagnosis of SPF intolerance in these children usually requires a challenge test to soy (73, 91), with quite different results (92). A jejunal biopsy was done 24 hours after a SP challenge in 18 infants who were maintained on a protein HF for 6–8 weeks after the onset of gastroenteritis. Ten infants had histological reactions, three of whom also with clinical reactions, and eight neither clinical nor his-

tologic reactions (92). Laboratory studies may reveal increase in the absolute PMN counts from before the oral challenge to 6–8 hours after the challenge, and blood, leukocytes, and eosinophilic debris in the stools (92).

In conclusion, because CMA frequently leads to small bowel damage, mucosal permeability to other proteins can lead to an enhanced systemic uptake of protein present during intestinal anaphylaxis and an immunological response to these proteins. The uptake of otherwise non-allergenic proteins may result in a similar reaction, thus broadening the allergic response (93). However, subsequent studies fail to support the hypothesis that sensitization occurring in the gastrointestinal tract may lead to significantly altered systemic responses (89).

B) Anaphylaxis

Clinical cross-reactivity to legumes is very rare in children, therefore explaining why soy allergy is so uncommon (94). Anaphylaxis has been mentioned in passing as a hazard of treatment with elimination diets (95), and its occurrence after the ingestion of SPFs appears to be an extremely rare phenomenon. To our knowledge, there are only 4 such reports (64, 95–97), including a 5-year-old soy allergic male who collapsed 5 minutes *after ingesting 88 mg SP* (64): CM is so potent an allergen that a drop is enough (98). Two more cases of shock to soy were published about 40 years ago (99, 100). In the first one (99) a baby developed a syndrome “closely resembling anaphylactic shock”. The second baby (100) also went into shock, but in both cases no data about clinical manifestations and treatment are available. The case reported by Mendoza et al. (101) seems to be a typical case of soy intolerance with vomiting and diarrhea in a child who was pale as are all children with these reactions.

In a survey of 1450 pediatric allergists from all over the world (67) no physician had ever seen a case of anaphylaxis following the use of SPFs. Instead the incidence of anaphylactic episodes might dramatically increase if transgenic soybeans containing Brazil nut albumin allergen were used as a source of methionine (102). However, the product was discontinued (Sampson, personal communication, 1996).

C) Skin symptoms

1) Atopic dermatitis

In our series (42) 247 (77.9%) children with a median age of 5 months had AD. Sixty-two (25%) had a positive RAST, and ten a positive challenge to soy (2.5%) (42).

2) Urticaria

Urticaria was the presenting symptom in 22 children (6.9%), only one of them (4.5%) had a positive

RAST to soy. No child had a positive soy challenge (42). Contact urticaria to soy milk may be present in AD children (95).

D) Respiratory symptoms

Although 29 patients (9.1%) had asthma and/or rhinitis, and five of them (17.2%) a positive RAST to soy; the challenge test was negative in 100% of cases (42). Respiratory reactions were elicited in 5% of 320 patients with AD (median age 4.4 years) challenge-tested with soy (103), in 6% of 480 3–19-year-old children with food hypersensitivity (44), and in 3% of 279 asthmatic children aged 3–19-year (104).

E) Oral allergy syndrome (OAS) symptoms

OAS was found in 7/8 soy allergic children at the soy DBPC challenge (64). To our knowledge, no such association has been previously reported.

Allergenicity in children

The first studies on the prevalence of soy intolerance date back about fifty years ago. Hill (70) concluded that soybean was a poor allergen. Glaser (75) found only an occasional infant sensitive to a SPF. Glaser also predicted that with the tremendous increase in the use of soybean not only as a dietetic ingredient but also as a basis for plastics and other products, sensitivity to soybean will undoubtedly become more common. Glaser (76) and Clein (77) reported that in allergic and nonallergic infants the prevalence of soy allergy was about 7%. Ratner et al. (28) concluded that “soybean oil, sauce, and cereals were devoid of allergenicity”. He was probably the first to recognize that a problem from the standpoint of allergy could be that of inhalation of soybean dust (28). Mortimer (78) commented that the figures of SPTs positivity to soybean were significantly high in her studies, however, she concluded that the correlation of positive SPTs with the clinical manifestations of allergy is about 7%.

Gerrard et al. (41, 46) were the first to recognize that children may be sensitive also to other substances incorporated in SPFs. Six related studies are summarized in Table 1 (41, 46–50). Freier et al. (67) evaluated a 30% incidence of soy allergy in infants fed SPFs in the treatment of gastrointestinal CM hypersensitivity, however, they did use SPFs in infants older than 6 months without adverse effects. Kahn et al. (68) comment that up to 5% of allergic infants with sleep disturbance and CMA can suffer from SP intolerance. In a recent study (79), soy milk challenge was positive in 10.3% of atopic children and in 17.2% of the whole population studied, but soy sensitivity appeared to be rare in patients with food intolerance. There was no difference between atopic and non-atopic children and between patients previously or never fed soy.

Table 1. Studies based on clinical history, SPTs or food challenge diagnosis

Study	Ref	No. of children	Soy allergy	Diagnosis	Comments
1) Gerrard et al.	41	75	36%	CH	retrospective study
2) Gerrard et al.	46	51	20%	CH	5/10 had no atopic symptoms
3) Kuitunen et al.	47	54	11%	FC	the children were on gluten-free diet
4) Jakobsson & Lindberg	48	20	35%	CH	the soy challenges were "performed" at home by the parents
5) Hill et al.	49	100	43%	FC	see note
6) Bishop et al.	50	97	47%	CH	diagnosis of adverse reactions was reported by parents

Mean of the 6 studies 32%

Notes: CH = clinical history, FC = food challenge, CMA = cow's milk allergy

1) Twenty-seven were sensitive either to SPFs or to other substances incorporated in the formula.

2) The authors noted in the five children that when one proprietary preparation was not tolerated, a second one was, suggesting either that the soy protein had been denatured in one and not in the other, or that other ingredients in the formula had caused symptoms.

3) Data on food challenges are lacking.

4) We do not know how many of the 1079 children followed-up for 2 years were exposed to soy feeding.

5) The SPF used in the trial contained sucrose and many of the infants studied were intolerant to sucrose, therefore Hill et al. never stated that 50% of the children with CMI intolerance in their study were also reactive to soy.

Our meta-analysis on the prevalence of soy allergenicity in children

Although in most papers emphasizing the allergenicity of SPFs no challenge to soy was made, nor were specific IgE to soy measured, the DBPCFCs, the standardization of allergenic extracts, and the rationalization of the combined use of SPTs and RAST are relatively recent acquisitions. It is of note that several of these works were done well before the philosophy of the "gold standard" was established, and some even before the diffusion of the RAST technique. With these premises, we shall survey studies drawing conclusions on the incidence/prevalence of soy allergy, also trying to meta-analyze pertinent studies.

We have analyzed several studies that have evaluated the issue of CM and soy allergy/intolerance in babies and children. In Table 2 we summarize (%)

the results of 14 such studies with 17 determinations in selected children aged 0–18 years with multiple FAs (20, 41, 44, 46, 48, 54–61), evaluated and diagnosed with clinical history (41, 46, 48, 58), SPT (57, 60), RAST (54, 55, 57, 58, 60, 61) and OFC/DBFC (20, 44, 48, 54, 56, 57, 59, 60, 61). Also comprised are the results of 455 positive DBPCFC in adults and children from 3 US hospitals (43). The results of works based mainly or exclusively on parents' reports (49, 50) are extremely difficult to compare with the other studies. Another study (71) failed to explain why the diet with SPF "was changed in 27.8% of cases", and whether the change was decided by the doctor or the parents, or due to a poor compliance or to intolerance to the formula.

As shown by Table 2, the mean percentage of soy allergy in 14 studies is 7.1%, while the mean prevalence of CMA is 24.9% (3.5:1). In healthy babies the mean incidence of CMA is 2.3% (98). In two

Table 2. Studies evaluating the incidence/prevalence of soy allergy in children aged 0–18 years compared to CMA

Year of publication	1967	1973	1979	1982	1984	1985	1988	1990	1996	1994	1994	1995	1995	1988						
Reference	41	46	48	54	55	56	20	57	44	58	59	60	61	43						
Age (years)	infants	infants	NS	0.1–11	0–4	0.3–10.5	5.3 M	1–3	<3	3–19	1	2	18 M	5.4 M	0–6	7–15	NS			
No./of children	150	59	20	68	86	54	160	21	74	111	1,314	112	355	507	115	710				
Diagnosis	H	H	OFCxCM	OFC	IgEs	OFC	DBFC	OFCxCM	DBFC	H,IgE	OFC	SPT,IgE	IgEs	OFC	DBPCFC					
			TR × soy	IgEs	0.7 y	2 y		SPT +IgE x soy					OFC							
								Total	3y											
Food	Mean																			
CM	24.9	NS	7.5	1.9	41	9	0	85	11	100	24	36,3	11.9	6.5	9.6	NS	14.3	33.9	14	18.9
SPF	7.1	36*	10*	35	1	6.6	0	0	5	9.5	0	10.5	2.3	1.9	2.9	0	0	1.6	1.5	6

OFC = Open food challenge, DBFC = double-blind food challenge, IgEs = RAST, SPT = skin prick test(s), H = clinical history and/or parents' reports, M = mean, NS = not specified * the authors specify that the prevalence may be due to other components of SPFs (see text), y = year(s), TR = telephone reporting, CM = cow milk, CMA = cow milk allergy, SPF = soy protein formula, NS = not specified.

Table 3. Results of studies employing challenge test to soy

Author(s)	Ref.	No. of subjects	Age (years)	Challenge type	Reactions to soy (%)
Sampson	20	204	5.2 (M)	DBPCFC	5
Bock	44	313	<3–19	DBPCFC	5.4
Bock et al.	43	710	NS	DBPCFC	6
Giampietro et al.	42	317	0.4 (M)	OFC	2.5
Kivity et al.	59	52	18 (M)	DBFC	0
Magnolfi et al.	64	900	0.1–18	DBPCFC	6.1
Total		2496			Mean = 4.2

Abbreviation: DBFC = Double-blind food challenge, DBPCFC = Double-blind, placebo-controlled food challenge, M = median, NS = Not specified, OFC = Oral food challenge.

studies of infants followed-up 2–3 years, 5.1 (57) and 6.6% (55) had adverse reactions to SPFs, however at the age of 2–3 years the prevalence was 0, thus demonstrating that the possible allergy is a transient phenomenon. The studies employing challenge tests for the diagnosis of soy allergy confirm the 14 studies we have reviewed. There are seven such studies in 2496 subjects (Table 3) (20, 42–44, 59, 64). The mean reaction rate to soy in these studies is about 4% including the results of a modified RAST with a 6% prevalence in CMA children (62). A possible bias of such studies is that they do not give population prevalence.

Several studies have demonstrated that both the RAST = 22% (42) and the SPT positivity to soy between 25% (20) and 73% (59) were reduced by food challenge to 2.5% (42), 5% (20) and 0% (59), respectively, as it is evident also for other foods (20). As regards the prevalences based upon clinical

history (41, 46) there is a percentage $\geq 25\%$ of parents forgetting data of their children (105). Concerning the clinical reactions reported by parents (39, 50), food challenges reduced them from 25% to 8% (106). Hence the mean of 7.1% (Table 2) and that = 4.2% of challenge studies (Table 3) are confirmed.

Consequently, we analyze the apparent discordance among the mean prevalence of data reviewed in Table 2, the results of challenge, and of controversial studies failing to favor the elucidation of the issue. According to our experience (15, 21) soy allergy does not occur as frequently as CMA (Table 2). We suggest that the reports stressing high figures of soy allergy (33, 41, 46–48, 50, 73, 107, 108) have substantiated a kind of acritical wisdom, that is “30–32% of children with CMA are also allergic to SPFs”. Quite different could be the issue of prevalence in infants and small children with intestinal presentation (47, 51, 73, 87, 97, 107–109). In Table 4 dealing with very selected populations of children the figures vary considerably, from 0 to 42.9% (mean 20%) in view of the long follow-up of some studies (47, 51, 108, 109). The most selected children, only nine and ten in two studies (73, 107), were admitted with a suspected diagnosis of soy intolerance (73, 107, 109). However, only in one study the diagnosis was done with DBPCFC (87). Studies reporting immunologic abnormalities or increases in infection morbidity in SPF-fed babies (110) were not confirmed in infants exclusively SPF-fed during the first six months of life, and no differences in the proportion of infants who seroconverted to oral poliovirus immunization were found according to the type of feeding (111).

Dealing with selected pediatric populations, we must be careful about drawing broad conclusions from *in vivo* and *in vitro* procedures and about assuming that these tests directly translate to allergic children fed CM or SPFs. Further, the methods used to detect and diagnose soy allergy were different in the studies analyzed as did the techniques of performing SPTs, also because all the incidences/prevalences should be evaluated as a quote of the general incidence/prevalence of CMA.

Diagnostic procedures

Skin prick tests

There is circumstantial evidence that most diagnoses are based on SPTs and RAST, of which we have demonstrated the unreliability, however the absence of a counterpart, such as challenge to soy, is almost total. DBPCFCs have confirmed only 5% of soy-positive SPT results (20), contrary to the diagnostic efficacy for most food allergens (112). Usually both SPT and RAST have a good negative predic-

Table 4. Results of studies evaluating the prevalence of soy intolerance in very selected populations of children with gastrointestinal CMA

Author(s)	Ref.	No. of children	Age (years)	Follow-up (years)	D	Reactions (%)
Perkiö et al. **	51	108	0.3	0.1–7.5	FC*	4.6
Kuitunen et al.	47	35	0.7	9	FC*	11.4
Powell	73	9	5.5	NS	OFC	42.9
Halpin et al.	107	10	0.2–0.3	3	C,L	40
Délèze & Nusslé**	108	18	5.2 (M)	15	C,L	22.2
Navarro et al.	97	42	infants	NS	C	4.7
Burks et al.	109	43	0.8 (M)	1.5	OFC	32.5
Sampson et al.	87	92	1.5 (M)	1	DBPCFC	0

* data on food challenges are lacking.

** retrospective study.

Note: in the studies by Powell and Burks et al. the children were admitted with a suspected diagnosis of soy intolerance.

Abbreviations: C = Clinical, D = Diagnosis, FC = Food challenge, L = Laboratory, M = Median, NS = Not specified, OFC = Open food challenge.

tive value (113). SPT to soy have a sensitivity of 77.6%, a specificity of 74%, a negative predictive value of 98%, however a positive one of 19.6%; therefore SPT to soy are less useful as positive indicator of clinical hypersensitivity (114), also due to a 67% rate of false positive SPTs (94). The positive predictive value of SPTs to soy is scarce (42), even if high quality extracts are used (113, 115). The value of negative SPTs to soy was recently stressed (64) since no child with negative SPT to soy had a positive challenge to soy (114).

Circulating IgE antibodies

The unreliability of the RAST test to soy makes the challenge test imperative when soy allergy is suspected. RAST was positive to soy in 89.8% children with AD, but the challenge test to soy was positive only in 10% of them (42). RAST to soy had a sensitivity of 0.66–0.67, a specificity of 0.64–0.80, a negative predictive value of 0.79–0.94, and a positive predictive value of only 0.18 (42, 116). The discordance between the RAST and the challenge test to soy fits well with the data reported by Bardare et al. (79) showing that 46% of children affected by FA had positive RAST to soy, but only in 17% of these children was the challenge test positive. Aas (112) showed that 100% of children with AD and with IgE antibodies to soy had negative challenge test to soy. It is therefore advisable to employ a modified RAST (62).

The concordance between SPTs and RAST is also poor: in a study on 90 children aged 1–14 years with pollinosis or skin symptoms SPTs were positive for soy in 2/45 (4.5%) and 8/42 (19%), respectively, whereas RAST was positive in 25 and 46.6%. In comparison, specific IgE to grasses were positive in 93.6% of pollen allergic patients tested (114). False positive or negative RAST may result from several factors such as non-specific binding of IgE antibodies, or high levels of total IgE, or IgE antibodies without clinical significance. Sera with elevated IgE levels such as those seen in AD children may produce false positive results due to increased nonspecific binding of IgE (112). As recently demonstrated, false positive RASTs may result from IgG anti-IgE autoantibodies that bind IgE, thus interfering with diagnostic IgE determination (117, 118).

Challenge test

Only DBPCFCs differentiate genuine cases of adverse reactions to soy. Open- or single-blind challenges can be done in infants and children when soy has a high likelihood of inducing reactions; negative responses to open challenges which raise the suspicion of a false-negative reaction should be con-

firmed by DBPCFC, except in cases of suspected life-threatening reactions.

The challenge test to soy is usually conducted as follows:

- 1) Prior to the test, parents should be instructed to eliminate all SPF-containing meals for 1–2 weeks, and to withdraw antihistamines for 7 days (according to half-life).
- 2) The procedure should be performed in the hospital under medical observation utilizing a standard scoring system, and with emergency equipment at hand to treat anaphylaxis.
- 3) At the end of the 2-week period, the medical équipe should perform a clinical examination of the child, and soy SPT, to confirm the previous diagnosis and exclude the possibility of present diseases or other issues that could contrast with the correctness of the procedure.
- 4) Soy is administered in the fasting state as follows:
 - A) a drop of a 13% soy solution (1.8g SP/dl = 0.018/ml) is put upon the inner border of the lower lip,
 - B) a further 1–2 ml of SPF is given after 15–20 minutes,
 - C) increasing doses of SPF are administered until a final dose of 200 ml is given,
 - D) if any symptoms secondary to the test are observed, the test in the hospital is terminated,
 - E) after the last administration of the tested SPF the child is to be watched for at least 4 hours and then discharged.

The reason for beginning with a little dose of allergen on the lower lip is explained by the 7.4–14.8% proportion of children experiencing severe reactions within minutes of ingesting a few drops of CM (98), and by the anaphylaxis following the administration of 88 mg SP (64).

DBPCFC to soy (with capsules of SPF) or placebo (with rice or corn flour) can be administered blinded in fruit juices on two different days (64).

The parents of children with no symptoms should be instructed to continue to give a SPF at home (200 ml a day) and to record any reaction and report at the following visit. Late reactions (after 3–7 days) (64) mirror those seen by us in CMA children after challenge.

In the survey of 1450 pediatric allergists all over the world, however, almost none of the responding physicians had ever done a DBPCFC with soy to prove its allergenicity (69).

Other diagnostic methods

We suggest adapting the hyperimmunization model for a possible use in children, in order that it could

Table 5. Main properties of soy-protein-based formulas

- *Not reacting with CM
- *Lower allergenicity (IgE Abs) than CM
- *Similar antigenicity (IgG Abs) to CM
- *Nutritional adequacy similar to CM formulas
- *Better palatability than highly HFs
- *Less expensive than highly HFs

CM = cow milk, HS = hydrolysate formulas

be employed for the screening of allergenic formulas in order to reduce the cost, the risks and the time necessary for the DBPCFC studies (32).

Clinical indications

Several papers have stressed the beneficial effects of SPF in the treatment of several conditions, but patient selection and inclusion criteria, and definition of symptoms/diseases were not well defined in all these trials. SPFs are used for different conditions including CMA, CM intolerance, lactose and galactose intolerance and in the management of infants with severe gastroenteritis (15, 17). SPFs are less expensive than HFs (67). Table 5 illustrates the main properties of SPF(s) and Table 6 (21) compares the antigenicity and allergenicity of HFs and SPFs. Because of residual allergenic epitopes and contamination with minute amount of intact proteins, HFs are not safe for children with IgE mediated CMA (119, 120), nor for babies with CM enterocolitis (121).

Treatment of allergy

We reported 20 infants (14 M, 6 F), aged 5–15 months (median 6 months) with AD due to CMA in whom a SPF dramatically improved the skin lesions (15). In 17/20 infants (85%) the SPF was well accepted, and insured a good control of AD during the 3-month study trial. The severity of AD lesions significantly decreased during the CM-free diet and the SPF feeding ($p < 0.005$), increased after CM-OFC-

challenge ($p < 0.005$), and significantly decreased again ($p < 0.005$) during the subsequent CM-free period. SPT were positive for CM in 72.2% of the babies, while no significant differences were recorded with regard to total IgE levels before and after the trial. Specific IgE for CM were positive in seven infants on admission and in six after the diet. All infants thrived during the 3-month diet and during the follow-up remained on the same growth percentile they had before starting the trial (15).

Allergy prevention

In our preventative studies (122, 123) the figures are quite similar according to the dietary manipulations (exclusive breast feeding for the first 6 months of life; reduction of CM and egg from the diet of the nursing mother, SPF supplement when breast milk was not sufficient; selected weaning after the 6th month of life in the study group, CM in the controls) associated with environmental measures stressing no smoking and no pets in the house, elimination of house dust, and day-care center attendance delayed to after 3 years. We showed that 14.5% (26/179) of the study group compared to the 38.5% (25/65) of the control group developed atopic manifestations during the follow-up ($p = 0.0000$), thus confirming that dietary and environmental measures are able to significantly prevent atopy onset in high-risk babies, at least until the age of 3 years and 8 months. A significant reduction of both the prevalence and the incidence of AD, FA and asthma was shown in 174 high risk children followed up to the age of 5 years, who received similar dietary and environmental preventative measures. The prevalence rates of atopic diseases were as follows, 1% FA, 0.5% AD, 9% asthma (124).

Additional studies comparing SPFs and CM formulas in atopy prevention are summarized in Table 7 (39, 40, 96, 125–133). With the exception of studies for allergy (96, 125, 127, 132, 133), no statistically significant differences were found, even when the figures were (very) high.

In Johnstone and Dutton's trial (125) 235 children with a family history of allergy were examined by a physician ten years after having been randomly chosen at birth to receive either a SPF or a CM formula. Allergy occurred in 18% of the soy group and in 50% of the CM-fed controls with significant differences for asthma and perennial allergic rhinitis. No difference occurred in the incidence of AD, which was very low in both groups.

Brown et al. (126) used SPF and CM formula without regard to family history, and infant foods were given ad libitum. Allergy occurred in 10.6% of children of the soy group (60% atopic) and in 13.3% of the controls, however, they concluded that a CM-

Table 6. Allergenicity and antigenicity of HFs and SPFs

	HFs			SPF
	Casein highly	Whey partially	Whey highly	
Antigenicity	–	+	+	+
Allergenicity	+	+	++	–
Cross-reactivity with IgE Abs to CM	+	+++	++	–

Modified from 21

free diet did not reduce the risk of a child developing allergy.

In the trial by Halpern et al. (127) 275 infants were fed SPF since birth, 42 stopped nursing before 2 weeks and were allocated to the soy group, and 315 were breast- and SPF-fed; infant foods were free except egg at 3 weeks in 50% of babies. The prevalence of soy allergy was 0.5%, however being higher the proportion of infants with CMA, the difference reached statistical significance.

Kjellman and Johansson (39) concluded that soy feeding did not reduce the incidence of CMA, but they permitted mothers to drink freely CM while nursing and failed to specify whether solid foods were introduced or at what age. Diagnosis consisted of medical evaluation of questionnaires and parental telephone reporting.

Chandra et al. (40) evaluated the effect of feeding whey HF, SPF and conventional CM formulas in high risk infants. Atopic disease developed in an equal number of babies fed SPF or CM (36%), but only five (7.4%) of those Good Start (GS)-fed. However the SPT were positive for CM proteins in 4/5 (80%) of GS-fed, and in 2/25 (8%) of SPF-fed babies (40) (Fisher 0.0026). In another study (130,131) there were no statistical differences.

For 4 years now we have run a prospective study to evaluate in "at risk" newborns the efficacy of pro-

phylactic dietary and environmental measures as those listed above (132). At the last follow-up (133), the cumulative prevalence of atopic disease was 17%: 125/732 manifested atopic symptoms; of them 83 (11%) developed AD/FA. Among the 125, 31/242 babies (13%) were exclusively breast-fed, 14/139 (10%) received exclusively SPF, 32/212 (15%) were breast milk and SPF supplement fed, and 48/139 (34%) CM-fed. The very low prevalence of atopic disease in the infants who followed the preventative measures (77/732 = 10.5%) with the lowest prevalence in SPF-fed babies (10%), and the highest (48/139 = 34.5%) in those who did not ($p = 0.0000$), stresses that such manipulations for the prevention of atopy in "at risk" babies are worthwhile (130) ($p = 0.0072, 0.0134$ and 0.0115 , respectively).

Bardare et al. (96) studied 900 infants found to be at risk for atopic disease. For 391 infants a preventative diet was prescribed that recommended breastfeeding for the first 6 months of life. Only SPF was recommended for breast milk supplementation, and introduction of solid foods was also carefully discouraged during the first six months. The infants whose parents complied with the prescribed diet were found to have a lower incidence of atopy during the first year of life (13.3%, $n = 158$) than infants whose parents had ignored or violated the prescribed diet, or infants whose parents were offered

Table 7. Prevention of atopic disease in at risk infants: results of 12 studies comparing SPF(s) with CM feeding

Authors	Ref	Year	No. of infants fed SPF or CM		F-U (y)	R	Results		Diag	Significance (p =)	
							SPF	CM			
Johnstone & Dutton	125	1966	115	120	3	+	AD	5	2	C	NS
							AR:	7	17	C	<0.001
							BA:	6	23	C	<0.05
Brown et al.	126	1969	85	196	2	+	S	10.6	13.3	C	NS
Halpern et al.	127	1973	261	349	7	—	S	0.5	1.8	C	NS
Kjellman & Johansson	39	1979	23	25	3	+	S	74	60	PR	NS
Gruskay	128	1982	79	201	15	—	3 a:S	20	25	C	NS
							15 a S	53	53	C	NS
							AD:S	41	34	ND	NS
Miskelly et al.	129	1988	228	233	1	+	BA:S	33	LV33	ND	NS
Chandra et al.	130	1989	41	40	1.5	+	AD:S	63	70	C	NS
Chandra et al.	40	1989	68	67	1	+	S	37	36	SPT	NS
Chandra & Hamed [^]	131	1991	68	67	1.5	+	S	27	17	SPT	NS
Businco et al.	132	1991	193	156	2	— [#]	S	5	13	C	0.0069
Bardare et al.*	96	1993	158	218	1	—	S	13	29	OFC	0.0003***
Machado et al.	133	1994	156	87	4	— [#]	S	17	32	C	0.0134*

In the study of Miskelly et al. 189/482 children were also breast-fed.

* SPF vs CM.

** The comparison with no compliant infants is more significant, $p = 0.0001$.

= see text.

[^] follow-up of 40, ^{^^} of 131.

Note: only one study (125) was retrospective.

Abbreviations: F-U = follow-up, y = year(s), R = randomization, CM = cow milk, S = soy milk, BA = bronchial asthma, AD = atopic dermatitis, AR = allergic rhinitis, NS = not significant, Diag = diagnosis, C = clinical evaluation, P = parental reporting, SPT = skin prick testing, OFC = oral food challenge.

no dietary recommendations (104) ($p = 0.0001$ prevention vs. no prevention).

As shown in Table 7, several controlled studies were randomized. Ours were randomized because the mothers were free to choose to breastfeed or not with no input by the investigators: we thought that the ethical norms did not allow us to suggest to highly motivated mothers to breastfeed or not only to adhere to a randomization, and so probably did the authors that failed to apply randomization. From a statistical point of view, only 16.6% randomized studies had statistically significant results, versus 66.6% of not randomized ones.

Treatment of other conditions

In recent years a poignant debate was created, which regarded the possible allergenicity of SPF in the prevention of infants at risk of atopy (134). Zeiger reviewing the issue (135) selected one "positive" study (125), the only retrospective one, and several "negative" ones (39,40,126,129,130) (Table 7), plus reactions to soy not employed in preventative manipulations in at risk infants (78, 136), one of which was via inhalation (136). He judged soy "not hypoallergenic" and advised against its use in the atopy prevention. It is of note that in his study less than half of highly motivated families adhered to withhold CM during the last trimester of pregnancy and above all while breast-feeding her infant at risk of atopy (137). We stress that all the studies positive for the use of SPFs that were disregarded in his review are the only studies with results supported by statistically significant differences (104, 127, 132, 133), and have the lowest figures of CMA (Table 7).

The issue of soy allergenicity through the inhalation route (25, 28, 136, 138, 139) is a critical one. We hypothesize that the high MW of intact soy globulin fractions cannot be absorbed easily by gastrointestinal mucus membranes, whereas the inhalation of the aeroallergen HPS may more readily sensitize adult asthmatics (136, 138). Indeed the easy release of the spiral-shaped HPS from soybean hull dust allows the protein to permeate the airway mucosal membranes to produce asthmatic reactions (25). We were not able to find a study addressing the different sensitizing power of the two routes. The high frequency of IgE-antibodies to soy compared with their poor clinical significance might also indicate an efficient gastrointestinal barrier to SP allergens.

Concluding remarks

The data analyzed so far appear not to support the "common wisdoms" regarding soy. SPFs have been used increasingly as alternatives for children with

adverse CM reactions, as well as for babies at risk for atopy, they are adequate from a nutritional point of view and are well accepted and economical. Gazing into the crystal ball points to several areas where more work and information are needed, and we simply conclude that Science is always one step forward. A reason of the lowest sensitizing power of SPF may be that soy is seldom found in children households, whereas the presence of CM is almost universal (140). In addition, it is clear that some SPFs contain epitopes, of which others are devoid, therefore the immunological properties of different SPFs should be ascertained. We feel that most controversies, until discussions take place on the use or not of SPF, may reside in the dietary and environmental measures and the care for mothers and infants that are found only in our studies. In each cohort of babies the infants were seen at our clinic at the age of 1, 3, 6, 9, 12 months and twice-a-year afterwards when a detailed history was taken and the presence of symptoms and signs of atopic disease were evaluated. Likewise, the mothers contacted us when the infants were sick. In this way we personally checked the symptoms and signs presented by the infants (122–124, 141). In our studies with 3–5-year follow-ups the frequency of soy reactions is therefore almost non existent, moreover several studies have demonstrated that soy adverse reactions are transient (55, 57).

We deem therefore that both the AAP (14) and the ESPGAN (16) should revise their Position Papers, since SPFs have provoked a clinical case of anaphylaxis every 22 years, a record surpassed only by home-made, meat-based infant formulas (142). In conclusion, we suggest that DBPCFC studies in larger cohorts of babies, also to exclude the possibility of a type II error in the data, may establish a more reliable prevalence of SPF allergy in different disorders associated with CMA.

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