

Soy and other protein sources

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Cow's milk allergy affects 2.2–2.8% children, mainly in their first year (1, 2). In view of the particular nutritional needs of the infants in their first year of life, if they cannot be breast fed they should be provided with a substitute of cow's milk protein formula. Ideally, this substitute should have all the characteristics of maternal breast milk: it should be of adequate nutritional value, have a pleasant taste and be hypoallergenic, hypoonimmunogenic and inexpensive. At present, the hypoallergenic casein or whey protein formulas derived from extensive cow milk protein hydrolysis are preferred. However, they have some disadvantages, such as a bitter taste and a high cost. Moreover, they carry a risk of cross-reactions that can occur in highly sensitive patients due to residual peptides (3–5).

In clinical practice, alternative protein sources from vegetable proteins such as soy, animal proteins, milk from different mammalian species or amino acid mixtures are employed. The safe use of these substitutes in infants who are allergic to cow's milk should comply with the criteria used for hypoallergenic formulas: they should be tolerated by 90% of infants who are allergic to cow's milk, with a 95% confidence limit (6).

Vegetable proteins: soy

The main source of vegetable proteins is soy, which belongs to the leguminous family and is widely used in the East, also to feed infants. Although soy milk was first proposed as a substitute for cow's milk in 1909, soy formula

was not used until 1929 (7, 8). The main economic and nutritional advantage of the soy bean depends upon its rich content of protein (40%) and fat (20%). Several commercial formulas (first generation) became available. They were based on fat-free soy flour which, however, has drawbacks. It has an unpleasant caramel-like colour and nutty taste, and causes carbohydrate intolerance with flatulence and foul-smelling stools from indigestible carbohydrates, such as stachyose, vitamin (A, K and B₁₂) and mineral deficiencies (calcium, zinc). It, moreover, has a high content of goitrogens and trypsin inhibitors.

Nutritional adequacy

A second-generation soybean formula developed in the 1960s was based on a soy protein isolate of at least 90% protein. The biological quality of soy protein isolates ranges from 65% to 85% that of casein and the protein level of soy formula is somewhat higher than that of cow's milk formula, at 19–22 g/l. The addition of L-methionine, however, improves the quality of the protein, making it comparable to that of casein, thus lowering the protein content of soy formulas. Infants fed on soy-fortified methionine formulas with a protein level of 15–16 g/l have been found to have a nitrogen balance and plasma amino acid concentrations closer to those of breast-fed infants (9). The soy isolate was also supplemented with L-carnitine and taurine to provide a protein content of 2.45–3.1 g/100 Kcal or 1.65–2.1 g/100 Kcal. The fat contained in soy

formulas is a mixture of vegetable oil, and the carbohydrates contained consist of maltodextrins, corn starch or sucrose. The presence of two different carbohydrates, sucrose and corn syrup hydrolysates confer the advantage of optimising carbohydrate digestion and absorption as well as calcium absorption. All soy protein formulas are lactose free (9). However, the presence of phytic acid in soy and vegetable protein sources initially gave rise to concern regarding the nutritional bioavailability and plasma concentration of minerals such as zinc, iron, calcium, magnesium and copper.

Phytic acid contains six negatively charged groups able to bind strongly with divalent cations. Human beings can neither absorb nor digest phytate because of the absence of the enzyme phytase in their digestive tract. Thanks to a process used to remove phytate by precipitation or enzymatic methods, it is now possible to manufacture low phytate soy formulas for which zinc and calcium absorption is similar to that occurring with cow's milk formula. To ensure calcium requirement an intake of soy formula greater than 500 ml/day should be provided (11).

As soy formulas contain 40–80 times more iron than breast milk they incur no risk of iron deficiency, irrespective of the low bioavailability of iron from soy protein. Moreover, infants fed on soy formulas have copper serum levels within the normal range. In fact, several clinical studies on the nutritional features of soy formulas given to full-term infants have shown normal growth, adequate protein nutritional status and normal bone mineralisation (9–12). Furthermore, no immunological abnormality or increase in infection morbidity was found in infants fed exclusively on soy formulas for 6 months, as reported previously (13, 25).

Some problems have been yet to be solved: first, the effect of the high concentration of aluminium in soy formulas derived from the mineral salts used in producing the formula. The only study that, to our knowledge, has been performed to investigate this aspect, failed to show alterations in plasma aluminium concentrations in soy formula-fed infants compared to breast-fed infants at 3 months of life. The toxicity of aluminium, however, is higher in infants with a reduced renal function as occurs in preterm infants and in children with chronic renal failure (14, 15).

Not much is known concerning the toxicity of high levels of manganese: 200–300 mcg compared with 50–100 mcg in cow's milk and 3–8 mcg in human breast milk. In particular, an evaluation should be made of any long-term effects it may

have on the central nervous system later in life, affecting for example behavioural or learning abilities (9). Last, but not least, a more careful evaluation should be made of the role of physiologically active substances such as phyto-oestrogens (isoflavones) (16, 17).

To our knowledge, there is no controlled study in literature addressing the long-term effects of early exposure to the high content of phyto-oestrogens in soy formula-fed infants. Moreover, soy-based formulas do not contain long chain polyunsaturated fatty acids and nucleotides. However, although commercially available soy formulas are generally nutritionally adequate, they should not be used in preterm infants and further efforts should be made to make them more similar to breast milk and also to establish the clinical importance of the different components present in vegetable protein sources. Finally, nutritional deficiencies may arise from the use of soy-based milks bought in health food stores because they are not checked for their composition of calcium, vitamins and energy. They are therefore unsuitable for children.

Allergenicity and antigenicity

Soy protein is immunogenic and allergenic, but not to the same extent as cow's milk (18). In experimental studies, in a passive cutaneous anaphylaxis animal model, soy proteins appear to be less sensitising than cow's milk proteins (19), and nor is a fatal anaphylactic reaction found to be triggered by soy protein in animals sensitised to soy proteins. On the other hand, anaphylaxis is triggered by cow's milk protein in all animals sensitised to cow's milk (20).

The main soy allergens consist of 7S and 11S globulinic fractions containing conglycinin and glycinin. The IgE binding epitope on a seed vacuole protein (P34) identified as Glyn Bd 30 KD is a major soybean allergen in children with soy allergy. The trypsin inhibitor, 80–90% of which is removed by the heat applied to prepare the formula, is a minor allergen (21).

Eastham studied extensively the antigenicity of soy formulas. In one of his studies, involving 25 infants fed on casein hydrolysate, cow's milk formulas or soy formulas, circulating antibodies developed in all infants with an initial rapid increase at 3 months, with a slight, or no, further increase thereafter (22). The author therefore concluded that soy-based formulas were at least as antigenic as cow's milk formulas. Nevertheless, in another of his studies, feeding rabbits with soy formulas led

to a more profound and complete low zone tolerance than feeding with cow's milk (23). Tolerance was found to develop at "fairly critical" small doses (i.e. low zone) in healthy intestinal mucosa. However, it is observed that in cases of cow's milk enteropathy or following gastro-enteritis mucosal permeability is increased, due to tissue damage, and the author suggests that an amount of antigen in excess of that required to maintain tolerance may reach the Peyer patches.

Epidemiology and clinical picture

The above findings may explain the variations in the allergenic features of soy described in different clinical studies. There are differences in methodology for patient selection, diagnostic criteria and duration of clinical trials, some of which are retrospective and others prospective. Moreover, most studies fail to perform double-blind placebo-controlled food challenges, and this could contribute greatly to the discrepancies between prevalence of soy allergy reported so far (24, 25).

A low prevalence (1.1%) of soy allergy evaluated on the basis of the outcome of oral challenges was reported recently in atopic children (26) and (0.3%) in a population-based study by Young et al. in the United Kingdom (27). In a selected population of children with food allergy and atopic dermatitis the prevalence was 4–5% (28, 29) and up to 7% in children with cow's milk allergy (30).

More recently, in a cohort of 93 infants and toddlers with IgE associated cow's milk allergy documented by double-blind placebo-controlled food challenge or with a convincing history of anaphylaxis to cow's milk, Zeiger et al. found that concomitant soy allergy occurred in 14% of cases, and concluded that a small minority of children with IgE-mediated cow's milk allergy can also have soy allergy (31).

Higher frequencies (30–50%) for soy reactions are reported in cases of non-IgE-mediated enterocolitis and of enteropathy syndromes (31, 32). Soy protein can, in fact, induce enteropathy in young children with villous atrophy similar to that caused by cow's milk protein intolerance (32, 33). The clinical manifestations of soy allergy range from local symptoms (cutaneous and/or gastrointestinal) to systemic reactions. However, anaphylaxis is rarely described, only two cases being reported in the literature (34, 35). The recently reported cases of a peanut co-allergy incurring anaphylactic reactions calls for caution, and further confirmation is required (36). Despite

the homology of the protein sequences in peanuts and soybeans (37), clinical studies conducted so far have shown that peanut allergic patients could safely eat other legumes and that very few patients who were highly sensitive to peanuts had any reactions to soy. If they did have a reaction, it was usually extremely mild.

The natural history of soy allergy is also in contrast with any finding of a peanut co-allergy and mainly of anaphylactic reactions. The great majority of patients with a soy allergy, unlike those with a peanut allergy, achieve tolerance at the age of 3 (1, 38), or 2 years after a positive oral challenge (39).

Diagnosis of soy allergy

The identification of *in vivo* and *in vitro* specific IgE antibodies for soy is not a reliable indicator of clinical reactivity (40). In a cohort of 93 cow's milk allergic patients, the skin prick test revealed a sensitivity of 69.2%, a specificity of 83.3%, a positive predictive capacity of 40.9% and a negative predictive capacity of 94.2% (31).

Furthermore, in one study aimed finding whether there is a correlation between food specific IgE concentrations and the risk of a positive challenge, the specificity of soy-specific IgE determined by RASTCAP-FEIA was too low, and never attained a predictive value of 90%: it was 50% at 65 KU_A/l (31), nor is IgE specific for soy detectable in non-IgE-mediated enteropathies. The challenge test is therefore indispensable for a diagnosis of soy allergy (31, 40).

Prevention of atopy

Randomised prospective studies on infants fed with soy formulas, especially those from atopic families, showed that soy protein had no greater preventive effect against the development of atopy in infancy than cow's milk formulas (41–43), consistent with its immunogenic and allergenic features (22). Nevertheless, in none of these studies were the soy allergy referred symptoms confirmed by double-blind placebo-controlled food challenge (24).

A controlled prospective cohort study on high-risk newborns randomised and masked to soy or cow's milk with a challenge-confirmed diagnosis is therefore required to clarify this issue, also in view of the changing figures on the prevalence of soy allergy in food allergic children (31).

Proteins from animal sources

Milks from different mammalian species have been proposed as an alternative substitute for cow's milk for cases in which soy or an extensively hydrolysed formula cannot be used, either because of allergic reactions or because of a refusal to drink them due to their unpleasant taste. Goat's milk (GM), marketed in many countries, is considered by the general public to be a safe alternative for children allergic to cow's milk (CM). However, some clinical studies have found a high cross-allergenicity between goat's milk proteins and cow's milk proteins. Studies using the ELISA and ELISA inhibiting assays in children with cow's milk allergy have shown that the alpha-casein proteins in cow, goat and sheep milks are highly cross-reactive (47). One recent study evaluated the allergenicity of goat's milk in children with cow's milk allergy by double-blind placebo-controlled food challenge and cross-inhibition immunoblotting with either CM or GM milk-derived proteins (48). At skin test, all the 26 cow's milk allergic children were positive for both CM and GM, and 24 of 26 were positive at double-blind placebo-controlled food challenge for GM.

The amount of GM eliciting a reaction after challenge was significantly greater than that for CM, thus confirming the finding of the lower concentration of cross-reacting allergens in GM determined by cross-inhibition immunoblotting. These data are consistent with findings made in a previous study on weaning rats, in which 100% of cow's milk sensitised rats reacted to GM (49). In their study on *in vitro* cross-reactivities between milk proteins from different animal species, Restani et al. (50) confirmed that the IgE antibodies of cow's milk allergic children can recognise milk proteins from other mammals (e.g. ewe, goat, buffalo). Interestingly, no reactivity to camel's milk was found, probably because of a lack of homologous epitopic areas.

These findings support the recommendation that goat's milk should not be given to children with cow's milk allergy, especially those with a high sensitivity, who are at a greater risk of anaphylactic reactions; they also provide some insight for further research on proteins from mammalian milks which, like camel milk, are phylogenetically different from cow's milk.

Mare's milk

Mare's milk, which is being increasingly prescribed as an "alternative" in the management of adverse reactions to foods, is characterised by its

low protein content (1.3 g–2.8 100 ml of cow's milk), richness in whey proteins (35–50%), pleasant taste due its high lactose content, a calcium/phosphorus ratio of 1.7, and an unsaturated:saturated fatty acids ratio of 1.32 (against 0.43 for cow's milk). Its composition is thus more similar to that of human milk than is cow's milk (51).

An Italian group (52) recently performed a controlled study on the tolerance of mare's milk in cow's milk allergic children. The authors selected a group of 17 children with high sensitivity to cow's milk proteins and found that only one of the 17 children reacted to the double-blind challenge with mare's milk. This child was also the only one found to be positive at the skin test with mare's milk. The finding made *in vivo* that 96% of children allergic to cow's milk tolerated mare's milk was confirmed by the IgE binding at the cross-inhibition immunoblotting. Moreover, Iacono et al. reported a highly satisfactory clinical response to ass milk in nine infants with severe gastrointestinal symptoms (53).

Equidae milk might therefore be modified for use as a safe and adequate substitute for cow's milk for the nutrition of cow's milk allergic human infants.

Elemental diet

Rarely, patients with severe IgE mediated cow's milk allergy or multiple food allergies and cow's milk enterocolitis syndrome react to extensively hydrolysed protein formulas. An elemental diet is therefore suggested for these patients. Mixtures of amino acids currently on the European market consist of nutritionally complete formulas, with carbohydrates (maltodextrins), fat (hybrid sunflower oil, soy oil and refined coconut oil), vitamins, minerals and trace elements.

In studies on an elemental infant formula using sensitive *in vitro* methods (ELISA-immunoblotting) no proteins were detected. The hypo-allergenicity of this formula has been confirmed by *in vivo* studies with DBPCFC and it was proposed as placebo in the oral challenge (54). Furthermore, breast-fed children with multiple food allergies have grown up on elemental formula after stopping breast feeding (55).

At present, because of their high cost (twofold that of an extensively hydrolysed protein formula) and low palatability, elemental formulas should be prescribed only to children with such a high sensitivity to cow's milk proteins that they are even allergic to the hydrolysate.

Conclusions

In the literature there is wide debate on the use and misuse of soy formulas (56). Attempts are now being made to formulate rational criteria for the selection of patients for whom soy formulas would be well tolerated and safe. This search should be facilitated by deeper insight that is now being gained on the features of soy allergenic epitopes, and by making a more reliable assessment of the prevalence of soy allergy both in general and selected populations of children with food allergy, and also by the finding that there is a close correlation between soy allergy and food-linked gastrointestinal disorders. The need for a modality to deal with this problem was pointed out in a recent position paper by the American Academy of Pediatrics. It was, in fact, suggested that "soy formulas although not hypoallergenic can be fed to infants with IgE-mediated cow's milk allergy, particularly after the age of 6 months. Soy formulas are not recommended for the treatment of infants with cow's milk non IgE-associated enterocolitis and enteropathies" (57). Furthermore, we are now able to identify the immunogenic profile of milks from mammals other than cows: this can be achieved by using *in vitro* (immunoblotting and cross-inhibition immunoblotting) as well as *in vivo* (skin test and double-blind placebo-controlled food challenge) methods. This step forward should enable us to select milks that do not share homologous epitopes with cow's milk proteins and consequently to identify the milk most suitable for each food-allergic infant.

Moreover, thanks to newly available technological processes, it might become possible to transform the milk-type chosen into a hypoallergenic formula, thus avoiding new sensitisations. It now therefore appears reasonable to assume that, in the near future, we will be able to tailor a cow's milk formula substitute for each child allergic to cow's milk.

References

1. HOST A, HALKEN S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990; 45: 587-96.
2. SCHRANDER JJP, VON DEN BOGARD JPH, FORGET PP, SCHRANDER-STUMPEL CTRM, KUIJTEN RH, KESTER ADM. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993; 152: 640-4.
3. BUSINCO L, CANTANI A, LONGHI MA, GIAMPIETRO PG. Anaphylactic reactions to a cow's milk whey protein hydrolysate (Alfa-Re, Nestlé) in infants with cow milk allergy. *Ann Allergy* 1989; 62: 333-5.
4. RUGO E, WAHL R, WAHN U. How allergenic are hypoallergenic infant formulae? *Clin Exp Allergy* 1992; 22: 635-9.
5. HILL DJ, CAMERON DJS, FRANCIS DEM, GONZALES-ANDAZA AM, HOSKING CS. Challenge confirmation of late onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance. *J Allergy Clin Immunol* 1995; 96: 386-94.
6. KLEINMAN RE, BAHNA S, POWELL GF, SAMPSON HA. Use of infant formulas in infants with cow milk allergy: a review and recommendations. *Pediatr Allergy Immunol* 1991; 2: 146-55.
7. RUHRAH J. The soybean in infant feeding. Preliminary report. *Arch Pediatr* 1909; 26: 496-501.
8. HILL L, STUART H. Soybean food preparation for feeding infants with milk idiosyncrasy. *JAMA* 1929; 93: 985-7.
9. LONNERDAL B. Nutritional aspects of soy formula. *Acta Pediatr* 1994; suppl. 402: 105-8.
10. KAY JL, DAESCHNER CW JR, DESMOND MM. Evaluation of infants fed soybean and evaporated milk formulae from birth to three months - a comparison of weight, length, hemoglobin, hematocrit and plasma biochemical values. *Am J Dis Child* 1960; 100: 264-76.
11. STEICHEN JJ, TSANG RC. Bone mineralization and growth in term infants fed soy-based or cow milk-based formula. *J Pediatr* 1987; 110: 687-92.
12. KOHLER L, MEEUWISSE G, MORTENSSON W. Food intake and growth of infants between six and twenty six weeks of age on breast milk, cow's milk formula or soy formula. *Acta Paediatr Scand* 1984; 73: 40-8.
13. ZOPPI G, GASPARI R, MANTOVANELLI F, et al. Diet and antibody response to vaccinations in healthy infancy. *Lancet* 1983; 2: 11-14.
14. LITOV RE, SICKLES VS, CHAN G. Metal plasma aluminum measurements in term infants fed human milk or a soy-based formula. *Pediatrics* 1989; 84: 1105-7.
15. KOO WK, KAPLAN LA. Aluminum and bone disorders with specific reference to aluminum contamination of infant nutrients. *J Am Coll Nutr* 1988; 7: 199-214.
16. SETCHELL KDW, ZIMMER-NECHEMIAS W, CAI J, HEUBI JE. Exposure of infants to phytoestrogens from soy-based infant formula. *Lancet* 1997; 350: 23-7.
17. LIENER IE. Implications of antinutritional components in soybean foods. *Crit Rev Food Sci Nutr* 1994; 34: 31-67.
18. MAY CD, REMIGIO L, BOCK SA. Usefulness of measurements of antibodies in serum in diagnosis of sensitivity to cow's milk and soy proteins. *Allergy* 1980; 35: 301-10.
19. McLAUGHLAN P, ANDERSON KJ, COOMBS RRA. An oral screening procedure to determine the sensitizing capacity of infant feeding formula. *Clin Allergy* 1981; 11: 311-18.
20. PIACENTINI GL, BENEDETTI M, SPEZIA E, BONER AL, BELLANTI JA. Anaphylactic sensitizing power of selected infant formulas. *Ann Allergy* 1991; 67: 400-2.
21. BURKS WA, JAMES RV, SAMPSON HA. Allergenicity of major component proteins of soybean determined by enzyme-linked immunosorbent assay (ELISA) and immunoblotting in children with atopic dermatitis and positive soy challenges. *J Allergy Clin Immunol* 1988; 81: 1135-42.
22. EASTHAM EJ, LICHAUCO T, GRADY MI, WALKER WA. Antigenicity of infants formulas: role of immature intestine on protein permeability. *J Pediatr* 1978; 93: 561-4.
23. EASTHAM EJ, LICHAUCO T, PANG K, WALKER WA. Antigenicity of infant formulas and the induction of systemic immunologic tolerance by oral feeding: cow's milk versus soy milk. *J Pediatr Gastroenterol Nutr* 1982; 1: 23-8.
24. CANTANI A, LUCENTI P. Natural history of soy allergy and/

- or intolerance in children and clinical use of soy protein formula. *Pediatr Allergy Immunol* 1997; 8: 59–74.
25. BUSINCO L, BRUNO G, GIAMPIETRO PG, CANTANI A. Allergenicity and nutritional adequacy of soy protein formulas. *J Pediatr* 1992; 121: S21–8.
 26. MAGNOLFI CF, ZANI G, LACAVA L, PATRIA MF, BARDARE M. Soy allergy in atopic children. *Ann Allergy Asthma Immunol* 1996; 77: 197–201.
 27. YOUNG E, STONEHAM MD, PETRUCKEVICH A, BARTON J, RONA R. A population study of food intolerance. *Lancet* 1994; 343: 1127–30.
 28. SAMPSON HA. The role of food hypersensitivity and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 1988; 81: 635–45.
 29. GIAMPIETRO PG, RAGNO W, DANIELE S, BARBIERI C, CANTANI A, BUSINCO L. Soy hypersensitivity in children with food allergy. *Ann Allergy* 1992; 69: 143–6.
 30. BOCK SA, ATKINS FM. Patterns of food hypersensitivity during sixteen years of double blind, placebo controlled food challenges. *J Pediatr* 1990; 4: 561–7.
 31. ZEIGER RF, SAMPSON HA, BOCK SA, et al. Soy allergy in infants and children with IgE associated cow's milk allergy. *J Pediatr* 1999; 134: 614–22.
 32. POWELL GK. Milk and soy induced enterocolitis of infancy. Clinical features and standardization of challenge. *J Pediatr* 1978; 93: 553–60.
 33. FREIER S, ERAN M, SURANYI Y. Antigen presentation. In: REINHARDT D, SCHMIDT E., eds. Food allergy. Nestlé Nutrition Workshop Series, vol. 17. New York: Raven Press, 1988: 89–95.
 34. MORTIMER R. Anaphylaxis following ingestion of soybean. *J Pediatr* 1961; 58: 90–2.
 35. DAVID TJ. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch Dis Child* 1984; 59: 983–6.
 36. FOUCARD T, MALMHEDEN YMAN I. A study on severe food reactions in Sweden – is soy protein an underestimated cause of anaphylaxis? *Allergy* 1999; 103: 261–5.
 37. SICHERER SH, SAMPSON HA, BURKS AW. Peanut and soy allergy: a clinical and therapeutic dilemma. *Allergy* 2000; 55: 515–21.
 38. BOCK SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987; 79: 683–8.
 39. SAMPSON HA, McCASKILL C. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *Pediatrics* 1985; 107: 669–75.
 40. SAMPSON HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997; 100: 444–51.
 41. BROWN EB, JOSEPHSON BM, LEVINE HS, et al. A prospective study of allergy in a pediatric population. *Arch Dis Child* 1969; 63: 388–93.
 42. KJELLMAN N-IM, JOHANSSON SGO. Soy versus cow's milk in infants with a biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years of age. *Clin Allergy* 1979; 9: 347–58.
 43. CHANDRA RK. Five-year follow-up of high risk infants with family history of allergy exclusively breast-fed or fed partial whey hydrolysate soy and conventional milk formulas. *J Pediatr Gastroenterol Nutr* 1997; 24: 380–8.
 44. ZEIGER RS. Dietary aspects of food allergy prevention in infants and children. *J Pediatr Gastroenterol Nutr* 2000; 30: S77–86.
 45. HILL LW. Immunologic relationship between cow's milk and goat's milk. *J Pediatr* 1939; 15: 157–62.
 46. McLAUGHLAN P, ANDERSON KJ, WIDDOWSON EM, COOMBS RR. Effect of heat on the anaphylactic sensitizing capacity of cow's milk, goat's milk and various infant formulae. *Arch Dis Child* 1981; 56: 165–7.
 47. SOUERGIN P, WALTER M, SCHILTZ E, DEICHMANN K, FORSTER J, MUELLER H. Allergenicity of alpha caseins from cow, sheep and goat. *Allergy* 1997; 52: 293–8.
 48. BELLIONI-BUSINCO B, PAGANELLI R, LUCENTI P, GIAMPIETRO PG, PERBORN H, BUSINCO L. Allergenicity of goat's milk in children with cow's milk allergy. *J Allergy Clin Immunol* 1999; 103: 1191–4.
 49. HOFFMAN KD, Ho D, SAMPSON HA. *In vivo* allergenic cross-reactivity of cow's milk and goat's milk (abstract). *J Allergy Clin Immunol* 1995; 95: S759.
 50. RESTANI S, GAIASCHI A, PLEBANI A, et al. Cross reactivity between milk proteins from different animal species. *Clin Exp Allergy* 1999; 29: 997–1004.
 51. PAGLIARINI F, SOLAROLI G, PERI C. Composition and nutritional quality of mare's milk. *Ital J Food Sci* 1993; 5: 3–10.
 52. BUSINCO L, GIAMPIETRO PG, LUCENTI P, et al. Allergenicity of mare's milk in children with cow's milk allergy. *J Allergy Clin Immunol* 2000; 105: 1031–4.
 53. IACONO G, CARROCCIO A, CAVATAIO F, MONTALTO G, SORESI M, BALSAMO V. Use of ass milk in multiple food allergy. *J Pediatr Gastroenterol Nutr* 1992; 14: 177–218.
 54. SAMPSON HA, JAMES JM, BERNHISEL-BROADBENT J. Safety of an aminoacid-derived infant formula in children allergic to cow milk. *Pediatr* 1992; 90: 463–5.
 55. ISOLAURI E, TAHVANAINEN A, PELTOLA T, ARVOLA T. Breast feeding of allergic infants. *J Pediatr* 1999; 134: 27–32.
 56. American Academy of Pediatrics Committee on Nutrition. Soy protein-based formulas: recommendations for use in infant feeding. *Pediatrics* 1998; 101: 148–53.
 57. American Academy of Pediatrics Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000; 106: 346–9.