Fifth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease

Safety of Soy-Based Infant Formulas Containing Isoflavones: The Clinical Evidence

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ABSTRACT Soy protein has been used in infant feeding in the West for nearly 100 y. Soy protein infant formulas have evolved in this interval to become safe and effective alternatives for infants whose nutritional needs are not met with human milk or formulas based on cow’s milk. Modern soy formulas meet all nutritional requirements and safety standards of the Infant Formula Act of 1980. They are commonly used in infants with immunoglobulin E–mediated cow’s milk allergy (at least 86% effective), lactose intolerance, galactosemia, and as a vegetarian human milk substitute. Largely as a result of research in animal models, concerns have been voiced regarding isoflavones in soy infant formulas in relation to nutritional adequacy, sexual development, neurobehavioral development, immune function, and thyroid disease. We discuss the available clinical evidence regarding each of these issues. Available evidence from adult human and infant populations indicates that dietary isoflavones in soy infant formulas do not adversely affect human growth, development, or reproduction. J. Nutr. 134: 1220S–1224S, 2004.

KEY WORDS: • isoflavones • phytoestrogens • soy-based infant formula • soy protein isolate

Soy-based infant formulas (SBIFs) have a long history of safe use in the United States and around the world. The development of SBIFs grew out of the need for a nonmilk-based formula alternative for infants who had allergy or intolerance to cow’s milk formulas. The first SBIFs contained soy flour and were introduced almost 100 y ago. Soy protein isolate (SPI), a purified, high-quality, highly digestible soy protein, replaced soy flour almost 45 y ago. SPI is the primary soy protein source in SBIFs worldwide. Recent debate regarding the relevance of certain data generated in animal models or retrospective human observations has led some scientists and lay groups to question the safety and efficacy of SBIF. In this review we present the clinical data relevant to controversial aspects of feeding infants soy-based formulas, including nutritional adequacy, reproductive development, neurobehavioral development, immune function, and thyroid disease.

History of SBIF

John Ruhrh (1) published the first report of use of a soybean-based formula for infants in 1909. In the 1920s Hill and Stuart (2) recommended soy for infantile eczema, and the first commercial SBIF was introduced in 1929. Early SBIFs contained soy flour, an ingredient with a lower protein digestibility and reduced total protein content relative to the SPI used in modern SBIFs. Soy flour–based formulas had a number of nonprotein components—such as soy carbohydrates, fibers, phytates, and protease inhibitors—that are largely absent from current SPIs. The limitations of formulas based on soy flour spurred the development of SPI, which replaced soy flour in the infant formula during the early 1960s. SPI was developed to have a high protein digestibility–corrected amino acid score. SPI is at least 90% protein on a dry-weight basis and has a digestibility of 97% or higher and a balanced high concentration of essential amino acids (3). In the 1970s, methionine and other complementary nutrients were added to standard SBIFs. In addition to methionine, modern SBIFs contain added iodine, carnitine, taurine, choline, and inositol. SBIFs meet all American Academy of Pediatrics recommendations (4), Infant Formula Act (1980 and subsequent amendments in 1986) requirements for term infants (5), and the U.S. FDA quality factors of supporting normal growth and having a high protein-efficiency ratio (6). Approximately 36% of infants in the United States, which amounts to ~1.4 million infants per year, receive SBIFs at some point in their 1st y of life (A. Nielson, unpublished, 2000–2002).

Indications for the use of SBIF for infants include immunoglobulin E–mediated milk allergy; postinfectious diarrhea

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3 Abbreviations used: IQ, intelligence quotient; SBIF, soy-based infant formula; SPI, soy protein isolate.
due to lactose intolerance; galactosemia; use as a vegan human milk substitute; and treatment of common feeding problems such as fussiness, gas, and spit-up. The American Academy of Pediatrics (4) supports the use of SPI-based formulas as safe and effective alternatives to provide appropriate nutrition for normal growth and development in term infants whose nutritional needs are not being met from human milk or formulas based on cow’s milk.

Zeiger et al. (7) in 1999 documented beneficial use of SBIF for infants with immunoglobulin E–associated cow’s milk allergy. This double-blind, placebo-controlled food challenge study of 93 infants found 86% of the cow’s milk–allergic study population to be soy tolerant. The authors indicated that this was probably an underestimate because one of the centers was a tertiary referral center that contributed 12 of the 13 cases of soy–allergic infants. The cow’s milk–allergic infants in this study exhibited growth improvement when placed on SBIF.

The researchers did not study cow’s milk–associated enteropathy because it is well known that dietary protein–associated enteropathy and enterocolitis often have transient soy protein hypersensitivity (4,7,8). Because of the reported high frequency of infants with this syndrome sensitive to both cow’s milk and soy antigens, SBIFs are not generally indicated in the management enteropathy or enterocolitis induced by cow’s milk protein (4,9).

Some recent policies regarding SBIFs in a number of countries, including the United Kingdom, New Zealand, Republic of Ireland, Australia, Canada, and Switzerland, have challenged the routine use of SBIFs. In 1996, the UK Committee on Toxicity of Chemicals in Foods, Consumer Products and the Environment (10) reviewed phytoestrogens with particular reference to SBIF; it endorsed the advice issued by the UK Department of Health that human milk and cow’s milk for at least 2 mo and weaned to cow milk.

A follow-up study of adults who were fed either soy or cow’s milk formulas for several months as infants at the University of Iowa found no differences in reported adult height or weight in males or females ~30 y later (19). Biochemical assessment of protein and iron nutriture demonstrated the adequacy of iron–fortified SBIFs (17,18,20,22). Serum albumin and hemoglobin levels were normal in SBIF-fed infants (18). These studies demonstrated that SBIF supports growth and nutritional status as well as cow’s milk formula.

Other studies of infants fed modern SBIF showed that bone mineralization was at least equal to that of infants fed cow’s milk formula or human milk (22–24). SBIFs have been documented to provide good nutrition for the infant even during the most rapid phase of growth. No adverse effects of SPI or soy isoflavones on growth have been observed in infants consuming SBIFs or after consumption of SBIFs.

**Nutrition adequacy**

SBIFs are formulated to meet all of the nutrient requirements of the growing term infant. A number of studies have documented normal growth and development in term infants fed SBIFs (4,17–20) (Fig. 1). Despite this, the Australian College of Pediatrics has claimed that SBIF is not nutritionally equivalent to milk formula, giving reasons such as lower biological value protein; gut losses of vitamins, minerals, and trace elements; and a need for more energy by infants consuming SBIF (21). Extensive clinical data show otherwise.

Growth studies conducted by Fomon and Zeigler (17) at the University of Iowa demonstrated that no growth differences occurred in either the first 1 mo or first 4 mo of feeding for male and female infants fed soy compared with cow’s milk formulas. Energy intakes to achieve this growth were not higher in the soy group. In a 1-y study of infants fed SBIFs compared with infants who were initially fed human milk and then weaned to a standard cow’s milk formula, there were no differences in the growth pattern between groups (18). A follow-up study of adults who were fed either soy or cow’s milk formulas for several months as infants at the University of Iowa found no differences in reported adult height or weight in males or females ~30 y later (19). Biochemical assessment of protein and iron nutriture demonstrated the adequacy of iron–fortified SBIFs (17,18,20,22). Serum albumin and hemoglobin levels were normal in SBIF-fed infants (18). These studies demonstrated that SBIF supports growth and nutritional status as well as cow’s milk formula.

**Reproductive development**

Concerns about the infant’s exposure to isoflavones and the possible link to altered processes dependent on gonadal steroids have been expressed by some scientists and, more re-

![Mean Weight (g) - Male Infants](https://academic.oup.com/jn/article-abstract/134/5/1220S/4688714)

**FIGURE 1** Comparison of soy formula with human milk/cow’s milk formula. Reprinted with permission from Lasekan et al. (18). *Exclusively breastfed for a least 2 mo and weaned to cow milk–based formula.
cently, the lay media. These concerns are associated with the hypothesis that phytoestrogens may share some properties with estrogen or selective estrogen receptor modulators (25).

Safford et al. (26) in a recent article described the complexity of extrapolating potential adverse effects observed in animal models of isoflavone exposure to human populations. They point out the gaps in our knowledge that limit our ability to learn from the available animal studies. For example, rodent studies investigating in utero exposure to isoflavones need to be interpreted in the light of the relatively lower estradiol levels in pregnant rodents compared with pregnant women. The fetal rat is exposed to picomole levels of estradiol whereas the human fetus is exposed to micromole levels of estradiol (27). Isoflavone exposure may perturb the equilibrium of very low normal background exposure of the more biologically sensitive reproductive organs of rodents. Safford et al. (26) also noted that the animal reproductive effects and human isoflavone exposure levels are not well established.

To address this issue, Fielden et al. (28) studied the effect of gestational and lactational exposure to genistein on testicular weight and sperm quality in adult mice at levels comparable with or greater than human exposure. Results showed no significant treatment-related effects on male offspring body weight, anogenital distance, seminal vesicle weight, or testis weight. However, not all studies concur with these findings (29). An animal study raised concerns about the effect of soy isoflavones on female reproductive organs (i.e., uterine cancer). Newbold et al. (30) studied neonatal mice injected with high levels of genistein at 50 mg/kg on days 1–5 after birth and reported findings of uterine adenocarcinomas at age 18 mo. The authors suggested that genistein is carcinogenic if exposure occurs during critical periods of development. Relevance to human populations is limited by differences among animal species in isoflavone metabolism, the use of isoflavones at a level many times higher that those absorbed by infants fed SBIFs, and health effects due to genistein as a result of injection cannot be extrapolated to genistein given orally.

In contrast, clinical studies showed that infants fed SBIF have normal reproductive development and later health. In an abstract, Businco et al. (31) studied 34 children who had been fed SBIFs who were then evaluated at a median age 29 mo. A detailed physical exam included signs of sexual maturation and bone density, metabolic markers of bone, and one marker of estrogen. The investigators’ conclusion was that phytoestrogens in SBIFs did not induce hormonal effects. In a study of young adults fed SBIF for several months as infants, Strom et al. (19) found no evidence of hormonal or other adverse effects. Over 811 subjects participated; 248 had received SBIFs and 563 had received milk-based formulas during their first 4 mo. For >30 primary hypotheses, no statistically significant differences were found in general health and development between the two formula groups in either females or males. The variables studied included anthropometrics, indexes of precocity, and many other nonreproductive and reproductive outcomes, including cancer and infertility. Of the endpoints assessed, two showed differences favoring cow’s milk formulas: duration of monthly menses (8 h shorter) and discomfort with menses (Table 1). However, those with a history of soy feeding did not seek more medical care relative to these differences. The authors stated that although the few marginal positive findings should be studied further, their findings were reassuring about the safety of SBIF. These clinical studies support pediatricians’ experience that sexual development and maturation are normal in infants fed SBIF (11,20,31).

Table 1: Follow-up study findings: soy vs. cow milk formula

<table>
<thead>
<tr>
<th>Outcomes with no differences</th>
<th>Height</th>
<th>Weight</th>
<th>Age of sexual maturation milestones</th>
<th>Menstrual cycle length</th>
<th>Missed periods</th>
<th>Spotting</th>
<th>Cramps</th>
<th>Breast tenderness</th>
<th>Pregnancy</th>
<th>Pregnancy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes favoring cow milk</td>
<td>Discomfort with menstrual period</td>
<td>Number of days requiring pads or tampons (difference of &gt;8 h)</td>
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Data from Strom et al. 2001 (19).

### Neurobehavioral development

A recent study by White et al. (32–34) in middle-aged Japanese American adults consuming tofu raised a concern regarding a possible soy effect on later cognitive function. Subjects’ diets in the cohort were assessed between 1965 and 1972 and their cognitive abilities were assessed in 1991–1993 when the subjects were between ages 71 and 93 y. An association between tofu consumption in midlife and reduced cognitive function and structural changes of the brain was reported in these Japanese-American males. However, in a carefully controlled short-term dietary intervention study, File et al. (35) showed that a high-soy diet (100 mg/d of total isoflavones) versus a low-soy diet (0.5 mg/d of total isoflavones) for 10 wk had no adverse effect on attention, memory, cognitive function, or mood in young healthy male and female students.

Studies in rodents consuming soy protein diets by Lephart et al. (36) indicated effects of soy isoflavones on aspects of brain structure and function, particularly in adult animals. Two retrospective clinical studies looked at measures of neurobehavioral development in children fed SBIFs and adults fed SBIFs as infants. Malloy and Berendes (37) evaluated 9- and 10-y-old children who had been fed SBIFs. Half of the children had been fed a chloride-deficient formula that was briefly on the market. Intelligence quotient (IQ) was measured in these children and in a reference group of children fed human milk. Subjects were grouped according to those who had no human milk exposure and were fed SBIF for variable periods of time and those who were fed human milk for at least 60 d before receiving SBIF. Infants were stratified by maternal education because of its known association with child IQ. There were no differences in outcome related to early SBIF vs. human milk feeding, not only for IQ but also for behavioral problems, learning impairment, and emotional problems. These findings indicate that early SBIF feeding did not affect IQ. Limitations of the study were that both groups received SBIF at some point and also that some had received a chloride-deficient formula.

Strom et al.’s (19) study of adults included data on educational outcome of infants fed SBIF or cow’s milk formula. The percentage of men or women who achieved some level of college or trade school education, whether fed SBIF or cow’s milk formula, was not different. Because larger (i.e., more than hundreds of infants) long-term prospective and retrospective neurodevelopmental studies are lacking, studies are currently
underway at the U.S. Department of Agriculture Arkansas Children’s Nutrition Center to further evaluate neurobehavioral and reproductive development in infants fed SBIF. The available clinical studies indicate no reason for concern regarding neurodevelopment of infants fed SBIF.

**Immune development**

In a recent study by Yellayi et al. (38), injections of the isoflavone genistein were associated with reduced immune function in adult mice. The authors suggested that infants fed SBIF and adults consuming soy supplements may develop impaired immune function. The animal model used for this was an ovariecetomized adult mouse injected with levels of genistein that were thought to be comparable with those reported in SBIF-fed infants. Criticism of the study included the facts that the experiments were not properly controlled (no untreated mice), the study design did not account for the age-related thymic involution process, and daily injections for 35 d added an uncontrolled stress known to influence immune function (Christopher T. Cordle, personal communication, Ross Products Division, Abbott Laboratories, 2004). The authors compared their results to studies done in Italy in the late 1970s and early 1980s (39–41) with small groups of infants fed soy flour–based formulas (not modern SPI-based formulas), which suggested that infants had a poor response to polio vaccine.

Modern SBIFs were shown to support immune system development in young, growing infants. Businco et al. (42) demonstrated that SBIFs did not interfere with the normal immune response to oral polio vaccine. Recently, Lasekan et al. (18), Ostrom et al. (43), and Cordle et al. (44) evaluated growth and measured immune function in infants randomly assigned to receive SBIF or SBIF with added nucleotides along with a concurrent human milk–fed reference group weaned to a standard cow’s milk formula. The outcomes of this study included infectious morbidity, antibody responses to recommended infant immunizations, and a comprehensive immune assessment. No differences were found in parental reports of diarrhea (presumably infectious) among the groups. Physician-documented diarrhea was higher in both SBIF groups than in the group fed human milk and weaned to cow’s milk formula. There were no differences in otitis media (inflammation of the middle ear) or antibiotic use. The differences seen in this study for diarrhea are typical of those seen in the presence and absence of breast-feeding (45,46). The comprehensive serologic immune assessment showed that antibody levels to common infant immunizations were similar for the feeding groups and were in the normal reference range for both SBIF-fed groups. Values for leukocyte populations for both SBIF-fed groups were also within the reference range. There were almost no differences in values for lymphocyte subtypes evaluated at ages 6, 7, and 12 mo. There were no differences in total T lymphocytes or natural killer cell lymphocytes between the SBIF- and human milk–fed infants. Furthermore, no differences were seen in naive helper T cells or memory effector helper T cells between the SBIF- and human milk–fed infants. The conclusions from this study were that infants fed SBIF demonstrated immune cell status similar to infants fed human milk and weaned to cow’s milk and that their responses to immunization were consistent with normal immune system development.

**Thyroid issues: goiter, hypothyroidism, and thyroiditis**

Goiter was associated with use of soy flour–based formula in the early to mid-1900s before iodine-fortified SPI-based formulas were available (47–49). Infants fed the soy flour formulas had increased gut losses of thyroxine. In vitro data showed an inhibitory effect of the aglycone of soy isoflavonones on thyroxine synthesis in the thyroid gland but only in the absence of iodine (50). This effect is also seen with other flavonoids.

Interestingly, animals fed a nutritionally complete soy-based diet including iodine have slightly higher thyroxine levels than do animals fed a casein-based diet (51). Current SPI-based infant formulas support normal growth and development. A key characteristic of hypothyroidism is slow growth, which, as reviewed above, is not characteristic of SBIF-fed infants.

Infants with congenital hypothyroidism unrelated to SBIF may require additional thyroid hormone supplementation and show slower initial normalization of thyroid stimulating hormone values (52–55). This is a diet-drug interaction apparently caused by slight changes in thyroxine bioavailability in the presence of SBIFs, possibly related to increased stool volume.

One study claimed an association of soy feeding with thyroiditis (56). This retrospective study involved 59 subjects with thyroiditis. The subjects were compared with a control group that was not matched for age and sex; there were more males in the control group although thyroiditis is primarily a female disease. Although it is well known that soy formula is used for children with allergies, this study did not have a covariate in the analysis for allergy history, a possible marker for immune dysregulation that is a feature of thyroiditis. Notably, only 34% of those with thyroiditis in the study ever received soy formula. No other reports have corroborated this observation.

**Conclusions**

SBIF is well recognized as a healthy alternative to human or cow’s milk. It has a long history of safe use and is a high-quality, plant-based protein alternative for infant formula. Recent in-depth reviews of the safety of dietary isoflavonones in soy have found that there is no conclusive evidence from animal or human adult or infant populations that indicates that dietary isoflavonones may adversely affect human health development or reproduction. Comprehensive literature reviews and clinical studies of infants fed SBIFs have resolved questions or raised no clinical concerns with respect to nutritional adequacy, sexual development, neurobehavioral development, immune development, or thyroid disease. SBIFs provide complete nutrition that adequately supports normal infant growth and development. FDA has accepted SBIFs as safe for use as the sole source of nutrition. Although large prospective or retrospective long-term studies involving more than a few hundred infants fed SBIF are lacking, the available evidence indicates that SBIF is safe.

**LITERATURE CITED**
