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Over-Estimation of Soy Allergenicity: Laboratory Versus Challenge Tests: A Meta-Analysis

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Abstract

Soybeans have been cultivated in Eastern countries for many centuries and soy protein formulas (SPFs) have been developed, which have been widely used for feeding infants with cow's milk (CM) allergy (CMA) since more 70 years. Several long-term studies have shown that the nutritional adequacy of SPFs allows normal growth and development when fed to normal and high risk infants. We emphasize that most studies base the diagnosis of soy allergy on clinical evaluation or anecdotal case histories reported by parents, but not on challenge tests, thus soy allergy has been highlighted in the last decades, due to an excessive reliance on skin prick tests (SPTs) and/or RAST. We deem that the incorrect definition of soy allergy and non appropriate diagnostic criteria have led to a large discrepancy on the prevalence of soy allergy in the medical literature which ranges from 3% up to 80%, but was very seldom compared to results of DBPCFC (double-blind placebo controlled challenge tests). In this paper we present factual evidence that objective scientific and laboratory data establish the true prevalence of soy allergy in children with CMA and in the general pediatric population. We demonstrate that the importance attributed to SPTs is completely not justifiable

Keywords: Cow's milk reactions, Gastrointestinal reactions, Soy allergy, Soy protein formulas, Skin prick tests, RAST, Challenge tests, Predisposed infants, Prevention, Atopic march

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Introduction

SPFs have been developed since 1929, and support normal growth, protein status, and bone mineralization when fed to normal infants. SPFs are used for different conditions including CMA, lactose and galactose intolerance and in the management of infants with severe gastroenteritis. Their use for prevention of atopy is controversial. Some studies have shown that feeding SPFs for the first six months of life significantly reduces the prevalence of atopic diseases in high risk babies. Several studies have confirmed the preventive effect of breastfeeding supplemented with SPFs [1-3] but others did not confirm this assumption [4,5].

Although the prevalence of soy allergy, calculated including also the studies based on SPTs, on clinical evaluation or anecdotal case histories reported by parents is 6.9%, 351% less than that of CM, in the last decade soy allergy has been overemphasized in the medical literature, but with surprisingly little scientific data to support this assumption. In these studies the diagnosis of soy allergy was not substantiated by scientific diagnostic criteria: neither challenge test to soy nor data on specific IgE to soy were available [1].

Soy protein is antigenic, and can be allergenic in selected cases, but this allergenicity is frequently emphasized without scientific confirmation [6]. We cite several reports based on SPT results or anecdotal data. For example Eastham et al. stress that "Our results confirm recent clinical documentation that soy-based formulas are not at least as antigenic as the milk-based and should be used with caution" [7]. It is of note that these authors measured the production of hemagglutinins to CM and soy proteins, which mainly belong to the IgG class (and not IgE). Consequently, they studied only soy antigenicity, since IgG express the antigenicity and not the allergenicity of a given protein, and are probably involved in the induction of tolerance to oral food antigens [3]. Gerrard et al. were more precise and declared that "A soy formula was offered 51 of the CMA babies. A fifth of the babies with CMA were allergic to SPFs. We noted in 5 instances 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" [8]. In another study the diagnosis of adverse reactions was reported by parents [9]. Merritt et al. [10] stressed that "it is known that SPF is less universally effective in managing symptoms of CM proteins sensitivity and the American Academy of Pediatrics recommends against its use for this purpose". The ESPGAN Committee on Nutrition considered "that available data do not support the view that such formulas (SPFs) should be the preferred choice when suspected, or proven adverse effects to CM protein is the indication". In order to substantiate this statement, the authors affirm (without quoting the source) that when SPFs are used as a substitute for CM in cases of CM protein intolerance (CMPI), allergy develops in a far higher number of children, up to 30-40% [11]. These not quoted figures probably stem from a subsequent work [12], where Eastham summarized previous data supposedly confirming the allergenicity of SPFs, declaring that when SPFs are employed in the treatment of CMPI children, allergy to soy develops in 15-50% of cases. However May et al. [13] definitely concluded that "It is unfounded to express a strong opinion about comparable antigenicity of CM and soy, as Eastham had done on the basis of limited data. More pertinent would be studies in which immunologic sensitization to soy protein (serum antibodies) would be compared to results of DBPCFC with soy products for identification of clinically-significant, symptomatic reactions".

Another issue is best recorded by Johnstone, who reported that pediatricians interviewed by him [14], told that "they were taught either by the head of their pediatric departments or by pediatric gastroenterologists in their training periods that soy was very allergenic". Instead in the survey of 1450 pediatric allergists all over the world, almost none of the responding doctors had ever done a DBPCFC with soy to prove its allergenicity. In addition to the incorrect definition of soy allergy, a common bias of most studies, is the incorrect quotations of previous studies as pointed out by the authors [14]. Authors of papers published even in outstanding journals and lecturers quote studies in which soy allergenicity is not documented with DBPCFC, in addition to reporting papers without consulting the original data. This bias seems to have been devised in order to support the theory that "soy is allergenic". An unspecified "high rate" of soy sensitization is extrapolated from blindly cited studies [15,16]. Schwartz et al. [17] while dealing with children with CMA, unexpectedly claim that "soy formula feedings do not prevent the development of IgE-mediated CMA and, in fact, they may encourage it (because) SPFs are both antigenic and allergenic".

As a consequence of this unscientific behavior, errors are perpetuated, leading to confusion that is deleterious for both patients and science.

Antigenicity or Allergenicity of SPF?

Although it is established that DBPCFCs are the golden standard for the diagnosis of food allergy, to our knowledge, only eight studies appropriately diagnosed soy allergy using DBPCFCs, found that only 3.5% of 2657 children showed soy sensitivity **(Table 1)** [18-25], while Bock found in 313 children an incidence of 5.6% for SPFs and of 22% for CM [21], with an increase of 393%. Further studies should establish the prevalence of soy allergy in different disorders associated with CMA. In contrast to hydrolysate formulas (HFs), SPFs do not cross-react with IgE antibodies to CM. Therefore SPFs could be used in babies with IgE-mediated CMA [1], but HFs should not be used in these infants, but only in children with food intolerance [26].

Gastrointestinal symptoms may occur in some SPF-fed children, however anaphylaxis following the ingestion of SPFs is extremely rare and have provoked a clinical case of anaphylaxis every 22.3 years [1].

It is true that severe gastrointestinal reactions to SPFs encompass the full gamut of disease seen with CMA in infancy [27]. We have reviewed eight pertinent studies [1] and found a mean of 20% of reactions, also considering two studies limited to 9 or 10 children and one that found a 0% prevalence [1,28]. This also means that 80-100% of infants and children with gastrointestinal disorders can ingest SPFs with impunity.

As regards the frequent cases of enterocolitis and colitis subsequent to SPF feeding, it is known that CMA frequently leads to small bowel damage, so mucosal permeability to other proteins can lead to an enhanced systemic uptake of protein present during intestinal anaphylaxis and to an immunological response to these proteins. The uptake of otherwise non-allergenic proteins may result in a similar reaction, thus broadening the allergic response [29]. However subsequent studies fail to support the hypothesis that sensitization occurring in the gastrointestinal tract may lead to significantly altered systemic responses [30]. In very selected populations of children the figures vary considerably, from 0 to 42.9% (mean 20%) [1], however the only study that employed DBPCFC for the diagnosis found a 0% prevalence [28]. The suggestion of giving infants with CM enteropathy/enterocolitis CM hydrolyzed formulas (HFs) [27] conflicts with 220 reactions documented in children [26].

Data on the soy natural history are scarce. A prospective survey on the natural history of CMA reported that only 2/39 children with CMA (5.13%) had adverse reactions to soy. However, it was shown that the 2 children tolerated soy by the age of 3 years, thus clarifying that soy intolerance was a passing phenomenon [31].

Laboratory versus DBPCFC: Our Meta-Analysis

It is an intricate affair, since laboratory allergy tests may not be concordant with the clinical symptoms. Both SPTs and RAST may lack sensitivity and specificity, therefore they should be used as a screening test and not for final decision-making. As regards RAST, in our study [32] RAST was positive to soy in 89.8% children with AD, but the challenge test to soy was positive only in 10% of them [32]. 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 0.10-0.18 [32,33]. The discordance between the RAST and the challenge test to soy fits well with the data reported by Bardare et al. [34,35] 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. We have shown that only 4/35 children (11.4%) with AD and with IgE antibodies

Table 1 Results of studies employing challenge test to soy.

Author(s)	Ref No. of children	Reactions to soy (%)	Age (years)	Challenge Type
Sampson et al.	18	204	5.2 (M)	DBPCFC
Bock et al.	19	313	5.4	DBPCFC
Bock et al.	20	710	NS	DBPCFC
Giampietro et al.	21	317	0.4 (M)	OFC
Kivity et al.	22	52	18 (M)	DBFC
Magnolfi	23	900	6.1	DBPCFC
Burks et al.	24	98	3.1	DBPCFC
Eigenmann et al.	25	63	2.3 (M)	DBPCFC

DBFC = Double-blind food challenge, **M** = median, **NS** = Not specified, **OFC** = Oral food challenge

to soy had positive challenge test to soy [19]. False positive or negative RAST can be caused by several factors [36], including the substantial demonstration of IgG anti-IgE autoantibodies that falsely appear as specific IgG, thus interfering with diagnostic IgE determination [37,38]. As a consequence, the unreliability of the RAST test to soy makes the challenge test imperative when soy allergy has to be established.

There is circumstantial evidence that most diagnoses are based on RAST, of which we have demonstrated the unreliability and on SPTs, however the absence of a counterpart, such as challenge to soy is almost total. From the recent study by Burks et al. [24] we conclude that we cannot agree with both their calculations, and their reliance on SPTs. When we calculate their percent ages [24], also to compare them with data of similar studies [18], we read their results differently **(Table 2)**. For this purpose, we have calculated the percentages of positive SPTs and DBPCFCs for the more prevalent foods in relation to the amount of positive SPTs and DBPCFCs among the total number of SPTs and DBPCFCs (performed in 165 and 98 children, respectively).

Consequently DBPCFCs have confirmed only 35.4% of SPT results, 72.8% of the concordance obtained by Sampson = 48.6% **(Table 3)** [18]. Therefore the importance attributed to SPTs [24] is completely not justifiable. The **Table 1** that we published in our paper to soy [1], can be adjourned.

The discrepancies till yet discussed may be explained by a study [38] comparing the allergenicity of two commercially available infant SPFs, a powdered and a liquid one, and found that reaginic antibodies to the liquid formula were significantly higher than to the powdered soy. For example in Italy we use powdered forms, while in the US is prevalent the use of ready-to-feed SPFs. In our study [1] we have meta-analyzed 17 different studies and concluded that history-based SPF allergy totals 27%, in SPT-RAST-open food challenge/DBPCFC-based epidemiological studies attains 3%, and in challenge test studies 4.01%. In the case of soy the SPT increase is of 700% [24], 450% [18], and in the studies so frequently cited attains 673%.

SPFs in Atopy Prevention

In a recent work [27] the American Academy of Pediatrics (AAP) has substantially responded positively to the request of revising their 1983 Position Paper. The AAP concludes that "recognizing that soy protein is antigenic does not mean that soy protein is highly allergenic" and above all that "most infants with documented IgE-mediated allergy to CM protein will do well on isolated SPFs". A drawback of AAP conclusion is when it is stressed that "the routine use of isolated SPFs has no proven value in the prevention of atopic disease in high-risk infants"

Twelve studies have evaluated SPFs in the prevention of allergic diseases [1]. We have noted that in one study diagnosis consisted also of parental telephone reporting [4], and that another study [5] evaluated the effect of feeding whey HFs (wHF), SPF, and conventional CM formulas in high-risk infants. Atopic disease developed in an equal number of babies fed SPF or CM (36%). However SPTs were positive for CM proteins in 4/5 (80%) of wHF-fed, and in 2/25 (8%) of SPF-fed babies (Fisher 0.0026) (a decrease by 72%), thus suggesting that sensitization to CM proteins in infants receiving this HF is exceptionally more frequent than in those fed a SPF. In several of these studies the prevalence of CMA attained high levels such as 60% [4] and 70% [5]. Only in the preventative studies by Johnstone and Dutton [2], Bardare et al. [34] and Cantani et al. [35] with high statistically significant differences, reactions to SPFs occurred in high-risk children in 9%, and to CM in 22.5% of cases (mean) [35], therefore the frequency of atopic disease is reduced of 250% in SPF-fed children. The same difference (2.2) is found in the only study in which diagnoses were made through OFC [34]. In a multicenter study comprising 2,291 babies with the cooperation of many Italian Maternity Hospitals, the babies breast- and/or SPF-fed and whose parents strictly followed the environmental measures had at four years of age a lower AD prevalence (13%) in comparison with CM-fed babies (34.5%) ($p = 0.0001$) As regards the type of feeding and the development of allergic sensitization there were very significant statistical differences: breast feeding (BF)-CM $p = 0.0049$, SPF-CM $p = 0.0069$, BF/SPF-CM $p = 0.0119$, BF + BF/SPF-

Table 2 Results of SPTs and DBPCFCs [24].

Food	Positive SPTs	Positive DBPCFC No and (%)	% of positive SPTs confirmed by DBPCFC
Peanut	55 (33.3)	27 (27.6)	49.1
Milk	31 (18.8)	14 (14.3)	45.1
Egg	57 (34.5)	33 (33.7)	57.9
Wheat	13 (7.9)	5 (5.1)	38.5
Cashew	16 (9.7)	4 (4.1)	25
Catfish	8 (4.8)	4 (4.1)	50
Soy	21 (12.7)	3 (3.1)	14.3
Cod	11 (6.7)	3 (3.1)	27.3
Chicken	17 (10.3)	2 (2.0)	11.8

Table 3 Results of SPTs and DBPCFCs [18].

Food	Positive SPTs	Positive DBPCFC No and (%)	% of positive SPTs confirmed by DBPCFC
Egg	89(55.6)	78 (38.2)	87.6
CM	39 (24.4)	22 (10.8)	56.4
Peanut	81 (50.6)	48 (23.5)	59.2
Wheat	24 (15)	8 (3.9)	33.3
Soy	45(28.1)	10 (4.9)	22.2
Fish	45(28.1)	15 (7.4)	33.3

CM p = 0.0001, BF/SPF + SPF-CM p = 0.0001. This data confirms that SPFs are adequate from a nutritional point of view [35] and can be used not only in infants with IgE-mediated CMA [27], but are also effective in the prevention of atopy [1].

Conclusion

Several biases of earlier studies have led to over-estimating soy allergy and to the common unfairness that SPFs are not safe in children with CMA. All the previously published studies on soy allergy should be critically re-evaluated. However, according to few studies which used DBPCFC, the prevalence of soy allergy in children with CMA seems to be much lower than usually reported. DBPCFC is mandatory to differentiate factual histories of adverse reactions to soy from unfounded associations perpetuated by faulty observations and citations. For those doctors and investigators who seem to ascribe a high prevalence to soy allergy [6,39], these impartial observations should encourage them to be more critical about their own conclusions. Further studies using DBPCFC are necessary to definitely establish the true prevalence of soy allergy in children with CMA and in the general pediatric population [1].

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