



CLINICAL REPORT

Use of Soy Protein-Based Formulas in Infant Feeding

Guidance for the Clinician in Rendering
Pediatric Care

Jatinder Bhatia, MD, Frank Greer, MD, and the Committee on Nutrition

ABSTRACT

Soy protein-based formulas have been available for almost 100 years. Since the first use of soy formula as a milk substitute for an infant unable to tolerate a cow milk protein-based formula, the formulation has changed to the current soy protein isolate. Despite very limited indications for its use, soy protein-based formulas in the United States may account for nearly 25% of the formula market. This report reviews the limited indications and contraindications of soy formulas. It will also review the potential harmful effects of soy protein-based formulas and the phytoestrogens contained in these formulas.

THE AMERICAN ACADEMY of Pediatrics (AAP) is committed to the use of human milk as the ideal source of nutrition for infant feeding. However, by 2 months of age, the majority of infants in North America are receiving at least some formula. Soy-based infant formulas have been available for almost 100 years.¹ Despite limited indications, soy protein-based formula accounts for approximately 20% of the formula market in the United States. Because an infant formula provides a source of nutrition for an extended interval, its nutritional adequacy must be proven, and the indications for its use must be substantiated and well understood. This statement updates the 1998 AAP review of soy protein-based formulas and addresses the ongoing concern of phytoestrogens in soy formulas.

COMPOSITION

Isolated soy protein-based formulas currently on the market are all free of cow milk protein and lactose and provide 67 kcal/dL. All are iron-fortified and meet the vitamin, mineral, and electrolyte specifications addressed in the 2004 guidelines from the AAP for feeding term infants² and established by the US Food and Drug Administration.³ The protein is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide a protein content of 2.45 to 2.8 g per 100 kcal or 1.65 to 1.9 g/dL. The fat content of soy protein-based formulas is derived primarily from vegetable oils. The quantity of specific fats varies by manufacturer and is usually similar to those in the manufacturer's corresponding cow milk-based formula. The fat content ranges from 5.02 to 5.46 g per 100 kcal or 3.4 to 3.6 g/dL. The oils used include soy, palm, sunflower, olein, safflower, and coconut. Docosahexaenoic and arachidonic acids now are added routinely.

In formulas, carbohydrate sources are corn maltodextrin, corn syrup solids, and sucrose, with content ranging from 10.26 to 10.95 g per 100 kcal or 6.9 to 7.4 g/dL. Until 1980, mineral absorption from soy formulas was erratic because of poor stability of the suspensions and the presence of excessive soy phytates.⁴ Because soy protein isolate formulas still contain 1.5% phytates, and up to 30% of the total phosphorus is phytate bound, they contain 20% more calcium and phosphorus than cow milk-based formulas and maintain the ratio of calcium to available phosphorus of 1.1 to 2.0:1. With the current formulations, bone mineralization, serum concentrations of calcium and phosphorus, and alkaline phosphatase concentrations in term infants through 12 months of age are equivalent to those observed in infants fed cow milk-based formulas.⁵⁻⁷ Because soy phytates and fiber oligosaccharides also bind iron and zinc,⁹ all soy-based formulas are fortified with iron and zinc.^{8,9}

Phytoestrogens in Soy Protein-Based Formulas

Of the many heat-stable factors present in soy formulas, the phytoestrogens are of particular interest in human health. Phytoestrogens consist of several groups of nonsteroidal estrogens, including isoflavones. Isoflavones are commonly found in legumes, with the highest amount found in soybeans.^{1,10} Concerns raised in relation to phytoestrogens/isoflavones include their potential negative effects on sexual development and reproduction, neurobehavioral development, immune function, and thyroid function. On the other hand, epidemiologic studies have

www.pediatrics.org/cgi/doi/10.1542/peds.2008-0564

doi:10.1542/peds.2008-0564

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words

soy protein, infant formula, infant feeding, cow milk protein allergy, nutrition, galactosemia, vegetarian

Abbreviations

AAP—American Academy of Pediatrics
IgE—immunoglobulin E

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2008 by the American Academy of Pediatrics

suggested a protective effect of isoflavones against a number of adult chronic diseases, including coronary heart disease and breast, endometrial, and prostate cancers.^{11,12}

The structural similarity of phytoestrogens with 17-estradiol has prompted studies on the possible effects of soy isoflavones on reproductive function and growth. Numerous toxicity studies in rats have demonstrated some effects on estrogen-related tissues, but overall maternal reproductive function and fetal development were unaffected.^{13–15} A recent study of the isoflavone genistein demonstrated adverse consequences of neonatal exposure in mice¹⁶; however, feeding of soy formula (and not individual components) has not demonstrated these adverse effects in animals.¹⁷

The possible effects of soy isoflavones on various forms of carcinogen-induced and estrogen-induced tumorigenesis have been investigated in animal models, but no clear conclusion can be drawn.^{18,19} Soy diets were reported to stimulate growth of estrogen-dependent mammary tumors in mice in a dose-dependent manner.^{20,21} Contrary to these results, phytoestrogens in typical dietary quantities were reported not to have estrogen-like activity in female ovariectomized macaque monkeys, but they antagonized estrogen-induced cellular proliferation in the breast.²²

In humans, very limited data to date suggest that soy phytoestrogens have a low affinity for human postnatal estrogen receptors and low potency in bioassays.²³ The absorption, distribution, metabolism, and excretion of soy isoflavones vary, depending on age and gender and among cultural groups; interindividual variability has been documented in several studies.^{24,25} However, differences in gender have been inconclusive.^{26–28} Analysis of maternal and cord plasma and amniotic fluid indicates placental transfer of these compounds after soy consumption; no deleterious effects were discerned in the fetuses of Japanese mothers with relatively high soy consumption.²⁹

Isoflavones are excreted in human milk, although the concentration is very low. The concentration of isoflavones in human milk reflects maternal diet, with omnivores demonstrating considerably lower concentrations of isoflavones compared with vegans.^{30,31} Setchell and Cassidy³² estimated that the amount of isoflavones ingested by infants fed soy-based formulas on a body weight basis exceeded those reported to increase the length of the menstrual cycle in adult women. However, an increased incidence of feminization in male infants³³ or an increased incidence of hypospadias in high soy-consuming populations³⁴ have not been observed. Even in infants fed soy-based formulas exclusively, the sulfate and glucuronide conjugates of phytoestrogens are identified in plasma, although both of these are rapidly excreted.²⁷ Data on reproductive health in young adults 20 to 34 years of age who had previously participated in a controlled feeding study of soy formula as infants demonstrated a longer duration of menstrual bleeding and greater discomfort in women exposed to soy as infants.³⁵ We cautioned against overinterpretation of their data, however, because there was no increase in menstrual

blood flow in the women exposed to soy formula as infants and no statistically significant differences in >30 other outcome variables measured.³⁵

Consumption of soy products by infants with congenital hypothyroidism complicates their management, as evidenced by a prolonged increase in thyroid-stimulating hormone when compared with infants not fed soy formula; the authors of 2 studies suggested closer monitoring and a possible need for an increased dose of levothyroxine.^{36,37} In infants receiving replacement hormone, the phytates may interfere with the uptake of exogenous thyroid hormone by binding the thyroxine within the lumen, increasing fecal loss, and reducing the efficacy of oral thyroid hormone.^{36,38} In an extensive review of the effects of soy protein and soybean isoflavones, little evidence was found that soy foods or isoflavones adversely affect thyroid function in iodine-replete individuals with euthyroidism.³⁹ This review also found that, similar to infants, adults with hypothyroidism may need additional doses of thyroid hormone with the concomitant use of soy foods because of the effects on absorption. Trials with dietary soy isoflavones have not reported adverse effects on thyroid function in rats.⁴⁰ These data suggest that there is a lack of sufficient evidence suggesting short-term or long-term adverse effects of soy consumption on endocrine function.

In summary, although studied by numerous investigators in various species, there is no conclusive evidence from animal, adult human, or infant populations that dietary soy isoflavones may adversely affect human development, reproduction, or endocrine function.

Aluminum in Soy Protein-Based Formulas

In 1996, the AAP issued a statement (since retired) on aluminum toxicity in infants and children and discussed the relatively high content of aluminum in soy-based formulas.⁴¹ Although the aluminum content of human milk is 4 to 65 ng/mL, that of soy protein-based formula is 600 to 1300 ng/mL.^{42,43} Mineral salts used in formula production are the source of the aluminum. Aluminum, which makes up 8% of the earth's crust as the third most common element, has no known biological function in humans.⁴³ The toxicity of aluminum is traced to increased deposition in bone and in the central nervous system, particularly in the presence of reduced renal function in preterm infants and children with renal failure. Because aluminum competes with calcium for absorption, increased amounts of dietary aluminum from isolated soy protein-based formula may contribute to the reduced skeletal mineralization (osteopenia) observed in preterm infants and infants with intrauterine growth retardation.⁴⁴ Term infants with normal renal function do not seem to be at substantial risk of developing aluminum toxicity from soy protein-based formulas.⁴²

USE IN TERM AND PRETERM INFANTS

Numerous studies have documented normal growth and development in term neonates fed methionine-supplemented isolated soy protein-based formulas.^{42,45–48} Average energy intakes in infants receiving soy protein-based

formulas are equivalent to those achieved with cow milk formulas.⁴² In infants fed soy protein-based formulas, the serum albumin concentration, as a marker of nutritional adequacy, is normal,^{46,49-51} and bone mineralization is equivalent to that documented with cow milk-based formulas in term infants.⁵⁻⁷ Literature reviews and clinical studies of infants fed soy protein-based infant formulas raise no clinical concerns with respect to nutritional adequacy, sexual development, thyroid disease, immune function, or neurodevelopment.¹ Additional studies confirm that soy protein-based formulas do not interfere with normal immune responses to oral immunization with poliovirus vaccine.^{52,53} The US Food and Drug Administration has approved these formulas as safe for use with infants.

On the other hand, soy protein-based formulas are not recommended for preterm infants. Serum phosphorus concentrations are lower, and alkaline phosphatase concentrations are higher in preterm infants fed soy protein-based formula than they are in preterm infants fed cow milk-based formula.^{54,55} As anticipated from these observations, the degree of osteopenia is increased in infants with low birth weight receiving soy protein-based formulas.^{50,56} Even with supplemental calcium and vitamin D, radiographic evidence of significant osteopenia was present in 32% of 125 preterm infants fed soy protein-based formula.⁵⁶ The cow milk protein-based formulas designed for preterm infants are clearly superior to soy protein-based formula for preterm infants.

USE IN DISORDERS OF CARBOHYDRATE METABOLISM

When strict dietary lactose elimination is required in the management of infants with galactosemia or primary lactase deficiency (extremely rare), soy protein-based formulas are safe and cost-effective. In addition, soy protein-based formulas can be a dietetic alternative for families wishing to avoid feeding their infants formulas containing animal products. Soy protein-based formulas with sucrose as the carbohydrate are contraindicated in sucrose-isomaltase deficiency and in hereditary fructose intolerance.

USE IN ACUTE DIARRHEA AND SECONDARY LACTASE DEFICIENCY

A number of studies have addressed the role of these formulas in the recovery from acute infantile diarrhea complicated by secondary or transient lactase deficiency. However, after immediate rehydration, most infants can be managed successfully with continued breastfeeding or standard cow milk or soy formula.^{57,58} In an extensive review, Brown⁵⁷ noted that the dietary failure rate of lactose-containing formulas was 22%, whereas that of lactose-free formulas was 12%. In a study comparing human milk, cow milk-based formula, and soy protein-based formula, no difference was found in the rate of recovery from rotavirus or nonrotavirus diarrhea on the basis of nutritional therapy.⁴⁹ However, the duration of diarrhea has been reported to be shorter in infants receiving soy protein-based formula,^{51,59} and the duration of liquid stools may also be reduced by adding additional

soy polysaccharide fiber⁶⁰ or by resuming a mixed-staple diet.⁶¹

Lactose free and reduced lactose-containing cow milk formulas are now available and could be used for circumstances in which elimination or a reduction in lactose in the diet, respectively, is required. Because primary or congenital lactase deficiency is rare, very few individuals would require a total restriction of lactose. Lactose intolerance is more likely to be dose dependent. Thus, the use of soy protein-based lactose-free formulas for this indication should be restricted.

USE IN COLIC AND "FORMULA INTOLERANCE"

Perhaps the most common reason for use of soy formulas by infant care providers is for relief of perceived formula intolerance (spitting, vomiting, fussiness) or symptoms of colic. Colicky discomfort is described by the parents of 10% to 20% of infants during the first 3 months of age.⁶² Although many factors have been implicated, parents frequently seek relief by changing infant formulas. Although some calming benefit can be attributed to the sucrose^{63,64} and fiber content,⁶⁵ controlled trials of cow milk and soy protein-based formulas have not demonstrated a significant benefit from soy.^{66,67} The value of parental counseling as to the cause and duration of colic seems greater than the value of switching to soy formula.⁶⁸ Because most colicky behavior diminishes spontaneously between 4 and 6 months of age, any intervention at that time can be credited anecdotally.

SEVERE GASTROINTESTINAL REACTIONS TO SOY FORMULA

As with cow milk protein-based formula, severe gastrointestinal reactions to soy protein-based formula have been described for >40 years⁶⁹ and encompass the full gamut of disease: enteropathy, enterocolitis, and proctitis. Small-bowel injury, a reversible celiac-like villus injury that produces an enteropathy with malabsorption, hypoalbuminemia, and failure to thrive, has been documented in at least 4 studies.⁷⁰⁻⁷³ In case series of infantile food protein-induced enterocolitis caused by cow milk protein, 30% to 64% of infants had concomitant soy-induced enterocolitis,⁷⁴⁻⁷⁷ with enterocolitis manifested by bloody diarrhea, ulcerations, and histologic features of acute and chronic inflammatory bowel disease.^{69,75,78-80} Afflicted infants have responded to replacing the soy protein-based formula with a hydrolyzed protein formula. It is theorized that the intestinal mucosa damaged by cow milk allows increased uptake and, therefore, increased immunologic response to the subsequent soy antigen. Eosinophilic proctocolitis, a more benign variant of enterocolitis, also has been reported in infants receiving soy protein-based formula.^{81,82}

These dietary protein-induced syndromes of enteropathy and enterocolitis, although clearly immunologic in origin, are not immunoglobulin E (IgE)-mediated, reflecting instead an age-dependent transient soy protein hypersensitivity. Because of the reported high frequency of sensitivity to both cow milk and soy antigens in infants, soy protein-based formulas are not indicated in

the management of documented cow milk protein-induced enteropathy or enterocolitis. Hydrolyzed protein formulas should be used for these infants. Most, but not all children, can resume soy protein consumption safely after 5 years of age.

SOY PROTEIN-BASED FORMULAS AND PREVENTION OF ATOPIC DISEASE

Any ingested large molecular weight protein is a potential antigen to the intestinal immune system, including soy protein. In soy protein isolate, 90% of the pulp-derived protein resides in 2 major heat-stable globulins: β -conglycin, with a molecular weight of 180 000; and glycinin, with a molecular weight of 320 000.⁸³ After enteric digestion, the number of potential antigens generated at the mucosal surface is enormous.⁸⁴ As a result, the *in vitro* demonstration of antigen-specific antibody can be difficult. The antigenicity of soy protein, suspected since 1934,⁸⁵ was documented in low-risk infants by Eastham et al in 1982.⁸⁶ Intrauterine sensitization has been documented by demonstrating antigen-specific antibody in human amniotic fluid.⁸⁷

Recognizing that soy protein is antigenic does not mean that soy protein is highly allergenic. In a prospective study of healthy infants fed human milk, cow milk formula, or soy protein-based formula, Halpern et al⁸⁸ documented true allergic responses in 0.5% and 1.8% of infants to soy formula and cow milk formula, respectively. This frequency is consistent with the summary by Fomon⁸⁹ that in 3 decades of study of soy protein-based formulas, <1% of soy formula-fed infants had adverse reactions. In a national survey of pediatric allergists, the occurrence of allergy to cow milk was reported at 3.4%, whereas allergy to soy protein was reported to be 1.1%.⁹⁰ Two large studies of infants with atopic dermatitis addressed the frequency with which a double-blind, placebo-controlled challenge with soy protein was positive. Sampson⁹¹ documented a positive soy allergy in 5% of 204 patients, whereas Businco et al⁹² implicated soy in 4% of 143 children.

In a recent meta-analysis of 5 randomized or quasi-randomized studies, the authors concluded that feeding with soy formula should not be recommended for the prevention of atopy in infants at high risk of developing allergy.⁹³ Furthermore, the use of soy protein-based formula during the first 3 months of age does not reduce the frequency of positive antibody responses to cow milk formula introduced later in infancy.⁹³ When human milk feeding is supplemented with soy formula in infants at high risk, the anticipated frequency of eczema by 2 years of age is not significantly reduced.^{94,95} Interpretation of these data are obscured by multiple alterations in the maternal diet and by environmental stimuli. However, isolated soy protein-based formula has no advantage over cow milk-based formula for supplementing the diet of a breastfed infant.

Regarding soy proteins and other food allergies, in 1 partly prospective, partly retrospective study of the risk factors for the development of peanut allergy, feeding of soy milk or soy protein-based formula was associated with the development of peanut allergy (odds ratio: 2.6;

95% confidence interval: 1.3–5.2).⁹⁶ However, in a randomized trial of soy formula feeding in infants with cow milk allergy, there was no association between soy formula ingestion with the development of peanut allergy.⁹⁷ Thus, the evidence that soy formula feeding increases the risk of developing peanut allergy is contradictory, and additional study is warranted.

Sensitization to soy has been reported in 10% to 14% of infants with cow milk allergy.^{98,99} One study documented similar adverse reactions to soy in IgE-associated and non-IgE-associated cow milk allergy (11% vs 9%).⁹⁹ A second study evaluated infants and children with IgE-associated cow milk allergy (ages 3–41 months), and 14% (95% confidence interval: 7.7–22.7) were determined to have soy allergy.⁹⁸ Thus, although most infants with IgE-mediated cow milk allergy will tolerate soy formula, because of the 10% to 14% crossover rate, the use of an extensively hydrolyzed protein formula rather than a soy formula may be considered in infants allergic to cow milk formula. Although reported in the literature, severe anaphylaxis after soy protein exposure is uncommon, especially in infants.^{100,101}

SUMMARY

1. In term infants, although isolated soy protein-based formulas may be used to provide nutrition for normal growth and development, there are few indications for their use in place of cow milk-based formula. These indications include (a) for infants with galactosemia and hereditary lactase deficiency (rare) and (b) in situations in which a vegetarian diet is preferred.
2. For infants with documented cow milk protein allergy, extensively hydrolyzed protein formula should be considered, because 10% to 14% of these infants will also have a soy protein allergy.
3. Most previously well infants with acute gastroenteritis can be managed after rehydration with continued use of human milk or standard dilutions of cow milk-based formulas. Isolated soy protein-based formulas may be indicated when secondary lactose intolerance occurs.
4. Isolated soy protein-based formula has no advantage over cow milk protein-based formula as a supplement for the breastfed infant, unless the infant has 1 of the indications noted previously.
5. Soy protein-based formulas are not designed for or recommended for preterm infants.
6. The routine use of isolated soy protein-based formula has no proven value in the prevention or management of infantile colic or fussiness.
7. Infants with documented cow milk protein-induced enteropathy or enterocolitis frequently are as sensitive to soy protein and should not be given isolated soy protein-based formula. They should be provided formula derived from hydrolyzed protein or synthetic amino acids.

8. The routine use of isolated soy protein-based formula has no proven value in the prevention of atopic disease in healthy or high-risk infants.

COMMITTEE ON NUTRITION, 2007–2008

Frank R. Greer, MD, Chairperson
 Jatinder J. S. Bhatia, MD
 Stephen R. Daniels, MD, PhD
 Marcie B. Schneider, MD
 Janet Silverstein, MD
 Nicolas Stettler, MD, MSCE
 Dan W. Thomas, MD

FORMER COMMITTEE MEMBERS

Robert D. Baker, Jr, MD, PhD
 Melvin B. Heyman, MD

LIAISONS

Donna Blum-Kemelor, MS, RD
 US Department of Agriculture
 Laurence Grummer-Strawn, PhD
 Centers for Disease Control and Prevention
 RADM Van S. Hubbard, MD, PhD
 National Institutes of Health
 Valerie Marchand, MD
 Canadian Pediatric Society
 Benson M. Silverman, MD
 US Food and Drug Administration

STAFF

Debra Burrowes, MHA

REFERENCES

- Merritt RJ, Jenks BH. Safety of soy-based infant formulas containing isoflavones: the clinical evidence. *J Nutr.* 2004;134(5):1220S–1224S
- American Academy of Pediatrics, Committee on Nutrition. Commentary on breast-feeding and infant formula, including proposed standards for formulas. *Pediatrics.* 1976;57(2):278–285
- Food and Drug Administration. Rules and regulations: nutrient requirements for infant formulas. 21 CFR Part 107. *Fed Regist.* 1985;50:45106–45108
- Bhatia J, Fomon ST. Formulas for premature infants: fate of the calcium and phosphorus. *Pediatrics.* 1983;72(1):37–40
- Hillman LS, Chow W, Salmons SS, Weaver E, Erickson M, Hansen J. Vitamin D metabolism, mineral homeostasis, and bone mineralization in term infants fed human milk, cow milk-based formula, or soy-based formula. *J Pediatr.* 1988;112(6):864–874
- Mimouni F, Campaigne B, Neylan M, Tsang RC. Bone mineralization in the first year of life in infants fed human milk, cow-milk formula or soy-based formula. *J Pediatr.* 1993;122(3):348–354
- Venkataraman PS, Luhar H, Neylan MJ. Bone mineral metabolism in full-term infants fed human milk, cow milk-based, and soy-based formulas. *Am J Dis Child.* 1992;146(11):1302–1305
- Erdman JW Jr, Fordyce EJ. Soy products and the human diet. *Am J Clin Nutr.* 1989;49(5):725–737
- Sandström B, Cederblad A, Lonnerdal B. Zinc absorption from human milk, cow's milk, and infant formula. *Am J Dis Child.* 1983;137(8):726–729
- Erdman JW Jr, Badger TM, Lampe JW, Setchell KD, Messina M. Not all soy products are created equal: caution needed in interpretation of research results. *J Nutr.* 2004;134(5):1229S–1233S
- Bhathena SJ, Velasquez MT. Beneficial role of dietary phytoestrogens in obesity and diabetes. *Am J Clin Nutr.* 2002;76(6):1191–1201
- Cross HS, Kallay E, Lechner D, Gerdenitsch W, Adlercreutz H, Armbrrecht HJ. Phytoestrogens and vitamin D metabolism: a new concept for the prevention and therapy of colorectal, prostate, and mammary carcinomas. *J Nutr.* 2004;134(5):1207S–1212S
- Lamartiniere CA, Zhang JX, Cotroneo MS. Genistein studies in rats: potential for breast cancer prevention and reproductive and developmental toxicity. *Am J Clin Nutr.* 1998;68(suppl 6):1400S–1405S
- Gallo D, Cantelmo F, Distefano M, et al. Reproductive effects of dietary soy in female Wistar rats. *Food Chem Toxicol.* 1999;37(5):493–502
- You L, Casanova M, Bartolucci EJ, et al. Combined effects of dietary phytoestrogen and synthetic endocrine-active compound on reproductive development in Sprague-Dawley Rats: genistein and methoxychlor. *Toxicol Sci.* 2002;66(1):91–104
- Jefferson WN, Padilla-Banks E, Newbold RR. Studies of the effects of neonatal exposure to genistein on the developing female reproductive system. *J AOAC Int.* 2006;89(4):1189–1196
- Rozman KK, Bhatia J, Calafat AM, et al. NTP-CERHR expert panel on the reproductive and developmental toxicity of soy formula. *Birth Defects Res B Dev Reprod Toxicol.* 2006;77(4):280–397
- Fritz WA, Coward L, Wang J, Lamartiniere CA. Dietary genistein: perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. *Carcinogenesis.* 1998;19(12):2151–2158
- Rao CV, Wang CX, Simi B, et al. Enhancement of experimental colon cancer by genistein. *Cancer Res.* 1997;57(17):3717–3722
- Ju YH, Allred CD, Allred KF, Karko KL, Doerge DR, Helferich WG. Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. *J Nutrition.* 2001;131(11):2957–2962
- Allred CD, Allred KF, Ju YH, Virant SM, Helferich WG. Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. *Cancer Res.* 2001;61(13):5045–5050
- Cline JM, Soderqvist G, Register TC, Williams JK, Adams MR, Von Shoultz B. Assessment of hormonally active agents in the reproductive tract of female nonhuman primates. *Toxicol Pathol.* 2001;29(1):84–90
- Liener IE. Implications of antinutritional components in soybean foods. *Crit Rev Food Sci Nutr.* 1994;34(1):31–67
- Kelly GE, Joannou GE, Reeder AY, Nelson C, Waring MA. The viable metabolic response to dietary isoflavones in humans. *Proc Soc Exp Biol Med.* 1995;208(1):40–43
- Xu X, Harris KS, Wang HJ, Murphy PA, Hendrich S. Bioavailability of soybean isoflavones depends upon gut microflora in women. *Hum Clin Nutr.* 1995;125(9):2307–2315
- Cruz ML, Wong WW, Mimouni F, et al. Effects of infant nutrition on cholesterol synthesis rates. *Pediatr Res.* 1994;35(2):135–140
- Huggett AC, Pridmore S, Malnoe A, Haschke F, Offord EA. Phyto-estrogens in soy-based infant formula. *Lancet.* 1997;350(9080):815–816
- National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction. Expert panel report on the

- reproductive and developmental toxicity of genistein. Available at: <http://cerhr.niehs.nih.gov>. Accessed September 18, 2007
29. Adlercreutz H, Yamada T, Wahala K, Watanabe K. Maternal and neonatal phytoestrogens in Japanese women during birth. *Am J Obstet Gynecol*. 1999;180(3 pt 1):737-743
 30. Setchell KD, Zimmer-Nechemias L, Cai J, Heubi JE. Exposure of infants to phytoestrogens from soy-based infant formula. *Lancet*. 1997;350(9070):23-27
 31. UK Food Standards Agency. Consultation on the Committee on Toxicology Report on Phytoestrogens and Health. Available at: <http://cot.food.gov.uk/cotreports/cotwgreports/phytoestrogensandhealthcot>. Accessed March 26, 2008
 32. Setchell KD, Cassidy A. Dietary Isoflavones: biological effects and relevance to human health. *J Nutr*. 1999;129(3):758S-767S
 33. Essex C. Phytoestrogens and soy based infant formula. *BMJ*. 1996;313(7056):507-508
 34. Paulozzi LJ. International trends in rates of hypospadias and cryptorchidism. *Environ Health Perspect*. 1999;107(4):297-302
 35. Strom BL, Schinnar R, Ziegler EE, et al. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA*. 2001;286(7):807-814
 36. Conrad SC, Chiu H, Silverman BL. Soy formula complicates management of congenital hypothyroidism. *Arch Dis Child*. 2004;89(1):37-40
 37. Jabbar MA, Larrea J, Shaw RA. Abnormal thyroid function tests in infants with congenital hypothyroidism: the influence of soy-based formula. *J Am Coll Nutr*. 1997;16(3):280-282
 38. Chorazy PA, Himelhoch S, Hopwood NJ, Greger NG, Postelton DC. Persistent hypothyroidism in an infant receiving a soy formula: case report and review of the literature. *Pediatrics*. 1995;96(1 pt 1):148-150
 39. Messina M, Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. *Thyroid*. 2006;16(3):249-258
 40. Son HY, Nishikawa A, Ikeda T, Imazawa T, Kimura S, Hirose M. Lack of effect of soy isoflavone on thyroid hyperplasia in rats receiving an iodine-deficient diet. *Jpn J Cancer Res*. 2001;92(2):103-108
 41. American Academy of Pediatrics, Committee on Nutrition. Aluminum toxicity in infants and children. *Pediatrics*. 1996;97(3):413-416
 42. Fomon SJ, Ziegler EE. Isolated soy protein in infant feeding. In: Steinke FH, Waggle DH, Volgarev MN, eds. *New Protein Foods in Human Health: Nutrition, Prevention, and Therapy*. Boca Raton, FL: CRC Press Inc;1992:75-83
 43. Hawkins NM, Coffey S, Lawson MS, Delves HT. Potential aluminum toxicity in infants fed special infant formula. *J Pediatr Gastroenterol Nutr*. 1994;19(4):377-381
 44. Koo WW, Kaplan LA. Aluminum and bone disorders: with specific reference to aluminum contamination of infant nutrients. *J Am Coll Nutr*. 1988;7(3):199-214
 45. Graham GG, Placko RP, Morales E, Acevedo G, Cordano A. Dietary protein quality in infants and children. VI. Isolated soy protein milk. *Am J Dis Child*. 1970;120(5):419-423
 46. Fomon SJ, Ziegler EE. Soy protein isolates in infant feeding. In: Wilcke HL, Hopkins DT, Waggle DH, eds. *Soy Protein and Human Nutrition*. New York, NY: Academic Press Inc;1979:79-99
 47. Köhler 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(1):40-48
 48. Sarrett HP. Soy-based infant formulas. In: Hill LD, ed. *World Soybean Research. Proceedings of the World Soybean Research Conference*. Danville, IL: Interstate Printers and Publishers Inc; 1976:840-849
 49. Haffeejee IE. Cow's milk-based formula, human milk, and soya feeds in acute infantile diarrhea: a therapeutic trial. *J Pediatr Gastroenterol Nutr*. 1990;10(2):193-198
 50. Kulkarni PB, Hall RT, Rhodes PG, et al. Rickets in very-low-birth-weight infants. *J Pediatr*. 1980;96(2):249-252
 51. Allen UD, McLeod K, Wang EE. Cow's milk versus soy-based formula in mild and moderate diarrhea: a randomized, controlled trial. *Acta Paediatr*. 1994;83(2):183-187
 52. Zoppi G, Gasparini R, Mantovanelli F, Gobio-Casali L, Astolfi R, Crovari P. Diet and antibody response to vaccinations in healthy infants. *Lancet*. 1983;2(8340):11-14
 53. Businco L, Bruno G, Grandolfo ME, Novello F, Fiore L, Amato C. Response to poliovirus immunization and type of feeding in babies of atopic families. *Pediatr Allergy Immunol*. 1990;1:60-63
 54. Naudé SP, Prinsloo JG, Haupt CE. Comparison between a humanized cow's milk and a soy product for premature infants. *S Afr Med J*. 1979;55(24):982-986
 55. Shenai JP, Jhaveri BM, Reynolds JW, Huston RK, Babson SG. Nutritional balance studies in very-low-birth-weight infants: role of soy formula. *Pediatrics*. 1981;67(5):631-637
 56. Callenbach JC, Sheehan MB, Abramson SJ, Hall RT. Etiologic factors in rickets of very-low-birth-weight infants. *J Pediatr*. 1981;98(5):800-805
 57. Brown KH. Dietary management of acute diarrheal disease: contemporary scientific issues. *J Nutr*. 1994;124(suppl 8):1455S-1460S
 58. Brown KH, Lake A. Appropriate use of human and non-human milk for the dietary management of children with diarrhoea. *J Diarrhoeal Dis Res*. 1991;9(3):168-185
 59. Santosham M, Goepf J, Burns B., et al. Role of a soy-based lactose-free formula in the outpatient management of diarrhea. *Pediatrics*. 1991;87(5):619-622
 60. Brown KH, Perez F, Pearson JM, et al. Effect of dietary fiber (soy polysaccharide) on the severity, duration, and nutritional outcome of acute, watery diarrhea in children. *Pediatrics*. 1993;92(2):241-247
 61. Maulén-Radován I, Brown KH, Acosta MA, Fernandez-Varela H. Comparison of a rice-based, mixed diet versus a lactose-free, soy protein isolate formula for young children with acute diarrhea. *J Pediatr*. 1994;125(5 pt 1):699-706
 62. Hide DW, Guyer BM. Prevalence of infant colic. *Arch Dis Child*. 1982;57(7):559-560
 63. Blass EM, Hoffmeyer LB. Sucrose as an analgesic for newborn infants. *Pediatrics*. 1991;87(2):215-218
 64. Rushforth JA, Levene MI. Effect of sucrose on crying in response to heel stab. *Arch Dis Child*. 1993;69(3):388-389
 65. Treem WR, Hyams JS, Blankschen E, Etienne N, Paule CL, Borschel MW. Evaluation of the effect of a fiber-enriched formula on infant colic. *J Pediatr*. 1991;119(5):695-701
 66. Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics*. 1982;70(1):7-10
 67. Thomas DW, McGilligan K, Eisenberg LD, Lieberman HM, Rissman EM. Infantile colic and type of milk feeding. *Am J Dis Child*. 1987;141(4):451-453
 68. Taubman B. Parental counseling compared with elimination of cow's milk or soy milk protein for the treatment of infant colic syndrome: a randomized trial. *Pediatrics*. 1988;81(6):756-761
 69. Cook CD. Probable gastrointestinal reaction to soybean. *N Engl J Med*. 1960;263:1076-1077
 70. Ament ME, Rubin CE. Soy protein: another cause of the flat intestinal lesion. *Gastroenterology*. 1972;62(2):227-234
 71. Perkkio M, Savilahti E, Kuitunen P. Morphometric and im-

- munohistochemical study of jejunal biopsies from children with intestinal soy allergy. *Eur J Pediatr*. 1981;137(1):63-69
72. Poley JR, Kein AW. Scanning electron microscopy of soy protein-induced damage of small bowel mucosa in infants. *J Pediatr Gastroenterol Nutr*. 1983;2(2):271-287
 73. Iyngkaran N, Yadov M, Looi LM, et al. Effect of soy protein on the small bowel mucosa of young infants recovering from acute gastroenteritis. *J Pediatr Gastroenterol Nutr*. 1988;7(1):68-75
 74. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics*. 2003;111(4 pt 1):829-835
 75. Powell GK. Milk- and soy-induced enterocolitis of infancy: clinical features and standardization of challenge. *J Pediatr*. 1978;93(4):553-560
 76. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. 1998;133:214-219
 77. Burks AW, Casteel HB, Fiedorek SC, Williams LW, Pumphrey CL. Prospective oral food challenge study of two soybean protein isolates in patients with possible milk or soy protein enterocolitis. *Pediatr Allergy Immunol*. 1994;5(1):40-45
 78. Halpin TC, Byrne WJ, Ament ME. Colitis, persistent diarrhea, and soy protein intolerance. *J Pediatr*. 1977;91(3):404-407
 79. McDonald PJ, Goldblum RM, Van Sickle GJ, Powell GK. Food protein-induced enterocolitis: altered antibody response to ingested antigen. *Pediatr Res*. 1984;18(8):751-755
 80. Jenkins HR, Pincott JR, Soothill JF, Milla PJ, Harries JT. Food allergy: the major cause of infantile colitis. *Arch Dis Child*. 1984;59(4):326-329
 81. Odze RD, Bines J, Leichtner AM, Goldman H, Antonioli DA. Allergic proctocolitis in infants: a prospective clinical pathologic biopsy study. *Hum Pathol*. 1993;24(6):668-674
 82. Machida HM, Catto Smith AG, Gall DG, Trevenen C, Scott RB. Allergic colitis in infancy: clinical and pathologic aspects. *J Pediatr Gastroenterol Nutr*. 1994;19(1):22-26
 83. Burks AW, Casteel HB, Fiedorek SC, Williams LW, Connaughton C, Brooks JR. Enzyme-linked immunosorbent assay and immunoblotting determination of antibody response to major component proteins of soybean in patients with soy protein intolerance. *J Pediatr Gastroenterol Nutr*. 1989;8(2):195-203
 84. Udall JN. Serum antibodies to exogenous proteins: the significance? *J Pediatr Gastroenterol Nutr*. 1989;8(2):145-147
 85. Duke WW. Soy bean as a possible important source of allergy. *J Allergy*. 1934;5:300-302
 86. Eastham EJ, Lichauco T, Pang K, Walker WA. Antigenicity of infant formulas and the induction of systemic immunological tolerance by oral feeding: cow's milk versus soy milk. *J Pediatr Gastroenterol Nutr*. 1982;1(1):23-28
 87. Kuroume T, Oguri M, Matsumura T, Iwasaki I, Yuzuru K. Milk sensitivity and soybean sensitivity in the production of eczematous manifestations in breast-fed infants with particular reference to intrauterine sensitization. *Ann Allergy*. 1976;37(1):41-46
 88. Halpern SR, Sellars WA, Johnson RB, Anderson DW, Saperstein S, Reisch JS. Development of childhood allergy in infants fed breast, soy, or cow milk. *J Allergy Clin Immunol*. 1973;51(3):139-151
 89. Fomon SJ. Introduction to section IV. In: Hamburger RN, ed. *Food Intolerance in Infancy: Allergology, Immunology, and Gastroenterology*. Carnation Nutrition Education Series. Vol 1. New York, NY: Raven Press;1989:201
 90. Johnstone DE, Roghmann KJ. Recommendations for soy infant formula: a review of the literature and a survey of pediatric allergists. *Pediatr Asthma Allergy Immunol*. 1993;7:77-88
 91. Sampson HA. Jerome Glaser lectureship. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol*. 1988;81(4):635-645
 92. Businco L, Bruno G, Giampietro PG, Cantani A. Allergenicity and nutritional adequacy of soy protein formulas. *J Pediatr*. 1992;121(5 pt 2):S21-S28
 93. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev*. 2004;(3):CD003741
 94. Bardare M, Vaccari A, Allievi E. Influence of dietary manipulation on incidence of atopic disease in infants at risk. *Ann Allergy*. 1993;71(4):366-371
 95. Giampietro PG, Ragno V, Daniele S, Ferrara M, Cantari A, Businco L. Soy hypersensitivity in children with food allergy. *Ann Allergy*. 1992;69(2):143-146
 96. Lack G, Fox D, Northstone K, Golding J, Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. *N Engl J Med*. 2003;348(11):977-985
 97. Klemola T, Kalimo K, Poussa T, et al. Feeding a soy formula to child with cow's milk allergy: the development of immunoglobulin E-mediated allergy to soy and peanuts. *Pediatr Allergy Immunol*. 2005;16(8):641-646
 98. Zeiger RS, Sampson HA, Bock SA, et al. Soy allergy in infant and children with IgE-associated cow's milk allergy. *J Pediatr*. 1999;134(5):614-622
 99. Klemola T, Vanto T, Juntunen-Backman K, Kalimo K, Korpela R, Varjonen E. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr*. 2002;140(2):219-224
 100. Moritmer EZ. Anaphylaxis following ingestion of soybean. *J Pediatr*. 1961;58:90-92
 101. Foucard T, Malmheden Yman I. A study on severe food reactions in Sweden: is soy protein an underestimated cause of food anaphylaxis? *Allergy*. 1999;54(3):261-265

Use of Soy Protein-Based Formulas in Infant Feeding

Jatinder Bhatia and Frank Greer

Pediatrics 2008;121;1062

DOI: 10.1542/peds.2008-0564

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/121/5/1062>

References

This article cites 93 articles, 26 of which you can access for free at:
<http://pediatrics.aappublications.org/content/121/5/1062.full#ref-list-1>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

Current Policy

http://classic.pediatrics.aappublications.org/cgi/collection/current_policy

Committee on Nutrition

http://classic.pediatrics.aappublications.org/cgi/collection/committee_on_nutrition

Fetus/Newborn Infant

http://classic.pediatrics.aappublications.org/cgi/collection/fetus:newborn_infant_sub

Nutrition

http://classic.pediatrics.aappublications.org/cgi/collection/nutrition_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<https://shop.aap.org/licensing-permissions/>

Reprints

Information about ordering reprints can be found online:
<http://classic.pediatrics.aappublications.org/content/reprints>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . *Pediatrics* is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2008 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Use of Soy Protein-Based Formulas in Infant Feeding

Jatinder Bhatia and Frank Greer

Pediatrics 2008;121;1062

DOI: 10.1542/peds.2008-0564

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/121/5/1062>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2008 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

