Journal of Pediatric Gastroenterology and Nutrition
42:352–361 © April 2006 Lippincott Williams & Wilkins, Philadelphia

Medical Position Paper

Soy Protein Infant Formulae and Follow-On Formulae: A Commentary by the ESPGHAN Committee on Nutrition

ESPGHAN Committee on Nutrition: *Carlo Agostoni, †Irene Axelsson, ‡Olivier Goulet, §Berthold Koletzko,[1] ||Kim Fleischer Michaelsen, ¶John Puntis, #Daniel Rieu,[3] **Jacques Rigo, ††Raanan Shamir, ‡‡Hania Szajewska,[2] and §§Dominique Turck

**University of Milano, Milano, Italy; †University of Lund, Malmö, Sweden; ‡Hôpital Necker Enfants-Malades, Paris, France; §Ludwig-Maximilians-University, Munich, Germany; ||The Royal Veterinary and Agricultural University, Frederiksberg, Denmark; ¶The General Infirmary, Leeds, United Kingdom; #University of Montpellier, Montpellier, France; **University of Liège, Liège, Belgium; ††Meyer Children's Hospital of Haifa, Haifa, Israel; ‡‡The Medical University of Warsaw, Warsaw, Poland; §§University of Lille, Lille, France. [1]Committee Chair; [2]Committee Secretary; [3]Guest*

ABSTRACT: This comment by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Committee on Nutrition summarizes available information on the composition and use of soy protein formulae as substitutes for breastfeeding and cows' milk protein formulae as well as on their suitability and safety for supporting adequate growth and development in infants. Soy is a source of protein that is inferior to cows' milk, with a lower digestibility and bioavailability as well as a lower methionine content. For soy protein infant formulae, only protein isolates can be used, and minimum protein content required in the current European Union legislation is higher than that of cows' milk protein infant formulae (2.25 g/100 kcal vs. 1.8 g/100 kcal). Soy protein formulae can be used for feeding term infants, but they have no nutritional advantage over cows' milk protein formulae and contain high concentrations of phytate, aluminum, and phytoestrogens (isoflavones), which might have untoward effects. There are no data to support the use of soy protein formulae in preterm infants. Indications for soy protein formulae include severe persistent lactose intolerance, galactosemia, and ethical considerations (e.g., vegan concepts). Soy protein formulae have no role in the prevention of allergic diseases and should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are considered for therapeutic use in food allergy after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge. There is no evidence supporting the use of soy protein formulae for the prevention or management of infantile colic, regurgitation, or prolonged crying. ***JPGN 42:352–361, 2006.*** **Key Words:** soy—infant formula—follow-on formula—food allergy—phytoestrogens. © 2006 Lippincott Williams & Wilkins

INTRODUCTION

Soy formula was first introduced in the United States for feeding young infants in the early 1900s (1). In 1929, soy formula was proposed as a cows' milk substitute for babies with cows' milk intolerance (2). Soy protein formulae are given at some time during the first year of life to approximately 25% of infants in the United States, 13% in New Zealand, 7% in the United Kingdom, 5% in Italy, and 2% in France (3–6).

During the past few years, concerns have been raised over potential risks of soy protein formulae, in particular with regard to high phytoestrogen contents. Authorities or pediatric societies from Australia, Canada, France, Ireland, New Zealand, Switzerland, and the United Kingdom have recently advised health professionals and caregivers that because of concerns raised and limited availability of data, the use of soy protein formulae in infants should be restricted to specific cases (7–9).

The purpose of this comment by the Committee is to review available information on the composition and use of soy protein formulae as substitutes for breastfeeding and cows' milk protein formulae as well as on their suitability and safety for supporting adequate growth and

Received October 18, 2005; accepted October 18, 2005.

Berthold Koletzko is Committee Chair, Hania Szajewska is Committee Secretary, and Daniel Rieu is a guest of the ESPGHAN Committee on Nutrition.

Address correspondence and reprint requests to Dominique Turck, Unité de Gastro-entérologie, Hépatologie et Nutrition, Clinique de Pédiatrie, Hôpital Jeanne de Flandre, 2, avenue Oscar Lambret, 59037 Lille cedex, France. (e-mail: dturck@chru-lille.fr).

development of infants. In preparing this comment, the Committee reviewed expert consensus documents on the use of soy protein formulae in dietetic products for infants (5,7–13). Products that do not meet the standards of infant and follow-on formulae or foods for medical purposes designed for infants, such as soy "milks" or juices and fermented soy products, that do not fulfill nutritional requirements of infants are beyond the scope of this review.

FROM SOYBEANS TO SOY PROTEIN ISOLATE FORMULAE

Soybeans comprise approximately 40% proteins, 35% carbohydrates, 20% fat, and 5% minerals (percent dry weight). Soybean products include oil and soy flour obtained from roasted soybeans ground into a fine powder. Soy protein isolates are derived from delipidated soy flour (90–95%) by elimination of soluble carbohydrates and mineral salts (5). Soy protein has a lower biologic value than cows' milk protein. The nitrogen conversion factor, which allows us to calculate the protein content from the total nitrogen content, is lower for soy protein isolate than for cows' milk protein. Soy and cows' milk proteins have a different amino acid pattern (i.e., soy protein contains lower amounts of methionine, branched chain amino acids lysine, and proline and higher quantities of aspartate, glycine, arginine, and cystine than cows' milk protein) (14). To ensure adequate growth, nitrogen balance, and plasma albumin concentrations, methionine supplements have been recommended (15,16). Because soy based products have a very low content of L-carnitine that may induce low plasma carnitine concentrations in infants (17), the addition of carnitine to soy formulae has also been recommended (7,18).

COMPOSITION OF SOY PROTEIN INFANT AND FOLLOW-ON FORMULAE

Recommendations and Regulations

The ESPGHAN Committee on Nutrition published recommendations on the composition of soy protein infant and follow-on formulae in 1990 (16). Soy protein infant and follow-on formulae marketed in the European Union must meet the compositional criteria defined by EU directives (19,20). For soy protein infant formulae, only protein isolates should be used, and the minimum protein content required by European legislation is higher than that of cows' milk protein infant formulae (2.25 g/100 kcal vs. 1.8 g/100 kcal) to account for potentially lower digestibility and therefore lower bioavailablility of soy protein compared with intact cows' milk protein. The main differences in compositional criteria between soy protein and cows' milk protein infant formulae, and between soy protein and cows' milk protein follow-on formulae, are listed in Table 1.

Nutritional Adequacy of Soy Protein Formulae

In the 1970s, Fomon et al. (21) studied infants fed, as desired, an infant formula based on methionine supplemented soy protein isolate with a protein content of 1.64 g/100 kcal and an energy content of 67 kcal/100 mL. Infants were fed the formula exclusively for 28 days and thereafter combined with complementary feeding until the age of 112 days. The infants had a similar growth pattern and similar normal markers of plasma protein metabolism as breast-fed infants. However, energy intakes were slightly higher than in infants fed a cows' milk formula with a protein content of 1.77 g/100 kcal. In a study designed to estimate the requirement of sulfur amino acids of infants up to the age of 112 days, a beneficial effect of L-methionine supplementation (7.5 mg/100 kcal) on nitrogen balance was only seen with a concomitant soy protein content of 1.8 g/100 kcal. A beneficial effect of methionine supplementation on weight gain or serum concentrations of urea nitrogen and albumin was only demonstrated at soy protein concentrations of 2.2 and 2.6 g/100 kcal, respectively (22).

Fomon et al. and other investigators demonstrated that infants exclusively fed methionine-supplemented soy protein formulae during the first 4 to 12 months of life showed weight gain and linear growth similar to that of infants fed conventional cows' milk protein formulae

TABLE 1. *Compositional criteria of soy protein isolate infant and follow-on formulae, alone or mixed with cows' milk protein, according to the Commission Directive 91/321/EEC of May 14, 1991 on infant formulae and follow-on formulae (19)*

	Soy protein infant formulae		Soy protein follow-on formulae	
	Minimum (/100 kcal)	Maximum (/100 kcal)	Minimum (/100kcal)	Maximum (/100 kcal)
Protein (g)*	2.25	3.0	2.25	4.5
Methionine (mg)	29	–	29	–
L-carnitine (μmoles)	7.5	–	–	–
Lactose (g)†	3.5	–	1.8	–
Iron (mg)	1	2	1	2
Zinc (mg)	0.75	2.4	0.75	–

*Soy protein isolate has to have a minimal chemical index of at least 80% in comparison with human milk protein for infant formulae and in comparison with human milk or casein for follow-on formulae.

†There is no minimal content for lactose when soy protein represents more than 50% of total protein.

(23,24). Studies were generally less than 1 year in duration, with exclusive soy protein formula feeding from birth to 4 months. Blood markers of protein metabolism in children fed soy protein formulae were not significantly different from those of infants fed cows' milk formulae. Healthy term infants fed a soy protein formula during their first year of life achieved a bone density similar to breast-fed or cows' milk formula fed infants (25,26). Outcome parameters included serum calcium, magnesium, phosphorus, alkaline phosphatase, parathyroid and 1,25-dihydroxyvitamin D concentrations, and bone mineral content measured with absorptiometry. These data indicate that soy protein formulae can be used for feeding term infants but have no nutritional advantage over cows' milk protein formulae.

In a randomized, controlled study performed in very low birthweight infants from 3 to 8 weeks of age, Hall et al. (27) compared a soy protein infant formula supplemented with calcium, phosphorus, and vitamin D (n = 17) with a whey-predominant premature infant formula (n = 15). Birth weight (1,206 ± 178 g) and gestational age (30 ± 1.9 weeks) of the soy formula-fed group were not significantly different from the whey formula-fed group (1,143 ± 158 g and 30 ± 1.8 weeks, respectively). The energy content of the whey formula was higher than that of the soy formula (81 kcal/100 mL vs. 67 kcal/100 mL), whereas the protein/energy ratio was identical in both formulae (3 g/100 kcal). The caloric (kcal/kg/day) and protein (g/kg/day) intake was not significantly different between each group because a greater volume of feed was consumed in the soy formula-fed infants. Those fed soy formula had lower weight gain (11.3 ± 2.3 g/kg/day) than infants fed whey-predominant formula (15.3 ± 2.5 g/kg/day) as well as lower protein and albumin blood concentrations. Bone mineralization pattern was the same in both groups. Although no more information is available in this population, the Committee concludes that soy protein formulae should not be used in preterm infants.

Phytate

Soy protein isolate contains some 1% to 2% phytate, which may impair the absorption of minerals and trace elements. In experimental animals and in human adults, phytate has a negative effect on intestinal zinc and iron absorption (28). A reduction in phytate contents of soy protein formulae can be achieved by precipitation methods or treatment with phytase. Reduction of the phytate content of soy formula increased the absorption and availability of zinc and copper in infant rhesus monkeys and rat pups and of iron in infants (29,30). Using stable isotope techniques in infants fed a soy protein isolate formula with low contents of phytate (<6 mg/kg liquid formula) or a conventional content (300 mg/kg liquid formula), Davidsson et al. (31) showed that zinc absorption was significantly greater with dephytinized formula (22.6% vs. 16.7%, $P = 0.03$), whereas no significant difference was observed for calcium, iron, copper, and manganese absorption.

Phytate may also interfere with iodine metabolism. Before the supplementation of soy formulae with iodine and the use of isolated soy protein instead of high-fiber soy flour in the mid-1960s, cases of goiter and hypothyroidism were described in infants fed soy formulae (32,33). The persistence of thyroid insufficiency despite the use of a high dose of levothyroxine has also been observed more recently in infants with congenital hypothyroidism fed soy protein formulae (34,35). A recent study showed that infants with congenital hypothyroidism fed soy protein formulae had a prolonged increase of thyroid stimulating hormone (TSH) when compared with infants fed nonsoy formulae. These infants need close monitoring of free thyroxine and TSH measurements and may need increased levothyroxine doses to achieve normal thyroid function (36). The mechanism of the prolonged increase in TSH blood concentrations is not clear. Malabsorption and increased fecal loss of the supplemented levothyroxine have been shown in animal studies performed before the use of isolated soy protein. Soy protein may also act as a goitrogen. A glycopeptide isolated from soy that blocks iodine uptake and decreases its organification has been described.

Information on the phytate contents of soy protein formulae used in Europe is not publically available. Such information should be disclosed by manufacturers. In view of the considerations discussed above, the Committee strongly recommends that phytate contents in soy protein infant formulae should be effectively reduced, for example, by precipitation methods or phytase treatment.

Nucleotides

The nucleotide content of soy protein formulae is much higher (approximately 310 mg/L) than that of human milk (68–72 mg/L) or cows' milk infant formulae (8–72 mg/L) (37). The Commission Directive 1991/321/EEC has approved the addition of nucleotides to infant and follow-on formulae with a total concentration of up to 5 mg/100 kcal, which is similar to reported data for free ribonucleotides in human milk (approximately 4–6 mg/100 kcal) (19). Because there is no adequate scientific basis at present to conclude that the addition of nucleotides in higher concentrations would provide additional benefits, the Committee discourages the further addition of nucleotides to formulae based on soy protein isolates given their high natural contents.

Aluminum

In 1996, the Committee on Nutrition of the American Academy of Pediatrics (AAP) highlighted the potential risk of aluminum toxicity in infants and children related to the use of soy protein formula contaminated with

aluminum (38). The source of the aluminum is thought to be the aluminum equipment used during the production of soy protein isolates and the nature of mineral salts used in formula production (3). Much higher concentrations of aluminum were found in soy protein formulae (500–2,400 μg/L) than in cow's milk protein formulae (15–400 μg/L) and breast milk (4–65 μg/L). However, daily aluminum intake remained less than 1 mg/kg, which the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives in 1989 considered as the tolerable intake of aluminum (39). Infants fed formulae with the highest contents of aluminum (2.35 mg/L) at the time of the publication would receive an aluminum dose less than 0.5 mg/kg per day at feed intakes up to 200 mL/kg per day. There is inadequate information on the aluminum content of soy protein formulae. Such information should be made available by manufacturers. Although long-term consequences of higher levels of aluminum observed in soy formulae are unknown, continued efforts should be made by manufacturers to reduce the aluminum content of soy protein formula.

Phytoestrogens

Phytoestrogens represent a broad group of plant-derived compounds of nonsteroidal structure that are ubiquitous within the plant kingdom and have weak estrogen activity (9,40). They are present in beans in general and soybeans in particular. Lignanes and isoflavones are the major classes of phytoestrogens of interest from a nutritional and health perspective. The main compounds contained in soy protein-based foods are the isoflavones genistein and daidzein (41). Isoflavones can bind to estrogen receptors, interact with enzyme systems influencing estrogenic activity, and exert weak estrogenic activity (42). It has been suggested that isoflavones may have anticancer properties in animals (43,44) and in human adults (45,46). Isoflavones may contribute to the prevention of cardiovascular disease, breast cancer, osteoporosis, and menopausal disorders (47), and they have been proposed to slow progression of renal disease in adults (48).

Infant formulae based on soy protein isolates contain relatively high concentrations of isoflavones (49). Isoflavone content found in soy formulae commercially available in the United States, United Kingdom, New Zealand, and France ranges from 17.5 to 47 μg/mL and from 123 to 281 μg/g of milk powder, with a higher proportion of genistein than of daidzein (8,50–53). Concentrations of isoflavones were much lower in cows' milk and breast milk samples, ranging from 0.1 to 5 μg/L in cows' milk (54) and from 1.6 to 13.6 μg/L (U.S.) and from 0 to 32 μg/kg (U.K.) in breast milk, respectively (8,41). Isoflavone content of breast milk varies with mother's diet. Setchell et al. (41) estimated that infants aged 1 to 4 months would receive 6 to 12 mg/kg bodyweight per day of total isoflavones, whereas an adult consuming 57 to 85 g of soy-based products may receive 50 to 100 mg of total isoflavones (i.e., 0.7 to 1.4 mg/kg/d).

Glycosidic conjugates of isoflavones present in soy protein formulae are hydrolyzed by intestinal glucosidases to their aglucon form, then are absorbed, metabolized in the liver to glucuronide and sulphate conjugates, and subsequently excreted in urine. Short-term studies have shown that no more than 30% of the ingested dose of isoflavones are recovered in urine and feces (41). Knowledge on the bioavailability of isoflavones is still incomplete in young infants (41,52). In 4-month-old infants exclusively fed soy protein isolate formula, Setchell et al. found plasma total isoflavone concentrations ranging from 552 to 1,775 μg/L, with a mean concentration of 980 μg/L. Mean (SD) plasma concentration was 684 (443) μg/L for genistein and 295 (60) μg/L for daidzein. These values were significantly higher ($P < 0.001$) than the mean values for plasma total isoflavone concentrations in infants fed either cows' milk formula (9.4 ± 1.2 μg/L) or breast milk (4.7 ± 1.3 μg/L) (41,50). On a molar basis, isoflavones demonstrated weak estrogenic activity relative to physiologic estrogens, possessing between 1×10^{-4} and 1×10^{-3} of the activity of 17 β-estradiol (55).

Phytoestrogens given at the high dosage contained in soy-based formulae adversely affected development and neuroendocrine function in different animal species (7,41,56). Isoflavones were found to cause infertility in sheep, known as "clover disease" (57). In utero exposure of rats to high doses of genistein impairs the pituitary secretion of luteinizing hormone (58).

It has been hypothesized that phytoestrogens have the potential to increase thyroid binding globulin (8). Any such increase could transiently increase the binding capacity for thyroxine, thus lowering free thyroxine concentrations. However, there are no data to suggest that phytoestrogens acting by this mechanism produce clinical effects. A retrospective telephone recall epidemiologic study found that children with autoimmune thyroid disease were significantly more likely to have been fed soy formula in infancy (31% vs. 13% in infants without autoimmune thyroid disease) (59). There was no group difference in the frequency and duration of breast feeding. The aglucons of genistein and daidzein were demonstrated to inhibit the activity of thyroid peroxidase purified from porcine thyroid glands when present at concentrations of 1 to 10 μM, resulting in iodinated isoflavone compounds. The presence of at least 150 μM of iodine per liter in the incubation mixture completely protected against the isoflavone-mediated thyroid peroxidase inactivation (60).

Few data are available on the potential consequences of exposure to high doses of phytoestrogens in human infants on the later sexual and reproductive development. A three-fold increase in the number of patients with premature thelarche seen between 1978 and 1981 in Puerto

Rico led to further investigation in a case-control study (61). Onset of thelarche before 2 years of age was significantly associated with consumption of soy protein isolate based infant formula and of various meats. However, less than 20% of cases were soy formula fed, which points to the importance of additional causative factors.

Strom et al. (62) conducted telephone interviews in 811 adults aged 20 to 34 years who had participated as infants during the years 1965 to 1978 in comparative but not randomized feeding trials with soy protein based infant formula (n = 248; 120 males) or cows' milk protein formula (n = 563; 295 males). Outcome measures were self-reported: pubertal maturation, menstrual and reproductive history, height, weight, and education levels. The study did not include any direct measurements of hormone levels. Females previously fed on soy formulae had a lower prevalence of sedentary activities (8.9 ± 3.4 hours/wk vs. 9.6 ± 3.5 hours/wk, $P = 0.05$), whereas there was no difference for males. No statistically significant differences were observed between groups in either men or women for adult height, weight, pubertal development, and incidence of thyroid disease. Women fed soy formula in infancy experienced a slightly but significantly longer duration of menstrual bleeding (by 0.37 days; 95% confidence interval [CI]: 0.06–0.68), with no difference in self-assessed intensity of menstrual flow. They also reported greater discomfort with menstruation (unadjusted relative risk for extreme discomfort vs no or mild pain, 1.77; 95% CI, 1.04–3.00). Pregnancies were reported by 42% of women fed soy-formulae and 48% of women fed cows' milk formulae (NS). Outcomes of pregnancies were not different, and neither were there differences between the groups in the prevalence of cancer, hormonal disorders, sexual orientation, or birth defects in the offspring. No conclusions can be drawn on possible effects on fertility in men previously exposed to soy-based formulae, considering their relatively young age at the time of the follow-up study. Although exposure to soy formulae in this study did not appear to be responsible for major health or reproductive problems, more information is needed on potential long-term effects of phytoestrogens.

Yellayi et al. (56) showed that subcutaneous genistein injections in ovariectomized adult mice produced dose responsive decreases in thymic weight of up to 80%. Genistein injection caused decreases in relative percentages of thymic CD4+CD8− and double positive CD4+CD8+ thymocytes, providing evidence that genistein may affect early thymocyte maturation and the maturation of CD4+CD8− helper T-cell lineage. Dietary genistein at concentrations that produced serum genistein levels substantially less than those found in soy protein formula-fed infants produced marked thymic atrophy.

In infants fed soy protein formula from birth to 4 months, Ostrom et al. and Cordle et al. (63,64) did not find differences compared with a control group that was breastfed for 2 months or more at 6 and 12 months of age for the level of immunoglobulins (Ig)G and A, the titre of antibodies against diphtheria, tetanus, poliovirus, and *Hemophilus influenzae* b, as well as the count of lymphocytes B, T, and NK. The only significant difference was the higher percentage of $CD57^+$ NK cells in the control group at 12 months.

Information on the phytoestrogen content of soy protein formulae should be made available by manufacturers. Although studies in humans are lacking, on the basis of available data in animal models, the Committee recommends that the content of phytoestrogens in soy protein formulae be reduced because of uncertainties regarding safety in infants and young children.

COMMENTS ON POSSIBLE INDICATIONS FOR SOY FORMULAE

Severe persistent lactose intolerance and galactosemia

Severe persistent lactose intolerance, including severe mucosal damage and the rare cases of hereditary lactase deficiency (McKusick 223000) and classic galactosemia (galactose-1-phosphate uridyltransferase deficiency) (McKusick 230400), are indications for the use of lactose free soy formulae (65). It should be noted that some soy protein formulae contain raffinose and stachyose that are cleaved in the digestive tract under the action of bacterial galactosidases, leading to the liberation of 1,4 galactose that may contribute to elevated galactose-1-P values in erythrocytes of galactosemic patients (66).

Acute gastroenteritis

A meta-analysis of clinical trials on the use of formulae in the management of acute gastroenteritis concluded that lactose-containing diets do not need to be withdrawn in the vast majority of cases, whereas lactose free diets were beneficial in a limited number of cases with severe dehydration (67). An ESPGHAN multicentric study has shown that the early use of lactose containing cows' milk formula after oral rehydration does not aggravate or prolong diarrhea in well-nourished infants presenting with acute gastroenteritis and mild to moderate dehydration and has the advantage of preventing malnutrition (68). Therefore, switching from lactose-containing formula to lactose free formula such as soy formulae is not routinely recommended in acute gastroenteritis (10). Moreover, there are theoretical concerns regarding the introduction of a new protein source in the presence of increased mucosal permeability, with a potential increased risk of allergic sensitization (69,70).

Cows' milk allergy

Before the availability of therapeutic formulae based on cows' milk protein hydrolysates, soy formula was the only dietetic product available for feeding infants with cows' milk protein allergy. However, soy protein is also a common allergen. The identification and characterization of soybean allergens have identified fractions containing conglycinin (molecular weight 180,000 d) and glycinin (molecular weight 320,000 d) as probably the major allergens and trypsin inhibitor as the minor allergen responsible for soy protein allergy (71). Patients with soy protein allergy present with either acute symptoms within a few hours after soy ingestion (i.e., urticaria, angioedema, vomiting, diarrhea, or anaphylactic shock) or with chronic symptoms (i.e. chronic diarrhea and failure to thrive, malabsorption, and villous atrophy) (72,73). Symptoms usually resolve after elimination of soy from the diet.

Among infants with cows' milk allergy fed soy protein based formulae, some 30% to 50% were reported to present with concomitant soy protein allergy, with a higher frequency reported in nonIgE-mediated enterocolitis-enteropathy syndrome (71,74–76). A review of 2,108 infants with cows' milk protein allergy followed at 33 Italian pediatric gastroenterology units reported that 50% of these infants had received soy protein-based formulae as the substitute for milk containing formulae. Soy protein formulae were discontinued in 47% of cases overall, ranging from 53% of infants younger than 3 months of age to 35% of children older than 1 year of age (4). The reasons for this discontinuation were not given in the publication.

In 1983, the AAP Committee on Nutrition discouraged the use of soy formulae in the dietary management of infants with documented allergy to cows' milk protein (77). The AAP Nutrition Committee concluded in 1998 that infants with documented cows' milk protein-induced enteropathy or enterocolitis are frequently sensitive to soy protein and should not be given soy protein formula routinely, whereas it emphasized that most infants with documented IgE-mediated cows' milk protein allergy will do well when fed soy formula (3). In 1990, the ESPGHAN Committee on Nutrition considered that available data did not support the view that soy formula should be the preferred choice in case of suspected or proven adverse effects to cows' milk protein (16). A joint statement of the ESPGHAN Committee on Nutrition and the European Society for Pediatric Allergology and Clinical Immunology stipulated that, in general, formulae based on intact soy protein isolates are not recommended for the initial treatment of food allergy in infants, although a proportion of infants with cows' milk protein allergy tolerate soy formula (11). The AAP Nutrition Committee stated in 2000 that infants with IgE-associated symptoms of allergy may benefit from a soy formula, either as the initial treatment or instituted after 6 months of age after use of a therapeutic hydrolysate formula (12).

The exclusion of soy protein from the diet of infants with IgE-mediated cows' milk protein allergy has been a controversial issue for a long time. In 93 children aged 3 to 41 months with IgE-mediated cows' milk protein allergy, Zeiger et al. (78) found a prevalence of concomitant soy allergy of only 14% (Table 2); 3% of the cohort were under 6 months of age at the time of evaluation and challenge. Diagnosis of soy protein allergy in this study was assessed by double-blind, placebo-controlled food challenge response to soy, open challenge response under the direction of a physician, or history of more than one immediate anaphylactic reaction to an isolated ingestion of soy. These investigators regard soy formula as a safe alternative to cows' milk formula for the vast majority of children with IgE-mediated cows' milk allergy, particularly those shown to have negative responses to soy challenge at the time of introduction of soy formula (78).

Klemola et al. (79) recently reported that the presence of concomitant soy allergy in infants with cows' milk allergy is less frequent than previously thought (Table 2). They conducted a prospective, randomized study to evaluate the cumulative incidence of allergy or other adverse reactions to soy formula compared with extensively hydrolyzed formula up to the age of 2 years in infants with

TABLE 2. *Studies on prevalence of soy allergy in immunoglobulin (Ig)E-associated cows' milk allergy (CMA) (78) and incidence of allergy to soy formula (SF) and extensively hydrolyzed formula (EHF) in cow's milk allergy (79)*

Reference	Study design	Allocation concealment	Blinding	Intention-to-treat analysis	Completeness to follow-up	Participants
Klemola et al., 2002 (79)	RCT	No	Single-blinded	Yes	Yes	n = 170 (with CMA confirmed by DBPCFC or history of an anaphylactic reaction)
Zeiger et al., 1999 (78)	Cohort study	NA	NA	NA	NA	n = 93, with IgE-mediated CMA

DBPCFC, double-blind, placebo-controlled food challenge; NA, not applicable RCT, randomized clinical trial; RR, relative risk; CI, confidence interval.

confirmed cows' milk allergy. The parents suspected adverse reactions significantly more often in infants randomly assigned to the soy formula than in infants randomly assigned to the extensively hydrolyzed formula (28%; 95% CI 18–39% vs. 11%; 95% CI 5–19%, respectively; relative risk [RR], 2.48; $P = 0.006$). Physicians diagnosed adverse reactions more often with soy than with the extensively hydrolyzed formula (10%; 95% CI 4.4%–18.8% vs. 2.2%; 95% CI 0.3%–7.8%, respectively; RR, 4.50; $P = 0.031$). Adverse reactions to soy were similar in IgE-associated and nonIgE-associated cow's milk allergy (11% and 9%, respectively). Adverse reactions were more common in younger (<6 months) than in older (6 to 12 months) infants (5 of 20 vs. 3 of 60, respectively, $P = 0.01$).

The use of soy formulae may play a role in the etiology of peanut allergy. Evaluating data from the Avon longitudinal study, a geographic-defined cohort study of 13,971 preschool children, Lack et al. (80) showed that peanut allergy was independently associated with intake of soy milk or soy infant formula during the first 2 years of life (odds ratio 2.6; 95% CI 1.4–5.0), suggesting the possibility of cross-sensitization through common epitopes. Soy protein fractions have been shown to be homologous to major peanut proteins (81). It is likely that children with allergy to cows' milk are at increased risk for food allergies, and soy consumption in infancy is increased in response to these atopic disorders. Indeed, a history of allergy to cows' milk (reported prospectively at 6 months) was significantly associated with peanut allergy ($P = 0.03$). In their study assessing the long-term effects of soy protein formulae, Strom et al. (62) showed that, as adults, females who had received soy formula in infancy more frequently used antiallergic and antiasthmatic drugs (18.8% vs. 10.1%, $P = 0.047$), whereas males showed a similar but nonsignificant trend (15.8% vs. 10.2%, $P = 0.08$).

The Committee concludes that for treatment of cows' milk protein allergy, the use of therapeutic formulae based on extensively hydrolyzed proteins (or amino acid preparations if hydrolysates are not tolerated) should be preferred to that of soy protein formulae. Given the limited number of infants studied (78,79) and the higher reported rate of adverse reactions to soy protein in infants under 6 months of age (79), the Committee recommends that soy protein formulae should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are used for therapeutic use after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.

Prevention of Atopic Disease

The role of soy protein formulae for the prevention of allergic disease in healthy and at-risk infants has been controversial (76,82) and is not supported by evidence from controlled trials (83–87). A recent meta-analysis of five randomized and quasi-randomized clinical trials with appropriate methodology concluded that soy formulae do not prevent food allergy in high-risk infants (13). The joint statement of the European Society for Paediatric Allergology and Clinical Immunology Committee on Hypoallergenic Formulas and the ESPGHAN Committee on Nutrition did not support the use of soy protein formulae for the prevention of allergy in at-risk infants (11).

Infantile Colic and Regurgitation

Soy protein formulae have been widely used in the industrialized countries for symptoms such as infantile colic, regurgitation, or prolonged crying without any convincing evidence for efficacy (23). Controversial data on the use of soy formulae have been obtained in infants with severe infantile colic attributed to cows' milk protein allergy (88,89). One randomized clinical trial showed a mean weekly duration of colic symptoms of 8.7 hours during treatment with soy formula, as compared with 18.8 hours during the control periods (mean difference = 10.1; 95% CI 3.8–16.5) (90). If persisting colic is defined as weeks in which there were 9 or more hours of colic symptoms, then colic persisted in only 31.6% of infants during the soy formula periods as opposed to 94.7% during the control periods (RR 0.33; 95% CI 0.017–0.65). The other randomized clinical trial of soy protein formulae did not allow firm conclusions to be drawn because of methodologic drawbacks (91). The meta-analysis of Lucassen et al. (92) collected 27

TABLE 2. *(continued).*

Age (mo)	Intervention group	Control group	Outcomes	Results	RR (95% CI)
2–11	SF (n = 80)	EHF (n = 90)	Parents suspected adverse reaction to the study formula	SF vs. EHF: 28% (95% CI 18–39) vs. 11% (95% CI 5–19)	2.5 (CI not given)
			DBPCFC confirmed adverse reaction to the study formula	SF vs. EHF: 10%; (95% CI 4.4–18.8) vs. 2.2%; (95% 0.3–7.8)	4.5 (1.1–18.4)
3–41	NA	NA	Soy allergy	14% (95% CI 7.7–22.7)	

controlled trials on the effectiveness of diets, drug treatment, and behavioral interventions on infantile colic. Soy protein formulae were not effective when only trials of good methodologic quality were considered.

Ethical and Religious Considerations

Some parents (e.g., vegans) seek to avoid cows' milk based formulae for their infants for religious, philosophical, or ethical reasons. Soy protein infant formulae is an acceptable alternative for these families.

CONCLUSIONS

1. Cows' milk-based formulae should be preferred as the first choice for feeding healthy infants that are not fully breast fed.
2. Soy protein based formulae should only be used in specified circumstances because they may have nutritional disadvantages and contain high concentrations of phytate, aluminum, and phytooestrogens, the long-term effects of which are unknown.
3. Indications for soy formulae include severe persistent lactose intolerance, galactosemia, religious, ethical, or other considerations that stipulate the avoidance of cows' milk based formulae and treatment of some cases of cows' milk protein allergy.
4. The Committee recommends that the use of therapeutic formulae based on extensively hydrolyzed proteins (or amino acid preparations if hydrolysates are not tolerated) should be preferred to that of soy protein formula in the treatment of cows' milk protein allergy. Soy protein formula should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are considered for therapeutic use after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.
5. Soy protein formulae have no role in the prevention of allergic diseases.
6. There is no evidence supporting the use of soy protein formulae for the prevention or management of infantile colic, regurgitation, or prolonged crying.
7. Manufacturers should aim to reduce the concentrations of trypsin inhibitors, lectins, goitrogenic substances, phytate, aluminum, and phytoestrogens in soy protein formulae.

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