

**COMMERCIAL INFANT FORMULAS:
COMPOSITION AND EFFECTS ON INFANT HEALTH OUTCOMES**

Infant Formula Product Monograph

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Despite extraordinary efforts by infant formula manufacturers to develop and promote marketable differences among their products, no single infant formula is generally recognized as superior by health care providers. Over half of the providers surveyed recently had no preference among formulas used for healthy infants, and suggested the mother choose from commercially available formulas. Of those who did have a preference, major commercial formulas were equally popular.¹

On the basis of available research, are there reasons to prefer one infant formula over another? This monograph critically reviews recent research into the effectiveness of commercial formulas in meeting infant health needs. It summarizes all relevant clinical and field trials which have evaluated one or more characteristics of commercial infant formulas, and includes several case reports involving infant formulas.

Studies have been included for review subject to these criteria: 1) The formulas or formula characteristics evaluated are commercially available in the United States. 2) Subjects are healthy full-term infants. Studies on pre-term infants (except following discharge from the hospital) are excluded. 3) The formula characteristics evaluated have not substantially changed since publication of the study, so that results remain relevant to formulas now on the market.

The monograph is organized according to the major differences among commercial formulas — ratios of whey to casein, purported allergenicity, fat blend, carbohydrate content, and nucleotide content. These differences provide the basis for sophisticated infant formula advertising directed toward pediatricians and other health care professionals. A sophisticated approach to the research basis for such advertising is important.

WHEY : CASEIN RATIO

Infant formulas (Table 1) provide protein in one of two forms, intact or hydrolyzed. Intact proteins from cow's milk are the most common. The ratio of whey proteins to casein can vary in these formulas, from 60:40 in whey-predominant formulas to 18:82 in casein-predominant formulas. Hydrolyzed protein, either casein hydrolysate or whey hydrolysate, provides an alternative to intact protein. Hydrolysate formulas are generally promoted as "hypoallergenic", and are discussed in the next section. This section reviews studies on formula variations in intact protein, specifically variations in whey to casein ratio.

The protein in cow's milk is about 80 percent casein, while that in human milk is about 80 percent whey proteins. One way to "humanize" cow's milk for human infants, therefore, is to adjust the levels of casein and whey to resemble human milk more closely. The so-called "whey-predominant" formulas (Enfamil[®]* and SMA[®]) have a whey:casein ratio of approximately 60:40. "Casein-predominant" formulas (Similac[®] and Gerber[®]) have a whey:casein ratio the same as cow's milk, approximately 18:82. Because of its closer approximation to human milk, possible advantages for the infant of a higher whey:casein ratio have been the subject of investigation.

Full-term healthy infants grow equally well whether fed human milk, whey-predominant, or casein-predominant formulas²⁻⁹ (Table 2). Although pre-term infants show plasma amino acid patterns more similar to breastfed infants when fed whey-predominant formulas,¹⁰⁻¹³ whey adjustment for term infants produces more equivocal results. Plasma amino acid patterns differ from breastfed infants at both high and low whey:casein ratios. While infants fed whey-predominant formulas consistently show higher plasma threonine^{2,4,6,7,9} those fed casein-predominant formulas tend to show higher tyrosine, higher phenylalanine, and lower tryptophan levels than breastfed infants.^{2,5,9} The physiological significance of these variations in plasma amino acid patterns is unknown but likely to be minimal. Threonine appears to be relatively non-toxic, and mean levels of all other amino acids in formula-fed infants fall within the range of normal fluctuations.

Two characteristics of the bovine whey and casein used in formulas may help explain the relatively small effect of whey adjustment. The bovine whey added to whey-predominant formulas is lower in alpha-lactalbumin and higher in beta-lactalbumin than human milk.¹⁴ This means that the simple adjustment of whey:casein ratio does not necessarily bring the formula amino acid pattern in line with that of human milk. In addition, the ratio of whey:casein used in whey-predominant formulas

* See Table 1 for commercial product manufacturers.

reflects older estimates of the ratio in human milk. Newer analyses have placed the human milk whey:casein at 80:20, considerably higher than the 60:40 ratio used in commercial formulas.¹⁵

"HYPOALLERGENIC" FORMULAS AND FORMULA TOLERANCE

True Allergic Reactions to Cow's Milk Protein

For infants at high risk of allergic reactions to cow's milk (such as family history) or for those with documented hypersensitivity to cow's milk, promoting extended breast feeding and delaying introduction of solid foods beyond six months are both recommended. But infants allergic to cow's milk who must be formula fed have two alternatives readily available: soy formulas (such as Isomil,[®] Pro-Sobee,[®] or Nursoy[®]) or formulas based on cow's milk protein which has been treated so as to reduce its allergenicity.¹⁶

Hypoallergenic formulas based on treated cow's milk protein have become more popular because soy formulas can provoke adverse reactions in up to half of infants with cow's milk protein allergies,¹⁷ and are not recommended in routine management of cow's milk allergy.^{16,18} Enzymatic hydrolysis of casein or whey proteins renders them less allergenic. Casein hydrolysate formulas, such as Pregestimil,[®] Nutramigen,[®] and Alimentum[®] contain casein that is extensively hydrolyzed to non-antigenic peptide fragments of less than 1200 mol wt. Whey hydrolysate formulas such as Good Start[®] are less completely hydrolyzed than the casein hydrolysates, and contain some antigenic peptides of more than 2000 mol wt.

Clinical trials with hypoallergenic formulas (Table 3) suggest that for infants with documented allergy or with high allergy risk, both casein hydrolysate and whey hydrolysate formulas can be helpful in preventing or alleviating allergic symptoms.^{17,19-23} The American Association of Pediatrics Committee on Nutrition (AAP-CON), however, suggests that whey hydrolysate formulas may remain too allergenic for infants with true cow's milk protein allergy.¹⁶ Indeed, anaphylaxis has been reported following ingestion of both whey hydrolysate^{24,25} and casein hydrolysate^{26,27} formulas in highly atopic infants.

Formula Intolerance

Formula fed infants in the U.S. commonly have their cow's milk formulas changed to soy formulas on the assumption that the infant is "allergic" to cow's milk proteins. In a prospective study of healthy newborn infants, 26% of all formula-fed infants followed by pediatricians in private practice had their formulas changed to non-cow-milk containing formulas by 4 months of age, mostly in response to complaints of crying and feeding problems.²⁸ In Britain, where maternity units usually start newborns on whey-predominant formulas, an equivalent percentage of infants (23%) had their

formulas changed to casein-predominant formulas within 6 weeks because of crying, colic, or "digestive symptoms."²⁹ Whereas American mothers often ascribe formula changes to "cow's milk allergy," British mothers often feel their babies are "more satisfied" when formulas are changed.

The tendency to change formula in response to common problems of infant care is unfortunately well established. The AAP-CON recommends that "colic, sleeplessness, and irritability are symptoms seen in almost all infants at some time during infancy" and should not prompt a change to soy formula.¹⁶ A substantial body of research addresses the question of the role of diet in colic, sleeplessness, and intestinal upset.

1. Colic

For several decades, a popular theory has held that colic is a specific allergic reaction to the proteins in cow's milk, but no research has definitively demonstrated that colic is affected by the composition of milk or formula ingested by the infant. Several lines of evidence suggest that colic is not an immune-mediated reaction to cow's milk protein: it occurs equally in breast- and formula-fed infants; it is highly responsive to placebo, suggesting that parental perceptions are important and that a true allergy to milk is unlikely; and, like normal infant crying behavior but unlike allergy, it tends to resolve at 10-12 weeks of age.³⁰

Two older studies from a Swedish laboratory supporting cow's milk allergy as the cause of colic^{31,32} have been criticized.^{33,34} A more recent survey of healthy infants under one year of age found that dietary protein hypersensitivity was not the cause of colic in healthy infants.³⁵ A study designed to correct the methodologic flaws that have led to these contradictory results showed that a change to a casein hydrolysate formula produced improvement in crying behavior in some colicky infants. The effect, however, diminished with time, was rarely reproducible, and was accompanied by a marked day-to-day variability in colic regardless of the formula fed.³⁶

2. Sleeplessness, Gastrointestinal Symptoms

Sleeplessness and intestinal upset may also prompt a change in formulas. One research center has reported correction of serious sleep disorders in infants ranging in age from 2.5 to 29 months by excluding cow's milk from their diet. They found both a reduction in average numbers of arousals per night and an increase in average total sleep time per day when infants were changed to a whey-hydrolysate formula.^{37,38} This work has not been independently confirmed by other researchers. Complaints from parents that iron-fortified formulas cause problems such as colic, constipation or loose stools, and spitting up lead some pediatricians to change to non-iron-fortified formulas, despite the need for iron fortification in formula-fed infants.³⁹ Two well-controlled studies showed that gastrointestinal side effects did not occur more often when iron-fortified formulas were fed.^{40,41} To date,

formula changes that result from sleep disorders or putative intolerance to iron fortification are not well supported by the research literature.

FAT BLEND

Clinical studies have not addressed the health effects of the current infant formula fat blends, which are designed by infant formula manufacturers to reproduce the fatty acid distribution of human milk. Using a blend of inexpensive fat sources that are well absorbed, with acceptable flavor, shelf stability, and melting point, commercial formula fat blends are comprised of two or more of the following oils (Table 1): 1) coconut oil — to supply readily digestible medium-chain triglycerides; 2) soy oil — a good source of alpha-linolenic acid; 3) corn or safflower oil — for linoleic acid; and 4) oleo (de-stearified beef tallow), high-oleic safflower, or palm olein as a source of monounsaturated fatty acids.

Two concerns have led the formula companies to re-evaluate their fat blends in the last decade. First, the use of coconut oil as part of the fat blend by all of the major formula companies has raised some concern among the public, where pressure to remove highly saturated tropical oils from processed foods has been very effective.⁴² Dietary fat modifications that are appropriate for adults, however, are not recommended for children under two years of age.^{43,44} A cholesterol-lowering fat blend is probably not necessary for formula-fed infants, who generally have serum cholesterols lower than their breastfed counterparts.⁴⁵ Research continues on the role of early diet on atherogenesis.

A second concern comes from new knowledge about the health benefits of the omega-3 family of fatty acids. Attention to the levels of the omega-3 parent fatty acid, alpha-linolenic acid, in infant formulas has led to increased use of soy oils in formula fat blends. Soy oil is a relatively rich source of alpha-linolenic acid, and is now a component of all major infant formulas except Similac® and Isomil®. It should be emphasized that the requirement for alpha-linolenic acid in growing infants is not known. In human milk, alpha-linolenic acid provides about 1% of the total fatty acids, and the ratio of linoleic to alpha-linolenic acid is around 10. In commercial formulas, alpha-linolenic acid provides from 0.5% to 1.0% of the fatty acids and the ratio of linoleic acid to alpha-linolenic acid ranges up to 50.⁴⁶

CARBOHYDRATE CONTENT

As in human milk, the only carbohydrate source in most commercial formulas is lactose. Exceptions are soy formulas, where lactose is avoided in the belief that lactose intolerance is a primary or secondary problem associated with cow's milk intolerance, and whey-hydrolysate formulas such as

Good Start,[®] where maltodextrin replaces 30 percent of the lactose in order to compensate for the increased osmolality of protein hydrolysates.

Formula carbohydrates are not a concern in healthy infants. Even in infants with acute or chronic diarrhea, current data do not suggest that lactose be routinely eliminated from the diet according to AAP-CON.⁴⁷ Carbohydrate absorption in general, however, may be problematic for infants with intractable diarrhea or short bowel syndrome.^{48,49,50} In these conditions, special attention can be given to the kind and amount of carbohydrate fed.

FORMULA NUCLEOTIDE CONTENT

One infant formula, SMA,[®] now has nucleotides added to the formulation. The rationale for this formula change was probably based both on the observation that human milk provides one to two milligrams of nucleotide nitrogen per day,⁵¹ and on animal research showing that dietary nucleotides are necessary for cell-mediated immune function.⁵² Only one study (sponsored by Wyeth, makers of SMA) evaluating the effects of dietary nucleotides on infant immune function has been published. Thirteen infants fed nucleotide-supplemented formula for the first four months of life were compared with those fed non-supplemented SMA or human milk. At two months of age, levels of natural killer cell cytotoxicity and interleukin-2 production by peripheral mononuclear cells were significantly higher in breastfed and nucleotide-supplemented infants. By four months, however, these outcomes again tended to be positive for nucleotide-supplemented and breastfed infant, but differences from unsupplemented infants were not statistically significant.⁵³ Independent confirmation of these findings are required, and longer term studies with larger population groups are needed to establish the clinical significance of nucleotide-supplemented formulas.

CONCLUSIONS

The unique features of research on infant formulas should be considered when evaluating the scientific basis for formula recommendations. First, a randomized and double-blind study design is impossible when the control group is breast-fed, as is often the case. Second, much of the research on formula effectiveness is sponsored or supported by the manufacturer of the formula under study. While a published report can be evaluated on its own merits, the interests of sponsors may, in general, exaggerate an already recognized bias toward positive rather than negative results among published research findings. And third, some important areas of research have not yet been addressed, such as the long-term effects of infant formulas on cardiovascular and immune health.

Nevertheless, the research on infant formulas is reassuring on several points. All of the major formula manufacturers are keeping abreast of current research and making changes as appropriate,

usually ahead of advisory or regulatory agencies such as American Academy of Pediatrics—Committee on Nutrition or the Food and Drug Administration. In addition, research shows that frequent formula switching to alleviate such common problems of infancy as colic, sleeplessness or spitting up, among others, is not necessary unless problems are caused by true milk protein allergy. And finally, all of the major commercial formulas promote normal growth and development. All can be used safely when needed as an alternative to breast feeding.

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TABLE 1. Comparison of Macronutrients in Routine Commercial Infant Formulas

formula class	commercial formula	protein		fat		carbohydrate	
		g/dl	whey: casein	g/dl	source	g/dl	source
casein-predominant	Gerber (Gerber Products)	1.5	18:82	3.6	60% soy 40% coconut	7.2	lactose
	Similac (Ross Laboratories)	1.5	18:82	3.6	50% corn 50% coconut	7.2	lactose
whey-predominant	Enfamil (Mead Johnson Nutritionals)	1.5	60:40	3.8	55% coconut 30% corn 15% soy	7	lactose
	SMA (Wyeth-Ayerst Laboratories)	1.5	60:40	3.6	33% oleo 27% coconut 25% high-oleic safflower 15% soy	7.2	lactose
casein-hydrolysate	Alimentum (Ross Laboratories)	1.9	0:100	3.8	50% MCT 30% safflower 20% soy	6.9	sucrose and modified tapioca starch
whey-hydrolysate	Nutrigen (Mead Johnson Nutritionals)	1.9	0:100	2.7	100% corn oil	9.1	corn syrup solids and modified cornstarch
	Pregestimil (Mead Johnson Nutritionals)	1.9	0:100	2.7	60% corn oil 40% MCT	9.0	corn syrup solids and modified tapioca starch
soy protein	Good Start (Carnation Company)	1.6	100:0	3.4	47% palm olein 26% soy 21% coconut 6% high-oleic safflower	7.4	lactose and maltodextrin
	Isomil (Ross Laboratories)	1.8	NA	3.7	50% corn 50% coconut	6.8	corn syrup solids; sucrose
soy protein	ProSobee (Mead Johnson Nutritionals)	2.0	NA	3.6	55% coconut 30% corn 15% soy	6.8	corn syrup solids
	Nursoy (Wyeth-Ayerst Laboratories)	2.1	NA	3.6	33% oleo 27% coconut 25% high-oleic safflower 15% soy	6.9	sucrose
soy protein	Soyalac (Loma Linda)	2.1	NA	3.7	100% soy	6.8	sucrose; corn syrup

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TABLE 2. Whey to Casein Ratio in Infant Formulas: Effect on Infant Growth and Plasma Amino Acid Levels*

study/ funding support	subjects	n	age at entry	feeding period (weeks)	control group	formula protein (g/dl)	whey:casein	outcomes (relative to control)	
								growth measures	plasma amino acids
Lonnedal <i>et al</i> 1990 ² Wei-Chuan Foods	healthy infants (China)	not rept.	newborn	12	human milk fed	1.4	55:45	no difference	↑ threonine
						1.4	60:40	no difference	↑ threonine
						1.4	20:80	no difference	↓ tryptophan
Bernbaum <i>et al</i> 1989 ³ Ross Laboratories	healthy premature infants at hospital discharge (U.S.)	10	38 weeks postconception	12	casein- predominant	1.5	"casein- predominant" (Similac)	(served as control)	
						1.5	"whey-predominant" (modified Similac)	no difference	
Rigo <i>et al</i> 1989 ⁴ Nestle (Carnation)	healthy full-term infants (U.S.)	10	newborn	1	human milk fed	1.5	60:40	no difference	↓ cystine ↓ histidine ↓ phenylalanine
						1.6	100:0 whey hydrolysate (Good Start)	no difference	↑ threonine ↓ proline ↓ tyrosine
Janas <i>et al</i> 1987 ⁵ Ross Laboratories	healthy full-term infants (U.S.)	10	newborn	8	human milk fed	1.23	18:82	no difference	↓ tryptophan ↑ isoleucine ↓ citrulline ↑ methionine ↓ phenylalanine
						1.23	34:66	no difference	(same as above)
						1.23	50:50	no difference	(same as above)
Berry <i>et al</i> 1986 ⁶ (abstract)	healthy newborns (U.S.)	12-15	1 week	6	casein- predominant	not rept.	"casein- predominant"	not reported	(served as control)
							"whey- predominant"	not reported	↑ threonine ↓ methionine ↓ proline
Janas <i>et al</i> 1985 ⁷ Ross Laboratories	healthy full-term infants (U.S.)	11-14	newborns	8	human milk fed	1.5	"cow's milk formula" (casein-predominant)	no difference	↑ phenylalanine ↑ valine ↑ methionine
						1.5	"whey- predominant"	no difference	↑ threonine ↑ phenylalanine ↑ branch-chain amino acids ↑ methionine ↑ lysine
Jarvenpaa <i>et al</i> 1982 ^{8,9} Wyetth Laboratories	healthy full-term infants (Finland)	10-11	newborns	12	human milk fed	1.5	18:82	no difference	↑ phenylalanine ↑ tyrosine ↑ branch-chain amino acids ↓ serine ↓ aspartate
						1.5	60:40	no dif. urence	↑ threonine ↑ branch-chain amino acids

TABLE 3. Hypoallergenic Formula Use in Infants At Risk of Cow's Milk Allergy

study/ funding support	study objective	n	age at entry / age at assessment	amount fed	feed	subjects with allergic reactions (n)
Sampson <i>et al</i> 1991 ¹⁷ Ross Laboratories	assess safety of casein hydrolysate formula for use in documented cow's milk hypersensitivity	23	8 months to 9.5 years / same	10 gm challenge over 90 minutes	Alimentum	none
Chandra <i>et al</i> 1991 ¹⁹ and 1989 ²⁰	assess effectiveness of infant feeding in preventing atopic disease in infants with family history	72	newborns / 18 months	exclusive diet for 4 months	Similac Isomil Good Start breast milk	29 30 18 15
Merritt <i>et al</i> 1990 ²¹ Carnation Company	alleviate gastrointestinal symptoms of cow's milk or soy milk formula allergy	18	2 weeks to 5 months / 6 to 11 months	only formula used for at least 5 weeks	whey-hydrolysate formula	3
Vandeplass <i>et al</i> 1989 ²² and 1988 ²³ Nestle Company	assess effectiveness of infant feeding in preventing atopic disease in infants with family history	15	newborns / 4 months	exclusive diet for 4 months	whey-predominant cow's milk formula whey-hydrolysate formula breast milk	8 0 1