
A BACKGROUND PAPER ON INFANT FORMULAS

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FOREWORD

The Federation of American Societies for Experimental Biology (FASEB) recognizes that its resources are particularly suited to marshalling scientific expertise for review and assessment of topics in the biological and medical sciences. The Life Sciences Research Office (LSRO) was established by FASEB in 1962 as an operational arm of the Executive Director's staff to conduct scientific review and analysis studies. Reports of LSRO studies are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators in specific areas of biology and medicine.

This background paper was prepared for the Office of the Associate Director for Nutrition and Food Sciences, Bureau of Foods, Food and Drug Administration (FDA) in accordance with the provisions of FDA Contract No. 223-79-2275. This document has been reviewed by the consultants listed in Section X and their viewpoints and opinions were incorporated; however, the listing of their names does not imply endorsement of the contents of this background paper.

This report discusses various topics related to infant formulas and provides background information for two public proceedings to be held by the FDA. The first public meeting, to be held on February 19-20, 1980 (9:00 a.m., Main Auditorium, HEW Building, 330 Independence Avenue, S.W., Washington, DC), will be concerned with quality assurance and quality control procedures; manufacturing, packaging, and labeling; and clinical testing as they relate to infant formulas. The second proceeding (at the same time of day and location) on March 12-13, 1980 will be a public hearing concerning current nutrient composition of infant formulas and possible revisions of existing regulations on infant formulas. This background paper covers topics to be presented at both public proceedings. Additional information on these two FDA proceedings has been published in the Federal Register (Vol. 45, No. 20, p.6702-6703, January 29, 1980).

In accordance with the policies and guidelines developed by the LSRO Advisory Committee, this report has been reviewed and approved for submission by the Chairman of the LSRO Advisory Committee. Reports prepared by LSRO do not necessarily reflect the opinion of the individual members of the FASEB constituent societies. The authors and LSRO are solely responsible for the contents of this report.

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I. INTRODUCTION

A. HISTORY OF THE DEVELOPMENT OF INFANT FORMULAS

The availability of satisfactory infant formulas is relatively recent. Until the 20th century, there was virtually no safe and reliable alternative to breast feeding and few infants not suckled by mothers or wet nurses survived their first year. While infectious diseases undoubtedly played a major role in mortality of all infants at this time, available statistics from the 18th and 19th centuries reveal an appalling mortality among infants who were not breast fed. At the Paris Foundling Hospital, of approximately 31,000 infants admitted from 1771 to 1777, more than 25,000 (80%) died before their first birthday. Records of the Dublin Foundling Hospital for the last quarter of the 18th century indicate only 45 of 10,272 infants admitted survived, a mortality rate of 99.6%!! In London in the early part of the 19th century, less than one of eight infants not breast fed survived their first year (Cone, 1976; Forsyth, 1911).

In the late 19th century, discoveries in biology and medicine provided a basis for development of substitutes for human milk. Causes of various infectious diseases were discovered and the need for sanitation was established. Benefits of pasteurization became well known about the turn of the century. The improved utility of cow milk for infant nutrition following heat treatment was discovered. Several physicians attempted to develop an adequate substitute for breast milk. Many of these early preparations were based on cow milk, modified to approximate the composition of human milk. The first marketed preparation was developed and patented in 1867 by the German chemist Justus von Liebig, who modestly termed it the "perfect infant food". It consisted of a mixture of wheat flour, cow milk, and malt flour, cooked with a little potassium bicarbonate to reduce the acidity of the mixture (Cone, 1976). The commercial success of this formula spawned a host of competitors during the last quarter of the 19th century. These proprietary foods could be divided roughly into three categories: 1) dried cow milk, combined with some cereal and sugar; e.g. Nestle's Food® and Horlick's Malted Milk®; 2) some form of malted carbohydrate, of which Mellin's Food®, a desiccated malt extract, was the most popular; and 3) a pure cereal to be used with fresh cow milk. The best known brand names of this last group were Eskay's Food®, Imperial Granum®, and Robinson's Potent Barley® (Cone, 1976).

* Trade names and products are mentioned in this document solely to provide specific information. Mention of a trade name or specific product does not constitute an endorsement of that product nor does lack of mention of similar trade names or specific products imply intentional oversight.
An important development in infant feeding occurred at the end of the 19th century when Heubner and Rubner published their calorimetric method of feeding, which made it possible to feed infants according to their caloric (energy) requirements. This was the starting point of all modern studies on infant metabolism (Cone, 1976).

Most of these efforts of the late 19th century were unsuccessful because many of the foods consisted of little more than concentrated solutions of soluble carbohydrates. They were used as the sole source of diet and resulted in great harm to many infants. The cereal diluents were added, not for their food value, but for their supposed action in preventing the formation of the large, indigestible, casein curds, which may occur in non-heat treated cow milk. Little attention was paid to the caloric requirements of the infant. It must be kept in mind that these efforts to develop substitutes for human milk were made long before nutritional needs and the identity of essential nutrients were established. Thus, until the early 20th century, the nursing mother and the wet nurse were the mainstays of infant nutrition. Since that time, the risk of nourishing the infant other than by breast feeding has declined markedly in the United States and other developed countries. The decline in risk has been related both to the control of infectious diseases and to the development of safe and reliable infant formulas.

The modern era of mixtures of known composition as all-inclusive foods for infants began in 1915 when Gerstenberger and colleagues developed an artificial milk in which the fat content had been adapted to simulate human milk. This first "formula" was achieved by adding various homogenized vegetable and animal fats and oils to skim cow milk to approximate the fatty acid content of human milk. The fluid mixture contained about 4.6% fat, 6.5% carbohydrate, and 0.9% protein (Gerstenberger et al., 1915). Four years later, Gerstenberger and Ruh (1919) successfully used this mixture in feeding about 300 infants. The investigators named their preparation S.M.A., for Synthetic Milk Adapted. Many products available today are modifications of this basic formula.

Before single-formula mixtures came into general use, evaporated milk was the most common base for infant feeding. In 1856, Borden developed a method of concentrating raw cow milk by vacuum evaporation and preserving the concentrate with added sugar (a product still available as condensed milk). In 1883, Myenberg improved this procedure by sterilizing unsweetened milk concentrate at 200° to 240°F (Cone, 1976). This allowed the preservation of unsweetened evaporated milk and at the same time modified the casein to yield a fine curd. Infants on formulas using this unsweetened evaporated cow milk fared as well as babies fed exclusively on breast milk, or on formulas from bottled pasteurized cow milk (Marriott and Schoenthal, 1929). The evaporated milk was inexpensive, easy to obtain, did not require refrigeration (rarely available at that time), and assured sterility in contrast
to the cow milk supplies of questionable purity then available. Consequently, from 1930 to 1950, evaporated milk became the most widely accepted and versatile ingredient for infant formulas. By 1960, it was estimated that 80% of formula-fed infants in the United States were given either evaporated milk or some milk preparation marketed in evaporated form (Cone, 1976).

During the past 20 years, commercial preparations have largely supplanted evaporated milk formulas because of their uniformity, convenience, nutritional quality, and safety. By 1972, less than 5% of all 2-month-old infants were receiving evaporated milk formulas, and a great majority were receiving commercially prepared formulas (Fomon, 1974). Another striking change in infant feeding practice has been the shift from powdered to liquid formulas. Powdered formulas, which comprised about 50% of the sales for commercially prepared formulas in 1950, comprise less than 5% of the market at present.

Since the 1940's, the success of commercially prepared infant formulas has stimulated the development of numerous formulations. According to Hambraeus (1977), several hundred varieties of proprietary infant formulas are available throughout the world. Most are based on cow milk, but a number have a vegetable-protein base. In the United States today, six proprietary formulations account for almost all of the infant formulas marketed for feeding normal infants (Fomon, 1975). In addition, a number of special formulas for use in clinical situations or for infants with specific inborn errors of metabolism are available as special dietary foods.

B. INFLUENCE OF PHYSIOLOGICAL CAPABILITIES ON NUTRITIONAL NEEDS OF INFANTS

The digestion and absorption of food components as well as excretion of waste products by the infant are limited by the physiological capabilities of its gastrointestinal and renal systems. These limitations must be considered in developing formulas which can adequately substitute for human milk at a time when nutritional needs are especially high. In early infancy, the sucking and involuntary swallow reflexes are the only mechanisms by which the infant can procure and ingest food (Graber, 1966). Food must therefore be in liquid form until coordination between complex tongue movements and mature swallowing reflexes develops. Stomach capacity is small, requiring frequent feedings to supply adequate amounts of nutrients for growth and development. A caloric density of 67 kcal/dl appears optimal for normal infants (American Academy of Pediatrics, 1976).

The newborn infant can digest fats, proteins, and carbohydrates and these abilities improve as the infant matures (Koldovsky, 1978). Although some initial digestion of protein and fat occurs in the infant's stomach by pepsin (Agunod et al., 1969) and gastric lipase (Cohen et al., 1971) respectively, both protein and fat are digested mainly in the infant's small intestine.
Pancreatic lipase activity is relatively high in the small intestine (Andersen, 1942; Hadorn et al., 1968); however, concentrations of bile acids in the small intestine of the young infant are below levels found in adults (Bongiovanni, 1965; Holt, 1972; Koldovsky, 1978; Norman et al., 1972). For example, in full-term infants, bile acid concentration in duodenal fluid is about 5 mg/ml, while in children and adolescents it normally exceeds 15 mg/ml. In addition, the specific forms and proportions of bile acids differ between infants and adults; deoxycholates are not present in infants, and the proportion of glycine and taurine conjugates differs (Bongiovanni, 1965; Koldovsky, 1978; Younoszai, 1974).

Absorption of fat improves as the infant matures (Fomon, 1974). In general, long-chain saturated fatty acids, such as those found in butterfat, are not absorbed as well as unsaturated fatty acids found in vegetable oils (Ziegler et al., 1972). The position of specific fatty acids in the triglyceride molecules may also influence the absorption of fatty acids (Filer et al., 1969).

Although the proteolytic enzymes, trypsin and chymotrypsin, are less active in infants than in adults (Andersen, 1942; Delachâume-Salem and Sarles, 1970), the extent of protein digestion does not differ appreciably from that of adults (Borgström et al., 1960). Amino acids from protein digestion are absorbed by active transport mechanisms; in addition, absorption of some intact proteins from foods occurs in the intestinal wall of infants (Koldovsky, 1978).

Except for starch, the capacity for carbohydrate digestion and absorption is well developed in the full-term infant (Anderson et al., 1972). If the infant receives no starch in the diet, α-amylase activity increases rather slowly during the first 6 months of life (Andersen, 1942); on the other hand, feeding starch to infants stimulates α-amylase activity (Zoppi et al., 1972). While starch is known to be digested by a glucamylase enzyme in the intestinal mucosa of young rats (Alpers and Solin, 1970), the existence and possible significance of this pathway in the human infant remain to be established.

In the small intestine, lactase activity is greater in the infant than in the adult; however, the activities of the disaccharidases, maltase and sucrase, are approximately the same in both age groups (Auricchio et al., 1965). Monosaccharides are well absorbed, although the absorptive capacity of infants may not equal that of adults (Gray and Ingelfinger, 1966; Holdsworth and Dawson, 1964; James, 1970; Malawer et al., 1965; Torres-Pinedo et al., 1966).

Certain waste products are excreted in solution via the urinary system. These waste products, termed the renal solute load, include electrolytes ingested in excess of body needs and metabolic end products from protein digestion and metabolism.
(Bergmann et al., 1974). A simple and direct relationship between renal solute loads and dietary concentrations of protein and minerals does not exist because some loss of water and metabolic end products occurs through the skin (sweat), lungs (water vapor), and gastrointestinal tract, and because ingested minerals and products of protein degradation (amino acids) are used to build new tissues. The total solute load of a formula is of little value in predicting its renal solute load because it may contain relatively high concentrations of soluble carbohydrates which, when metabolized, yield essentially no solutes for renal excretion.

However, the renal solute load is an important determinant of the quantity of water excreted through the kidney. The ability of the kidney either to concentrate urine (Edelmann et al., 1960; Polacek et al., 1965; Winberg, 1959) or to dilute renal solute load by excretion of excess water (Kleinman, 1978) is less in the young infant than in older infants, children, or adults. Although proprietary formulas fed at proper concentrations provide ample water (1.5 ml/kcal/day) for all routes of water loss including urinary excretion, Bergmann et al. (1974) cautioned that under circumstances of limited fluid intake or excessive water losses, diets with high renal solute loads may stress the limited capacity of the continually developing kidney reabsorption system.
II. REQUIREMENTS OF INFANT FORMULAS

A. PHYSICAL CHARACTERISTICS

Infant formulas are available as powders, liquid concentrates, and ready-to-feed products. Originally, virtually all formulas were available as powders and were intended for use in hospitals. In the early 1950's, concentrated liquid formulas became available and rapidly replaced the powders. Concentrated liquids, in turn, were largely supplanted by ready-to-feed formulas when these became available in the 1960's. In the current marketplace, most products for home use are either the ready-to-feed liquids or concentrated preparations to be diluted with water prior to use. Ready-to-feed prepackaged formulas constitute about 40% and powdered forms less than 10% of the formula marketed in the United States currently.

All infant formulas are, or upon preparation will produce, emulsions of edible oils in aqueous solutions. While it occurs only rarely in commercially available formulas because of the presence of stabilizers, separation of fat can occur in infant formulas. During normal shelf life, the fat can be redispersed by shaking the container. However, in the absence of stabilizers, or with storage beyond shelf life, the separated fat becomes progressively firmer and cannot be redispersed with normal shaking. Floating flakes of separated fat may result.

Infant formulas may also manifest protein agglomeration if the storage time is excessive. This agglomeration may range from slight grainy development through increased viscosity and formation of gels, to eventual precipitation of protein. Although fat separation and protein agglomeration do not affect the safety or nutritional adequacy of the formulas, they present an objectionable appearance. In addition to use of stabilizers, infant formulas are dated as to the period of shelf life during which separation and agglomeration will not occur.

Thickening and stabilizing agents are used frequently to provide uniform consistency and to prolong stability of liquid formulas. For example, carrageenan is a stabilizing agent in many infant formulas sold in the United States. Conditions of use are specified in the Code of Federal Regulations [21 CFR 172.620]* (Food and Drug Administration, 1979). The Codex Alimentarius

* Citations such as 21 CFR 172.620 refer to a particular part or section (e.g. 172.620) in the Code of Federal Regulations, Title 21. Food and drugs, parts 100-199 rev. 1979 edition. Published by the Office of the Federal Register, General Services Administration, copies are available from the U.S. Government Printing Office, Washington, DC 20401.
Commission (1976) has, in its Recommended International Standards for Foods for Infants and Children, promulgated guidelines on maximum levels of use for a number of thickening agents and emulsifiers including guar gum, locust bean gum, distarch phosphate, acetylated distarch phosphate, phosphated distarch phosphate, hydroxypropyl starch, carrageenan, lecithin, and mono- and diglycerides. In the United States, use of these substances as stabilizers, thickening agents, or emulsifiers is covered by FDA's Generally Recognized as Safe [21 CFR 182 et seq.] and food additive [21 CFR 170 et seq.] regulations. Each commercially prepared infant formula may contain one or more of these substances; however, in no case are all used in one formulation. The European Society for Paediatric Gastroenterology and Nutrition (ESPGAN Committee on Nutrition, 1977) concluded that insufficient data were available on certain of these substances. It recommended that thickening agents for technological purposes should not be included in those formulas used in European countries for infants younger than 4 months of age.

B. MICROBIOLOGICAL SAFETY

The need for control of microbial contamination in, and strict exclusion of pathogenic organisms from, infant formulas is a generally accepted principle of pediatric nutrition. Microbial contamination of powdered or prepared formulas may alter their nutritional quality as a result of microbial growth and metabolism. More importantly, inadvertent introduction of enteric bacterial, viral, or other pathogens can result in diarrhea and subsequent fluid and electrolyte imbalances. Because the infant typically receives its entire nutrient supply and most of its water from the formula, microbiological integrity of formulas has received considerable attention at every stage of formulation, production, preparation, and use. Assurance of microbiological safety is a major objective of quality control and quality assurance procedures. Guidelines of the Infant Formula Council* (1973) require liquid formulations to be free of all viable pathogens and their spores, and of other organisms which may cause product degradation. Such commercially sterile products will remain free of microbial effects as long as the container remains intact. Powdered formulas are essentially free of microorganisms, and the required heating during final preparation (as indicated on label directions) destroys most microorganisms introduced during preparation.

* The Infant Formula Council (5775 Peachtree-Dunwoody Road, Suite 500-D, Atlanta, Georgia 30342) is a voluntary, nonprofit, trade association composed of five companies engaged in manufacture and marketing of commercial infant formulas (Loma Linda Foods, Mead Johnson & Co., Ross Laboratories, Syntex Laboratories, and Wyeth Laboratories).
C. DIGESTIBILITY

When milk comes into contact with hydrochloric acid in the stomach, it coagulates to produce a precipitate or curd. The curd contains most of the casein and calcium of the milk, leaving whey proteins and lactose in the watery portion. Unprocessed cow milk produces tough, rubbery curds which may be somewhat difficult for young infants to digest. Fresh human milk contains less casein than cow milk and produces soft, flocculent, more digestible curds in the stomach. Homogenization, evaporation, boiling, and drying reduce the curd tension of cow milk. Infant formulas containing cow milk are sufficiently processed to avoid any problems with curd production.

D. NUTRITIONAL ADEQUACY

The Food and Drug Administration has published a regulation covering nutrient composition of infant formulas [21 CFR 105.65] which is based largely on guidelines proposed by the Committee on Nutrition (American Academy of Pediatrics, 1967). Continued research on infant nutritional needs and collection of clinical data relating to infant formulas have emphasized the need to review these standards. Thus, modified guidelines were proposed by the Committee on Nutrition (American Academy of Pediatrics, 1976). Similarly, other authorities, including the Canadian Food and Drug Directorates, the Codex Alimentarius Commission's Committee on Foods for Special Dietary Use, and the Food and Nutrition Board of the National Academy of Sciences, have developed recommendations on nutritional aspects of infant formulas. The Food and Nutrition Board (National Research Council, 1980) has recently revised and published its Recommended Dietary Allowances (RDA's) of nutrients for various segments of the U.S. population including infants (Table 1, page 33).

The current FDA regulations and most recommendations of other authorities apply to formulas prepared for healthy infants from birth to 12 months of age. The FDA has indicated an intent to update the regulations on nutrient composition of infant formulas in the near future. The Committee on Nutrition, American Academy of Pediatrics, is currently reevaluating the 1976 proposed guidelines and its amendments. A summary of the Committee's deliberations will be presented at the public hearing on March 12-13, 1980.

The recommended minimum nutrient levels proposed by the Committee on Nutrition (American Academy of Pediatrics, 1976) are compared in Table 2 (page 34) with those required under current FDA regulations. The Committee adopted a single standard that applies to both milk-based and milk-substitute formulas and recommended maximum levels for several of the nutrients. Unmodified cow milk and evaporated milk at usual dilutions do not meet the proposed guidelines of the Committee on Nutrition. Aspects of nutrient composition of formulas are discussed in more detail in a later section.
E. AVOIDANCE OF ADVERSE REACTIONS

Foods may evoke a wide variety of signs and symptoms ranging from mild discomfort to life-threatening shock. Such reactions may be brought about by a variety of mechanisms, including: a) intestinal enzyme deficiencies, e.g., lactase deficiency; b) contaminants, e.g., microbial toxins; c) noxious natural constituents; d) neurologic and psychologic disturbances; and e) immunologic injury or activity (May and Bock, 1978). It is this last mechanism that is the basis of food hypersensitivity. However, there is a tendency for both laymen and medical personnel to categorize any adverse reaction to food as hypersensitivity or allergy, even when no immunologic basis can be demonstrated.

In the young infant, formula or breast milk and later cow milk may be the sole source of nutrition. Thus, adverse reactions are frequently attributed to the nutrient source or its constituents. As noted by Eastham and Walker (1979), adverse reactions to cow milk in formulas may involve a number of mechanisms ranging from mechanical obstruction and effects of osmolality to a hypersensitivity for specific milk proteins. Clinical intolerance to cow milk is most frequently associated with lactose and protein of the milk (Woodruff, 1976). Most investigators agree that intolerance to milk proteins is quite complex and that additional research on the immunologic capabilities of the infant gastrointestinal tract is needed (Woodruff, 1976).

The normal response to cow milk protein ingestion progresses from immunologic responsiveness in infancy to unresponsiveness (tolerance) in adulthood (Eastham and Walker, 1979). The estimated incidence of hypersensitivity to cow milk ranges from 0.1 to 8.0% (Eastham and Walker, 1979; Goldstein and Heiner, 1970). This variation reflects differences in diagnostic criteria, methods of data analysis, and possibly concomitant occurrence of adverse reactions other than true immunologic hypersensitivity to cow milk. It is important to recognize that all formulas for normal infants contain protein or hydrolysed proteins that are "foreign", that is, immunologically different from proteins of the human body. The immunological competence of the infant's gastrointestinal tract is currently an area of intensive investigation.

Congenital lactase deficiency may cause adverse reactions in a small number of infants. This type of milk intolerance is rare and results from an inborn error of metabolism. In addition, some low-birth-weight infants born during the seventh or eighth month of gestation may exhibit an inability to metabolize the quantity of lactose found in breast milk or infant formulas because of low levels of enzyme production. This is a temporary adverse reaction that most infants will outgrow. The most frequently encountered condition is lactose intolerance, which may be acquired by infants fed breast milk or formulas containing lactose as the
principal carbohydrate. Carbohydrate intolerances including lactose intolerance occur in infants and adults, but are distinct conditions which should not be confused with milk intolerance (Woodruff, 1976).

It should be recognized that complete immunologic evaluation is rarely performed because the immunological system of the infant continues to evolve rapidly during the first few months. The ready availability of formulas as substitutes for breast milk and of formulas with nutrient sources other than cow milk for use in place of milk-based formulas affords convenient alternatives where milk intolerances or hypersensitivities are suspected.

While the accurate diagnosis of causality of adverse reactions ranging from milk intolerance to specific protein hypersensitivity can be quite complex, the treatment is relatively straightforward and depends on avoidance of the suspected causal agent. For infants, this can be difficult, because most formulas simulate human milk and many formulas are milk-based. Infants who are intolerant to cow milk for whatever reason require diets that are milk-free or contain reduced quantities of milk constituents. Since these infants may be maintained on such formulas for many months, care must be taken to provide those essential nutrients normally furnished by human milk. Thus, soy-based and other milk-free products are formulated to meet the nutrient composition regulation of FDA with respect to vitamins and minerals. Fomon (1974) noted that about 10% of all infants in the United States are fed soy-based formulas because of concern about milk intolerance and milk allergy. However, in some cases, special dietary foods (formulas) are required for adequate nutrition of infants with particular metabolic disorders and hypersensitivities.
III. TYPES AND USES OF INFANT FORMULAS

A. FORMULAS FOR FULL-TERM INFANTS

Fomon (1974) cited convenience, microbiological safety, lack of documented evidence of the superiority of breast feeding, and absence of physician enthusiasm for breast feeding as reasons for the increased and widespread use of formula feeding in the United States. In 1972, about 70% of infants 2 months of age and 30% of those 6 months of age were receiving commercially prepared formulas (Martinez, 1973).

Since 1974, there has been a reversal of this trend in the United States. Filer (1978) reported that 80% of mothers in the western United States were breast feeding their infants when they went home from the hospital in 1976, compared with 44% in 1972. At 6 months of age, 37% of the infants were still being breast-fed. The same trend, but less marked, was found among mothers in southern and eastern United States; that is, 45% of the infants were breast-fed on discharge from the hospital contrasted with 22 to 24% in 1972. The incidence of infants at 6 months of age being fed human milk was 37% in western states and 18 to 20% in eastern and southern parts of the United States. Additional evidence for increased incidence and duration of breast feeding has been collected by Martinez and Nalezinski (1979) who surveyed 11,610 mothers by questionnaire in late 1978. From the 6456 responses and from data collected similarly since 1971, they reported that the frequency of breast feeding in hospitals doubled (from 24.7% in 1971 to 46.6% in 1978) during the 8-year period. Similarly, the number of mothers prolonging breast feeding rose dramatically during this same time period. In 1971, incidences of breast-feeding infants 3 to 4 and 5 to 6-month-old were 8.2% and 5.5%, while in 1978 these were 26.8% and 20.5%, respectively.

While the relative merits of breast versus formula feeding are beyond the scope of this brief background paper, prevailing opinion favors breast feeding of infants whenever possible (American Academy of Pediatrics, 1976; American Medical Association, 1979; Infant Formula Council, 1979). Thus, throughout the history of infant formula development, medical and commercial efforts have focused on developing products which can provide those nutritional and other benefits found in human milk.

A number of studies that indicate growth rates of formula-fed infants are essentially similar to those of breast-fed infants. For example, Fomon et al. (1971) and Jackson et al. (1964) showed that gains in length and weight were slightly greater for both male and female infants fed formulas than the gains of breast-fed infants. However, Filer (1980) in a review of current feeding practices and health consequences, concluded that growth of formula-fed infants was equal, but not superior to that of breast-fed infants.
As indicated earlier, several types of formulas have been developed for normal infants as well as for infants suffering from inborn errors of metabolism and other disorders. Commercial formulas for normal infants are basically milk-, soy-, protein hydrolysate-, or meat-based. The general composition of these types of infant formulas is summarized in Table 3 (page 35).

Fomon (1974) has recommended that all formulas, except those prepared for use in specific disorders, should provide 7 to 16% of their calories from protein, 30 to 55% from fat; at least 1% of the calories should come from linoleic acid, and the remainder from carbohydrates. The FDA specifies that formulas or supplementary sources of nutrients must provide 15% of the total calories as fat and 2% as linoleic acid (present as a glyceride) [21 CFR 105.65]. The minimum requirements for the various nutrients per 100 kcal as required by FDA and as recommended by the Committee on Nutrition (American Academy of Pediatrics, 1976) are shown in Table 2.

1. Milk-based.

Because the ratio of carbohydrates to protein in fat-free milk solids from cow milk is less than is desirable for infant formulas, milk-based formulas are fortified with some form of carbohydrate. This is usually lactose, although since 1970 corn syrup solids have been used in some formulations because they are less expensive than lactose and of equivalent caloric value. Formulas in this category contain added vitamins and minerals in accordance with guidelines of the American Academy of Pediatrics; some formulations are fortified with additional iron.

2. Whey-adjusted.

By combining whey with nonfat cow milk, the ratio of whey proteins to casein can be made to approximate that of human milk (60:40). In cow milk, casein accounts for 80%, and whey only 20%, of the protein. Whey is usually demineralized by electrodialysis or ion exchange, and minerals are added separately to the formula in amounts similar to the concentrations found in human milk.


The most widely used milk-free formulations are derived from soybean components. Originally, soy flour was used as the source of protein, but these preparations tended to produce loose, malodorous stools. Formulas containing protein from water-soluble soy isolates overcame these difficulties and have almost completely supplanted soy-flour formulas. It was estimated that about 10% of infants in the United States were fed soy-isolate formulas in 1973 (Fomon, 1974). Vegetable oils provide the fat content, and corn syrup solids and/or sucrose supply the carbohydrate in these formulas. Vitamin K is also added at a level of 100 µg/litre (American Academy of Pediatrics, 1971).
4. Protein hydrolysate-based.

Protein hydrolysate-based formulas constitute another group of formulas which are used for infants sensitive to intact proteins of milk or other foods. These formulas contain enzymatically hydrolysed casein; thus, the nitrogen sources are essentially free amino acids and simple polypeptides. These formulations also contain sucrose and tapioca starch as the carbohydrate sources. Other nutrients are added in amounts necessary to meet nutrient composition regulations. They are used for infants with severe or multiple adverse reactions or allergies to foods, with persistent diarrhea or other gastrointestinal disturbances, or with lactose intolerance.

B. SPECIAL FORMULAS

There are several conditions which require more individualized nutritional management. These include the normal infant born prematurely or having a birth weight of less than about 2500 g and those infants with certain diseases and disorders. In all cases, nutritional management is focused upon providing nutrient intakes that permit the infant to achieve an optimal rate of growth approaching the potential of that individual. Thus nutritional management is essentially treatment developed on an individual basis, altered frequently on the basis of infant response.

For infants weighing less than 1500 g at birth or larger infants with respiratory distress, inability to suckle, or other disorders, parenteral or enteral feeding may be necessary.

In the case of normal low-birth-weight infants (2500 g or less at birth), no commercially available formula is completely satisfactory. Again, the particular condition or status of such infants requires individualized formulation of the dietary by the attending physician to optimize the potential for rapid growth and development.

In general, special formulas for low-birth-weight infants contain higher levels of protein and minerals and less lactose (Fomon, 1974). Fat, calcium, and phosphorus should be readily absorbable. The lactose content should be reduced by one-third to one-half and corn syrup solids substituted as an easily absorbable carbohydrate source. The total calorie content should be 80 to 100 kcal/dl with about 11% of calories from protein and 50% from fat.

There are a number of products developed for various nutritional disorders, particularly inborn errors of metabolism. They are formulated for specific purposes and intentionally are deficient in one or more nutrients. For example, formulations are available for infants sensitive to or unable to metabolize specific amino acids or proteins; for infants with congestive cardiac
failure requiring low sodium intake; for infants with various steatorrheal disorders requiring altered fat or carbohydrate intakes; and, for infants with enzymic or other deficiencies. Such specialized products are not designed for normal infants, are more expensive, and are used typically under direct medical supervision.

Because these special formulations are deficient in or supplemented with additional quantities of one or more nutrients, they are not designed to provide adequate amounts of nutrients for normal infants. Use of these "medical foods" is limited to disorders and conditions where the infant is, for all practical purposes, treated on an individual basis by appropriate medical specialists. This type of limited use requires that attending medical and pediatric nutrition specialists have considerable flexibility in developing sole source nutrient formulations that meet the specific nutritional needs of the infant.
IV. QUALITY CONTROL AND QUALITY ASSURANCE

A. CURRENT REGULATIONS

Manufacturers of infant formulas must comply with current standards related to the manufacturing, processing, packing, or holding of human food [21 CFR 110] and adhere to regulations governing the production of thermally processed, low-acid foods packaged in hermetically sealed containers [21 CFR 113]. These sections of the Code of Federal Regulations specify requirements for personnel, buildings and facilities, equipment, production and process controls, and record maintenance. A temporary tolerance for polychlorinated biphenyl compounds has been set at 0.2 ppm for infant and junior foods [21 CFR 109.30(a)(8)]. In addition to these regulations, infant formula manufacturers have voluntarily developed and adopted additional guidelines for manufacturing procedures and for quality assurance monitoring. These guidelines and measures are summarized in a recent statement of the Infant Formula Council (1979).

B. STANDARDS ON QUALITY OF RAW MATERIALS

The Code of Federal Regulations [21 CFR 110.80] requires inspection of raw materials and ingredients to ensure their suitability for incorporation into human food. The Infant Formula Council developed analytical procedures to ensure that all ingredients, including vitamin and mineral premixes, meet specifications for quality. Component and ingredient testing may be done by the manufacturer or the supplier of the raw materials, in which case, the data on each lot is reviewed by the manufacturer to assure that quality specifications have been met. As contaminants are identified in the environment, raw materials are tested for presence of these contaminants. To date, a majority of environmental contaminants of concern to formula manufacturers have been fat-soluble and would be present in the lipid fraction of raw materials. Because the fat fraction is removed in processing and replaced by specially refined edible oils, the possibility of environmental contaminants of raw materials entering finished products is greatly reduced. However, when the presence of contaminants is suspected, materials are routinely tested for their presence (Infant Formula Council, 1979).

C. MONITORING OF FORMULA COMPOSITION

Each lot or batch of infant formula is evaluated by the manufacturer during processing to ensure that its composition meets prescribed specifications. According to the Infant Formula Council (1979), protein, fat, total calories, and total solids in the formulas are measured directly and the carbohydrate content is
calculated by difference. Each lot or batch is also analyzed for at least one vitamin or mineral added as a part of a premix to ensure that the formula contains the correct amounts of added micronutrients. An alternate procedure to actual micronutrient analysis is the review of manufacturers' records to verify that proper addition of previously analyzed premixes was made.

When production of a batch is completed, samples are analyzed to monitor adherence to nutrient composition standards and absence of microbial contamination. This latter procedure may require 2 or 3 weeks' storage of samples under various conditions; however, none of the batch is released until these tests are completed and quality has been assured. At intervals during the shelf life of each product, samples from each batch are analyzed for stability of nutrient composition and possible introduction of microbial contaminants (Infant Formula Council, 1979).

D. CONTROL OF MICROBIAL CONTAMINATION

Guidelines for assurance of the safety of food in the Code of Federal Regulations [21 CFR 110; 21 CFR 113] include specifications on control of microbial contamination. The Infant Formula Council has stated that its members not only meet but also exceed the FDA regulations in regard to procedures designed to reduce and eliminate microbial contamination (Infant Formula Council, 1979). The organization has developed a manual of standard procedures for the evaluation of the microbial quality of infant formula products (Infant Formula Council, 1973). Similarly, the Codex Alimentarius Commission (1976) and the United Nations Protein Advisory Group (1972) have recommended microbiological and sanitary standards for the production and use of powdered and liquid infant formulas. Great care is taken to prevent microbiological contamination during manufacture; however, it may occur when container integrity is lost because of defects or physical abuse of the container. Preparation of formula in the home, that is, mixing of powdered formulas or dilution of liquid formulas, can be a source of microbial contamination, particularly where knowledge of the importance of sanitation is minimal. Use of canned preprepared formulas, disposable plastic bottle liners, and readily sterilizable bottles afford convenient methods of avoiding this problem. While convenience is acknowledged as a major factor, recognition of freedom from microbial contamination is an attribute which has contributed to the rapid acceptance of ready-to-use formulations for home use.

Gastrointestinal disorders of infants caused by enteric bacterial or viral pathogens from commercially prepared infant formulas are infrequent (Fomon, 1974). Strict adherence to guidelines for microbiological safety is standard practice for the infant formula industry (Infant Formula Council, 1979). Similarly, this aspect of infant feeding is stressed to hospital
nursery personnel and new mothers by pediatricians and paramedical personnel. The most important measures for control of microbial growth continue to be effective cleansing of bottles and nipples and the avoidance of formula storage at temperatures above 10°C (Fomon, 1974).

E. MAINTENANCE OF RECORDS

Processing and production information must be recorded and maintained [21 CFR 113.100]. Manufacturers of infant formulas keep detailed records of batch production and of individual lots to allow verification and identification of ingredient sources and adequacy of processing (Infant Formula Council, 1979). The required period of record maintenance is 1 year from the date of manufacture [21 CFR 113.100]. Producers of infant formulas maintain records for at least 1 year past the shelf life of the product or for a minimum of 2 years after production (Infant Formula Council, 1979). In addition, the reporting of problems with formulas to manufacturers and distributors is a matter of standard practice for pediatricians, pharmacists, and others involved in pediatric nutrition.
V. NUTRIENT COMPOSITION

A. SOURCES OF NUTRIENTS

The inclusion of various ingredients in formulas is based upon knowledge of the digestive capabilities of infants and the relative bioavailability of the nutrient sources. These formulas are designed to approximate the nutrient composition of human milk. Sources of proteins, fats, and carbohydrates in formulas for normal full-term infants are listed in Table 3.

Because nutrient composition of the protein sources used in formulas differs, the amounts of added vitamins and minerals may vary. However, all products are formulated to meet or exceed the minimal amounts of vitamins and minerals recommended by the Committee on Nutrition (American Academy of Pediatrics, 1976) (see Table 2).

B. NUTRIENT REQUIREMENTS

Nutrient requirements, in terms of body weight, are greater in infancy than at any other time during life. The rate of growth is at its maximum during the first year; the birth weight typically doubles by 4 months of age and triples by 1 year of age (Fomon, 1974; Pipes, 1977). Nutrient intake must support this rapid rate of growth and development as well as provide for energy expenditures required for tissue maintenance and motor and neural activities. Nutrient requirements for low-birth-weight and full-term infants have been determined from: "(1) analogy with breast-fed infants, (2) direct experimental evidence, (3) extrapolation from experimental evidence relating to human adults or to infant or adult animals, (4) reports of intakes by individuals who developed evidence of deficiency (indicating inadequate intake) and reports of intakes by healthy individuals, and (5) theoretically based calculations" (Fomon, 1974).

Based upon requirements estimated by one or more of these methods, the Food and Nutrition Board of the National Research Council established Recommended Dietary Allowances (RDA's), which are levels of nutrients that will meet the needs of most healthy infants (National Research Council, 1980) (see Table 1).

Using information on levels of nutrients providing "good growth and development in healthy, full-term infants," the Committee on Nutrition (American Academy of Pediatrics, 1976) proposed standards for minimal and, in cases of potential harmful effects, maximal levels for nutrients in formulas prepared for healthy infants less than 1 year of age. The Committee established a single standard for both milk-based and milk-free formulas:
"Where experience with milk-based formulas has disclosed no deficiency, the Committee has proposed minimum standards that avoid the need for supplementation of these formulas but require supplementation only of milk-substitute formulas, e.g. with vitamin K, inositol, etc."

The Committee intended that these standards for normal infant nutrition would also provide a reference base for formulas developed for infants and children with special nutritional problems. As noted previously, these guidelines are currently being reviewed and revised by the Committee on Nutrition, American Academy of Pediatrics.

A comparison of nutrient intake supplied by the amount of formula meeting the mean energy allowance for infants up to 6 months with the RDA's for infants in this age range is presented in Table 1. The revised RDA's (to be published in 1980) include a special category for certain vitamins and minerals where information upon which to base allowances is limited. The ranges of estimated safe and adequate daily dietary intakes for these vitamins and minerals are also indicated in Table 1 (see footnote e). The National Research Council has cautioned against intakes of selected minerals above the upper limits of the suggested ranges because of the potential for toxic effects.

Little attention has been given in the RDA's to the amounts of specific anions, other than phosphorus (as phosphate) and more recently chloride, in infant formulas. Intake of phosphorus has been related to intake of calcium in establishing RDA's for these minerals. In human milk the ratio of calcium to phosphorus is 2:1 whereas in cow milk it is 1.2:1. In neonates, a high phosphate intake has been associated with hypocalcemic tetany (American Academy of Pediatrics, 1978; Mizrahi et al., 1968). Based on such reports the current ratio set forth in the RDA's is 1.5:1 (National Research Council, 1980). The Committee on Nutrition (American Academy of Pediatrics, 1976) recommended that the calcium:phosphorus ratio in infant formulas be between 1.1 and 2.0:1.0.

Although trace minerals are usually added as sulfate salts, acceptable levels of sulfate and other anions have not been specified. Nitrate salts of vitamins and trace minerals are not used currently; however, nitrates in minute quantities may be present in formulas containing vegetable products and in water. The Committee on Nutrition has stated that the consumption of nitrates from domestic drinking water supplies and in foods poses no hazard; however, the Committee noted that nitrate contamination of drinking water might occur from runoff of fields fertilized with nitrates (American Academy of Pediatrics, 1970).
Until 1980, the Food and Nutrition Board had made no recommendation for the amount of chloride in the diet (National Research Council, 1980). Its current recommendation is 275 to 700 mg/day for infants up to 6 months of age. The Committee on Nutrition (American Academy of Pediatrics, 1976) proposed minimal levels of sodium (20 mg/100 kcal), potassium (80 mg/100 kcal), and chloride (55 mg/100 kcal) in infant formulas based on the amounts found in human milk. It further specified:

"The ratio of sodium to potassium (expressed in mEq) should not exceed 1.0 and the ratio of sodium plus potassium to chlorine should be at least 1.5. Ideally, ratios similar to those in human milk should be used (sodium to potassium, 0.5; sodium plus potassium to chlorine, 2.0)."

The concentration of these minerals also partially determines osmolality, a measure of the osmotic pressure of the solution. This physical property is dependent upon the number of particles in a given volume. In milk- and soy-based formulations, soluble minerals and carbohydrates are the main determinants of this important physical property. Osmolality is measured by the extent to which the number of particles in solution depresses the freezing point or vapor pressure of that solution.

Another commonly used term, osmolarity, is related to the number of particles in one litre of solution. It cannot be measured directly, but may be calculated from the following formula developed by Tomarelli (1976):

\[
\text{Osmolarity (mOsm/l)} = \frac{\text{Osmolality (mOsm/kg H}_2\text{O)}}{x \text{ kg H}_2\text{O/l solution}}
\]

There continues to be considerable confusion related to the proper use of the terms osmolality and osmolarity. As Tomarelli (1976) has cautioned, "... when the term osmolarity is quoted, it is uncertain whether this is incorrect terminology or whether the osmolarity has been calculated from the osmolality." For dilute solutions there is little difference in osmolality and osmolarity, but for relatively concentrated solutions such as infant formulas, osmolarity may be only 80% of the osmolality. Osmolality is the more accurate term, and its use should be encouraged.

Osmolality of infant formulas may affect the well-being of infants. Solutions of high osmolality may draw large quantities of water into the small intestine, causing diarrhea and possibly dehydration and disruption of electrolyte balance (Abrams et al., 1975; Chambers and Steel, 1975). An association between feeding of hyperosmolar products and necrotizing enterocolitis has also been reported (Krouskop et al., 1974; Santulli et al., 1975). The Recommended Dietary Allowance for water intake of infants is 1.5/ml/kcal/day (National Research Council, 1974). Proprietary formulas for full-term infants (67 kcal/dl) supply about this amount.
The Committee on Nutrition (American Academy of Pediatrics, 1976) recommended that formulas for healthy infants have osmolarities of no more than 400 mOsm/l. Comparison between this recommendation and laboratory reports of osmolalities of infant formulas is difficult. Osmolality of breast milk was reported to be 286 mOsm/kg water (Paxson et al., 1977) and 300 mOsm/kg water (Tomarelli, 1976). Measurement of osmolalities of several ready-to-feed and reconstituted liquid concentrate formulas (67 kcal/dl) indicated a range of 223 to 319 mOsm/kg water (Paxson et al., 1977; Tomarelli, 1976), well below the maximal concentration suggested by the Committee on Nutrition. As might be expected, osmolalities of formulas prepared from powdered products are more variable than those of the reconstituted liquid concentrates (Paxson et al., 1977). Specialized dietary products, such as those which are hypercaloric and used under direct medical supervision, may exceed the recommended osmolarity of 400 mOsm/l (Paxson et al., 1977; Tomarelli, 1976).

C. EXAMPLES OF PAST PROBLEMS

As described in an earlier section, the formulations developed as substitutes for human milk prior to the mid-20th century frequently were nutritionally inadequate or imbalanced. Since the development of modern infant formulas during the past three decades, it is significant that relatively few problems with such formulations have occurred. This is remarkable when one considers the millions of infants fed formulas during this 30- to 40-year period.

However, examples of some past problems provide a perspective on safety and reliability of infant formulas. Reports of deficiency diseases and nutrient imbalances in infants fed various formulas highlight the importance of accurate information on their composition and related nutritional properties. The most frequent disorder attributable to formula feeding is an intolerance of the neonate to cow milk. Goldman (1975) stated that 10,000 to 30,000 infants in the United States are affected yearly by such intolerance. Fomon (1974) estimated that approximately 10% of infants in the United States are fed soy-isolate formulas because of concern over allergy or sensitivity to cow milk.

A major concern in infant feeding has been the possible overloading of the immature renal capacity by excessive excretory products such as urea. Serum concentrations of urea in normal infants reflect the percentages of dietary calories provided from proteins. Formula-fed infants have a greater protein intake than those who are breast-fed. In the United Kingdom, Davies and Saunders (1973) reported that blood urea concentrations in healthy infants were significantly higher among bottle-fed infants consuming formulas reconstituted from powdered milk-based products than among breast-fed infants. The investigators suggested that
these high values possibly reflected the tendency of many British mothers to use excessive amounts of powder in preparing those types of liquid formulas, thus providing a high protein concentration. This situation appears unique to those specific powdered formulations used in England at that time.

In the early 1970's, there was considerable speculation that prepared infant foods might provide excessive salt intake for normal infants in the United States. On the basis of animal experimentation, Dahl (1968) hypothesized that a high sodium intake in the infant's diet might predispose to hypertension in adult life. This concern led to a recommendation that the level of salt added to strained and junior foods not exceed 0.25% (Filer, 1971), and the voluntary reduction in the salt added to infant foods by most manufacturers in the United States. It should be noted that there is no direct proof that a relatively large salt intake by the infant is a predisposing factor in the development of hypertension either at the time of intake or in later life.

Human milk and cow milk contain about 7 and 22 meq sodium and 11 and 29 meq chloride per litre, respectively (Fomon, 1974). These ranges have been recommended by the Committee on Nutrition (American Academy of Pediatrics, 1976). Commercially prepared infant formulas contain amounts of sodium and chloride within the recommended ranges. The Committee on Nutrition (American Academy of Pediatrics, 1979a) recently reviewed the status of sodium intake by infants. It concluded that no adverse reactions could be identified when total sodium intake averaged 3 meq/kg/day up to 6 months of age. Available data suggested that human milk provides about 1 meq/kg/day and that the amount of sodium in the diet of infants less than 6 months of age had been reduced from about 3 to 2 meq/kg/day by the reduction or elimination of salt from strained and junior foods (American Academy of Pediatrics, 1979a). There is little evidence that this level of sodium intake by infants up to 6 months of age is in any way harmful; nor is there evidence that intakes up to 9 meq/kg/day predispose infants to subsequent hypertension. In infants over 6 months of age, adult food items and cow milk constitute the major sources of sodium and chloride.

Hyperosmolar formulas may adversely affect low-birth-weight infants during their early neonatal period. Book et al. (1975) reported an increased incidence of necrotizing enterocolitis in low-birth-weight infants fed an elemental formula reported to have an osmolarity of 650 mOsm/l during their first week of life, when incidence of the disease was compared with controls fed a standard formula (osmolarity = 359 mOsm/l). However, Roy et al. (1975) did not report this effect in low-birth-weight infants fed essentially the same elemental formula. The Committee on Nutrition (American Academy of Pediatrics, 1976) recommended that formulas for normal infants have solute concentrations no greater than 400 mOsm/l, and that warning statements and explicit directions for dilution should be included in the label statements.
Infants fed cow milk formulas may develop late neonatal hypocalcemia despite the high calcium content of the milk. Condon et al. (1970) suggested that poor calcium absorption may be a factor and that high phosphate intake, insoluble salt formation with fatty acids, and low lactose content of certain formulas may also be contributory factors. Healy (1972) reported acidosis and failure to thrive when seriously ill neonates were fed a formula based on casein hydrolysate. Although this product was buffered to pH 6.5, Healy suggested that its high amino acid content may have overstressed the homeostatic mechanisms of those infants studied. This product has been reformulated to eliminate this problem, and no instances of acidosis have been reported subsequently.

In the 1950's a few cases of vitamin A deficiency were reported among infants receiving formulas made from defatted soy flour (Cornfeld and Cooke, 1952; Wolf, 1958). Acute epidermal and retinal bleeding episodes were described by Goldman and Deposito (1966) in infants fed casein hydrolysate-, or meat-based formulas and receiving sulfa drugs or antibiotics, or suffering from severe diarrhea. Antibiotic therapy would adversely affect intestinal flora and synthesis of vitamin K; diarrhea interferes with synthesis and absorption of vitamin K. All infants responded favorably to administration of vitamin K. As a precaution, the vitamin is now added to those formulas where the level is below 4 μg vitamin K/100 kcal formula (American Academy of Pediatrics, 1976).

Skin lesions were noted in infants fed milk-based formulas with low levels of linoleic acid (Cuthbertson, 1976; Hansen et al., 1963). The lesions disappeared with diets containing 1 to 2% of the calories in the form of linoleic acid. Currently available formulas contain 2 to about 20% of calories as linoleic acid or linoleates. Cow milk normally is low in linoleic acid, containing only 20 to 25% as much as human milk. Conversely, high levels of polyunsaturated fatty acids (PUFA) increase the requirement for tocopherol. Formulas for low-birth-weight infants should be supplemented with tocopherols if adequate amounts are not in proportion to the PUFA content (Phelps, 1979).

Occasional deficiencies of some water-soluble vitamins were reported among infants fed early formulations. For example, a low level of folic acid and vitamin C in one proprietary formula resulted in megaloblastic anemia (May et al., 1950). While soy products contain low levels of thiamin naturally, further loss of the vitamin during the processing of soy led to thiamin deficiency in infants receiving unsupplemented soy formulas (Cochrane et al., 1961; Davis and Wolf, 1958). Pyridoxine may be destroyed by high temperatures or prolonged heating during processing. Several investigators in the 1950's reported convulsive seizures in infants receiving a commercially prepared formula (American Academy of Pediatrics, 1966; Coursin, 1954). During the period 1951–1953, Coursin (1954) observed 54 infants from (5 weeks to 2 months of age) with hyperirritability and recurrent seizures. All had been fed a
commercial liquid cow milk formula (SMA®) from birth and had received no supplemental feedings of solid foods or of pyridoxine. No cases were encountered among infants fed the powdered form of the formula. In 1953, a relatively heat-stable form of pyridoxine was added to the commercial formula, and no additional cases of the syndrome have been reported (Fomon, 1974).

The Committee on Nutrition (American Academy of Pediatrics, 1976) recommended that infants who are not breast-fed should receive iron-fortified formulas. It also recommended that all formulas should contain at least the level of iron in human milk (about 1 mg/l) and that the iron be in a bioavailable form. It should be noted that during the early portion of the past decade, neither iron-fortified formulas nor iron-fortified dry infant cereals were commonly fed after 5 months of age in the United States (Fomon, 1974). Iron and zinc, and perhaps other trace minerals, are more readily bioavailable from breast milk than from infant formulas. Infants with acrodermatitis enteropathica, a severe and often fatal gastric disorder of zinc metabolism, now treated by zinc supplementation of the diet, frequently survived when breast milk, but not cow milk formula, was fed (Barness, 1979). Before soy formulas were supplemented with iodine, goiter was occasionally reported in infants consuming these formulas and was associated with the presence of goitrogens in soy flour, which are not present in soy-isolates (Hydovitz, 1960; Ripp, 1961; Shepard et al., 1960).

A recent example of possible nutrient imbalance in formula-fed infants is the report of metabolic alkalosis in three 5- to 6-month-old infants fed a soy-based formula (Neo-Mull-Soy®) for periods of 3 to 6 months (Roy and Arant, 1979) and in six infants fed the same formula for periods of several weeks to 6 months (Hellerstein et al., 1979). The syndrome is characterized by failure to gain weight, loss of appetite, and lethargy as well as the hypokalemic, hyponatremic, hypochloremic metabolic alkalosis. The clinical presentations of affected infants are indistinguishable from those of Bartter's syndrome. In the initial report, analysis of the formula revealed exceptionally low chloride concentrations: 1 to 2 meq/l (Roy and Arant, 1979). Addition of potassium chloride (3 to 4 meq/kg/day) to the diet corrected the electrolyte imbalances within 8 days. Roy and Arant (1979) concluded that the three infants became hypochloremic while being fed a formula deficient in chloride. Hellerstein et al. (1979) corrected the alkalosis by rehydration and supplemental potassium chloride administration. They also called attention to the association of the alkalosis with use of Neo-Mull-Soy®.

The recommendations of the Committee on Nutrition (American Academy of Pediatrics, 1976) suggest the levels of sodium, potassium, and chloride in infant formulas should be 6 to 17, 14 to 34, and 11 to 29 meq/l, respectively. These levels are considered necessary and adequate for normal growth and nutrition of
infants (National Research Council, 1980) (see Table 1). According to the manufacturer, Neo-Mull-Soy® provides about 11.5 meq/l sodium, 23 meq/l potassium, and 9.7 meq/l chloride. These levels are essentially similar to the concentrations of those ions found in human milk (Fomon, 1974). Based on manufacturer's data, the ratio of sodium to potassium would be 0.5 and the ratio of sodium plus potassium to chloride would be 3.6. Both ratios are consistent with the recommendations of the American Academy of Pediatrics (1976); that is, the former ratio should not exceed 1.0 and the latter should be at least 1.5. While the ratios of these electrolytes are within those recommended, the concentration of chloride (by itself) is slightly below the recommended level (9.7 meq reported versus 11.0 meq recommended).

Garin et al. (1979) have also reported a case of severe metabolic alkalosis in a male infant fed Neo-Mull-Soy®, rice cereal, strained fruits, and strained meats from age 3 to 5 months. Clinical manifestations were essentially similar to those reported by Roy and Arant (1979) and Hellerstein et al. (1979) except that the infant had a positive stool test for Giardia lamblia and a subsequent course of quinacrine therapy in the 4th month.

Following the original report of an association between metabolic alkalosis and the soy-based formula in mid-1979, the Center for Disease Control (Anonymous, 1979) identified 31 additional cases of infants with metabolic alkalosis. Feeding histories were available in 27 cases, of which 26 were on the same proprietary formula (Neo-Mull-Soy®). After diagnosis of the metabolic alkalosis, infants were placed on chloride supplement and responded favorably but reverted when returned to the original formula. As of August 31, 1979, 118 cases of metabolic alkalosis associated with the use of Neo-Mull-Soy® or a closely related special formula (Cho-Free®) had been identified by the Center for Disease Control.

The reasons why certain infant formulas may contain low chloride levels are unknown. Garin et al. (1979) noted that there has been a trend toward reduction in sodium chloride content of infant foods, based partially on the hypothesis that such a diet may afford protection against hypertension in later life (see page 22). The level of chloride in the soy-based formulas could be related to alteration of chloride levels by substitution of other sodium salts for sodium chloride; however, there are no published data to support or refute this speculation. The Infant Formula Council (Gelardi, 1980a) has indicated that no efforts were made by four manufacturers to alter formulations to reduce sodium chloride levels in infant formulas.

Another possible reason for low chloride levels might be the inadvertent removal of chloride during treatment of water for fluoride removal. The Committee on Nutrition (American Academy of Pediatrics, 1979b) has suggested that fluoride supplementation of
infant diets should depend on its concentration in drinking water. For infants and children from 2 weeks to 2 years of age, the Committee recommended a total intake of 0.25 mg/day fluoride. Thus, if domestic water supplies contained natural or added fluoride at 0.3 ppm or above, no fluoride supplement would be needed. The Infant Formula Council (Gelardi, 1980a) has stated that two manufacturers had used nonfluoridated water and thus made no changes in processing to accommodate the recommendations on fluoride levels. Two other manufacturers reported that specific comparison of chloride levels in water before and after installation of ion-exchange filtration systems to reduce fluoride in water to be used in infant formulas resulted in no reduction in chloride content of infant formulas.

The source of soy protein isolate or its processing during formulation might affect the chloride level in the final product. For example, use of hydrochloric acid in acidification of soy isolate could be expected to add some chloride ions to the final product. Gelardi (1980a) has indicated that four manufacturers have not changed soy protein isolates within the past several months. With the exception of this information, the effects of soy isolate source or processing as a factor in altered chloride levels is theoretically possible but unsupported by published data at this time.

Kaufman et al. (1979) suggested that hyponatremic, hypokalemic, and hypochloremic metabolic alkalosis observed in the three infants reported by Roy and Arant (1979) may have been the result of some factor other than low level of chloride in the formula. Based on studies with rats fed low-chloride diets, Kaufman et al. (1979) suggested the low-chloride, relatively high-citrate diet of the three infants might have served to maintain (but not cause) metabolic alkalosis. They pointed to chloride and extracellular volume depletion as well as high sodium excretion (as a consequence of continued bicarbonate excretion) as possible contributory factors. Garin et al. (1979) postulated the observed chloride deficit was related to inadequate dietary intake of chloride but suggested that the condition of metabolic alkalosis was maintained by increased proximal renal tubular reabsorption of bicarbonate, which in turn, was related to reduced extracellular water volume resulting from a deficit in available chloride ions.

Thus, while some factors which are associated with the metabolic alkalosis in these infants fed diets with low chloride content have been identified, the exact causal mechanisms and role of other contributory factors remain to be established.
VI. REGULATORY CONSIDERATIONS

A. NUTRITION STANDARDS

For regulatory purposes, FDA has included infant formulas in the category of foods for special dietary use; specifically "uses for supplying particular dietary needs which exist by reason of age, including but not limited to the ages of infancy and childhood" [21 CFR 105.3]. The Code of Federal Regulations also defines the term "infant" as "persons not more than 12 months old." As noted previously, FDA guidelines on nutrient composition have been derived from those developed by the Committee on Nutrition (American Academy of Pediatrics, 1976). The Committee on Nutrition is currently reevaluating these guidelines and will provide the FDA with a report on proposed revisions of their guidelines on formulas for normal infants.

The nutritional needs of low-birth-weight infants and those with metabolic disorders or diseases are unique as well as highly specific. Thus, there is a need for sufficient flexibility in regulations to allow proper and medically sound nutritional intervention on an individual case-by-case basis.

B. NUTRITION LABELING AND DATING

Labeling requirements of foods intended for special dietary use by infants must include the common or usual name for each ingredient, including spices, flavoring, and coloring, as well as specific animal or plant sources of each ingredient if this is not indicated by the common name. If a food is intended to simulate or to substitute partially or completely for human milk, labeling must be more extensive. In such foods, the label must state, in percent by weight or weight per unit volume, the content of moisture, protein, fat, available carbohydrate, ash, crude fiber, and available energy in the product as prepared for consumption.

Infant formulas or other foods which may be used as the sole source of dietary protein, particularly in early infancy, must contain no less than 1.8 g protein/100 kcal formula. The protein source must have a biological quality, as measured by protein efficiency ratio, at least equal to that of casein. Alternatively, if the protein is of lower quality, the formula must contain an amount of protein per 100 kcal that meets this standard. In addition, the biological quality of the protein in such foods must be no less than 70% that of casein. If the above conditions are not met, the label must state "this product should not be used as the sole source of protein in the infant diet" [21 CFR 105.65].
Infant formulas (unless intended to regulate the intake of fat for special dietary purposes) must contain at least 15% of available kilocalories from fat and at least 2% of available kilocalories from linoleic acid or linoleates. Otherwise, the label must state that additional sources of these nutrients are needed [21 CFR 105.65(c)(6)].

The amounts of vitamins and minerals per 100 kcal specified by FDA [21 CFR 105.65(c)(5)] (see Table 2) must be contained in the formulas as prepared for consumption. Labels of products containing less than these quantities must state that amounts of the vitamins and minerals below the specified minimum levels should be supplied in the total diet [21 CFR 105.65(c)(5)].

Open dating of powdered, concentrated, and ready-to-feed infant formula packages and containers is a standard practice of the manufacturers belonging to the Infant Formula Council (Gelardi, 1980b). The dating is prominently displayed or stamped on the container and normally indicates an expiration or "use before" date. Removal of outdated products from the retail outlet is a responsibility of the retail vendor. Data on vendor compliance are scarce; however, manufacturers do control retail and wholesale supplies by rate of marketing.

C. FORMULA TESTING

According to the Infant Formula Council (1979), product formulation and reformulation are based on medical or nutritional research, changes in medical concepts of nutritional support, availability of improved nutrient sources, or improved processing technology. Reformulation may be suggested by the staff of the manufacturer or by pediatric or other medical specialists.

Reformulations are initiated only after detailed nutrient specifications are reviewed. The guidelines of the Committee on Nutrition (American Academy of Pediatrics, 1976) are the major reference for such nutrient specifications; however, other relevant sources, as well as opinions of knowledgeable specialists in pediatric clinical nutrition, are consulted. In cases of reformulation of products, minor changes are verified through routine surveillance procedures while major changes are preceded by product development studies, including stability determinations, pre-clinical nutritional studies, and appropriate clinical testing.

New or reformulated products are examined by manufacturers to determine the extent of clinical evaluation necessary (Infant Formula Council, 1979). The evaluation involves consultations with experts in nutrition, pediatrics, and clinical nutrition regarding the possible needs for animal and human feeding trials. These may include metabolic studies and growth trials, acceptance and tolerance studies as well as allergenicity studies when necessary. Most clinical trials are conducted under contract with
reputable pediatric research centers and clinics. Such studies are reviewed and approved by ethical standards committees or boards of the respective institutions prior to their initiation. Ethical considerations related to human experimentation and the limited number of pediatric clinical centers in the United States are constraints on clinical testing of infant formulas.
VII. RESEARCH NEEDS

As noted previously, this brief overview of the history and current status of infant formulas is intended for use as a background paper for two public proceedings to be held by FDA on February 19-20, 1980 and March 12-13, 1980, concerning nutritional composition and other regulatory considerations related to infant formulas. Safe, reliable, and nutritionally complete infant formulas are acceptable alternatives to breast feeding. Modern infant formulas provide all nutrients known to be required for growth and development of normal infants in quantities that are similar to those found in human milk. They supply the infant with sufficient calories, protein, readily absorbable carbohydrate and fat, and adequate supplies of vitamins and minerals in a liquid form which simulates the low protein, low solute, and low electrolyte load of human milk. Nevertheless, unanswered questions concerning infant nutrition and the "ideal" infant formula remain. It is recognized that many topics will be discussed at the FDA's proceedings, but it is important to identify certain issues related to research needs which are as yet unresolved. The following paragraphs identify some aspects of infant nutrition and use of infant formulas that appear to require additional research emphasis. No priority is implied in the order of presentation.

• Since 1971 there has been an increase in the number of breast-fed infants and a prolonged duration of breast feeding of infants in the United States. This underscores the need for continued epidemiological study of infant diets. Information on nutritional adequacy of infant diets should be collected and analyzed on a continuing basis. Such information is important to the objective evaluation of the role of infant formulas in meeting nutritional needs of infants.

• Modern infant formulas are designed to simulate human milk nutritionally. Recent advances in knowledge of human milk composition indicate that several nutritionally important substances are present in human milk but are currently not components of formulas for normal infants. While the essentiality of these substances has not been established, the desirability of their inclusion in infant formulas should be considered; for example:

1. Cholesterol is present in milk of all mammals, but formulas based on vegetable oils and nonfat milk are essentially free of cholesterol. An exogenous source of cholesterol is not needed for myelination of the central nervous system as the infant can synthesize the substance. Why is cholesterol present in human milk? Should it be present in formulas?
2. Human milk and milk-based formulas contain carnitine, a substance important in fatty acid metabolism. Does the young infant synthesize sufficient amounts of carnitine, or should carnitine be added to all formulas?

3. Taurine, an amino acid, which is not yet known to be essential for normal growth and development, is present in human milk. Evidence suggests it is essential to normal growth and development of cats. What is its role in human growth and development?

- The amino acids and proteins in human and cow milk are present in somewhat different ratios. Does the amino acid content of cow milk adequately meet the nutritional needs of low-birth-weight infants? Should supplemental sulfur-containing amino acids be added to milk-based formulas?

- Additional studies on the possible influence of differences in milk composition on cell development and tissue characteristics in early infancy are desirable.

- Evidence is accumulating that trace minerals such as cobalt, molybdenum, and selenium may play an important role in growth and development. What are the roles of these and other trace minerals in growth and development of the infant during gestation, infancy, and early childhood?

- Are the trace elements now incorporated into infant formulas present at adequate levels and in biologically available forms?

- There is a need for carefully controlled experiments on absorption, metabolism, and excretion of electrolytes by infants maintained on human milk and various infant formulas.

- The immediate postnatal weeks are the period of greatest nutritional need in terms of nutrient requirements for cell division, cell enlargement, and maturation of tissues and organs. There is a need for additional research on the effects of nutrition in infancy on adult health and disease; for example:
1. Is the level of energy and/or protein intake during infancy associated with obesity in adolescents and adults?

2. Does the level of sodium intake by infants predispose them to hypertension in adult years?

3. Do the patterns of saturated and unsaturated fat intake from human milk or various types of infant formulas influence the level of high-density lipoproteins, the development of hyperlipidemia, or the early development of atherosclerosis?

Problems related to balance of nutrients and nutritional adequacy arising from consumption of formulas as sole sources of nutrients have been relatively rare. What ethically acceptable protocols for clinical testing would be most useful in predicting possible problems?
Table 1. Comparison of Recommended Nutrient Intakes for Normal Full-Term Infants

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>RDA 1979 (0-6 mo)</th>
<th>FDA 1971 Regulations (Minimum)</th>
<th>Committee on Nutrition 1976 (Minimum)</th>
<th>Nutrient</th>
<th>RDA 1979 (0-6 mo)</th>
<th>FDA 1971 Regulations (Minimum)</th>
<th>Committee on Nutrition 1976 (Minimum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>570-870</td>
<td>670</td>
<td>670</td>
<td>Vitamins (cont.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein (g)</td>
<td>13.2</td>
<td>12.1</td>
<td>12.1</td>
<td>Biotin (ug)</td>
<td>35e</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>Essential fatty acids (% kcal)</td>
<td>2b</td>
<td>2</td>
<td>3</td>
<td>Choline (mg)</td>
<td>—</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inositol (mg)</td>
<td>—</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Vitamins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>1400 (420ug)c</td>
<td>1675 (503ug)c</td>
<td>1675 (503ug)c</td>
<td>Calcium (mg)</td>
<td>360</td>
<td>335</td>
<td>335</td>
</tr>
<tr>
<td>Vitamin D (IU)</td>
<td>400 (10ug)d</td>
<td>268 (6.7ug)d</td>
<td>268 (6.7ug)d</td>
<td>Phosphorus (mg)</td>
<td>240</td>
<td>168</td>
<td>168</td>
</tr>
<tr>
<td>Vitamin K (ug)</td>
<td>12e</td>
<td>27</td>
<td></td>
<td>Magnesium (mg)</td>
<td>50</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Vitamin E (IU)</td>
<td>4.5</td>
<td>2</td>
<td>2</td>
<td>Iron (mg)</td>
<td>10</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(3mgαT.E.)f</td>
<td></td>
<td></td>
<td>Iodine (ug)</td>
<td>40</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Ascorbic acid (mg)</td>
<td>35</td>
<td>52</td>
<td>54</td>
<td>Zinc (mg)</td>
<td>3</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Thiamin (ug)</td>
<td>300</td>
<td>168</td>
<td>268</td>
<td>Copper (ug)</td>
<td>500-700e</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Riboflavin (ug)</td>
<td>400</td>
<td>402</td>
<td>402</td>
<td>Manganese (ug)</td>
<td>500-700e</td>
<td>—</td>
<td>34</td>
</tr>
<tr>
<td>Pyridoxine (ug)</td>
<td>300</td>
<td>235</td>
<td>235</td>
<td>Sodium (mg)</td>
<td>115-350e</td>
<td>—</td>
<td>134</td>
</tr>
<tr>
<td>Vitamin B12 (ug)</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>Potassium (mg)</td>
<td>350-925e</td>
<td>—</td>
<td>536</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>—</td>
<td>—</td>
<td>1.68</td>
<td>Chloride (mg)</td>
<td>275-700e</td>
<td>—</td>
<td>369</td>
</tr>
<tr>
<td>(mg equiv)</td>
<td>6</td>
<td>5.36</td>
<td></td>
<td>Fluoride (ug)</td>
<td>100-500e</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Folacin (ug)</td>
<td>30</td>
<td>27</td>
<td>27</td>
<td>Chromium (ug)</td>
<td>10-40e</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Pantothenic acid (mg)</td>
<td>2e</td>
<td>2</td>
<td>2</td>
<td>Selenium (ug)</td>
<td>10-40e</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Molybdenum (ug)</td>
<td>30-60e</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

a Figures listed in these columns represent the amounts of each nutrient an infant would receive if consuming one litre of formula, based on energy allowances in the revised RDA's (National Research Council, 1980).

b As specified in the 1974 RDA's (National Research Council, 1974).

c Retinol equivalents. One retinol equivalent equals 3.33 IU vitamin A activity from retinol.

d Cholecalciferol. Ten ug cholecalciferol equals 400 IU vitamin D.

e Estimated safe and adequate daily dietary intakes. Because there is less information on which to base allowances, some figures were provided as ranges of recommended intakes (National Research Council, 1980).

f T.E. = α - tocopherol equivalents; one mg d - α - tocopherol equals 1 α T.E. The activity of d - α - tocopherol is 1.49 IU/mg.

g One niacin equivalent equals 1 mg of niacin or 60 mg of dietary tryptophan.
Table 2. Nutrient Levels of Infant Formulas (per 100 kcal)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>FDA 1971 Regulations Minimum</th>
<th>1976 Recommendations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protein</strong> (g)</td>
<td>1.8</td>
<td>1.8</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td><strong>Fat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g)</td>
<td>1.7</td>
<td>3.3</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>(% cal)</td>
<td>15.0</td>
<td>30.0</td>
<td>54.0</td>
<td></td>
</tr>
<tr>
<td><strong>Essential fatty acids (linoleate)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% cal)</td>
<td>2.0</td>
<td>3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mg)</td>
<td>222.0</td>
<td>300.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitamins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (IU)</td>
<td>250.0</td>
<td>250.0 (75ug)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>750.0 (225ug)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>D (IU)</td>
<td>40.0</td>
<td>40.0</td>
<td></td>
<td>100.0</td>
</tr>
<tr>
<td>K (ug)</td>
<td>—</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (IU)</td>
<td>0.3</td>
<td>0.3 (with 0.7 IU/g linoleic acid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (ascorbic acid) (mg)</td>
<td>7.8</td>
<td>8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;1&lt;/sub&gt; (thiamin) (ug)</td>
<td>25.0</td>
<td>40.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;2&lt;/sub&gt; (riboflavin) (ug)</td>
<td>60.0</td>
<td>60.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;6&lt;/sub&gt; (pyridoxine) (ug)</td>
<td>35.0</td>
<td>35.0 (with 15 ug/g of protein in formula)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;12&lt;/sub&gt; (ug)</td>
<td>0.15</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ug)</td>
<td>—</td>
<td>250.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ug equiv)</td>
<td>800.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folic acid (ug)</td>
<td>4.0</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantothenic acid (ug)</td>
<td>300.0</td>
<td>300.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biotin (ug)</td>
<td>—</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choline (mg)</td>
<td>—</td>
<td>7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inositol (mg)</td>
<td>—</td>
<td>4.0</td>
<td></td>
<td></td>
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<tr>
<td><strong>Minerals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>50.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>25.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>6.0</td>
<td>6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>1.0</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine (ug)</td>
<td>5.0</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>—</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper (ug)</td>
<td>60.0</td>
<td>60.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manganese (ug)</td>
<td>—</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>—</td>
<td>20.0 (6 meq)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>60.0 (17 meq)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>—</td>
<td>80.0 (14 meq)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>200.0 (34 meq)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Chloride (mg)</td>
<td>—</td>
<td>55.0 (11 meq)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>150.0 (29 meq)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Modified from Committee on Nutrition (American Academy of Pediatrics, 1976)

<sup>b</sup> Retinol equivalents

<sup>c</sup> Calcium to phosphorus ratio must be no less than 1.1 to 1.0 nor more than 2.0 to 1.0

<sup>d</sup> Milliequivalents for 670 kcal/1 of formula
Table 3. Major Nutrients of Formulas for Normal Full-Term Infants

<table>
<thead>
<tr>
<th>Types</th>
<th>Use</th>
<th>Protein Source</th>
<th>Protein g/100 kcal</th>
<th>Protein % kcal</th>
<th>Fat Source</th>
<th>Fat g/100 kcal</th>
<th>Fat % kcal</th>
<th>Carbohydrate Source</th>
<th>Carbohydrate g/100 kcal</th>
<th>Carbohydrate % kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk-based</td>
<td>Routine</td>
<td>Nonfat cow milk</td>
<td>2.2–2.3</td>
<td>9</td>
<td>Vegetable oils</td>
<td>5.4–5.5</td>
<td>48–50</td>
<td>Lactose</td>
<td>10.5–10.8</td>
<td>41–43</td>
</tr>
<tr>
<td>Whey–adjusted</td>
<td>Routine</td>
<td>Nonfat cow milk plus demineralized whey</td>
<td>2.2</td>
<td>9</td>
<td>Vegetable and oleo oils</td>
<td>5.4</td>
<td>48</td>
<td>Lactose</td>
<td>10.8</td>
<td>43</td>
</tr>
<tr>
<td>Soy isolate</td>
<td>Cow milk sensitivity</td>
<td>Soy isolate</td>
<td>2.7–3.7</td>
<td>12–15</td>
<td>Vegetable oils</td>
<td>5.1–5.6</td>
<td>45–51</td>
<td>Corn syrup solids and/or sucrose</td>
<td>9.9–10.2</td>
<td>39–40</td>
</tr>
<tr>
<td>Casein hydrolysate</td>
<td>Protein sensitivity</td>
<td>Casein hydrolysate</td>
<td>2.8–3.3</td>
<td>11–13</td>
<td>Corn oil or corn oil and medium-chain tri-glycerides</td>
<td>3.9–4.0</td>
<td>35</td>
<td>Tapioca starch and glucose, sucrose, or corn syrup solids</td>
<td>13.1–13.6</td>
<td>52–54</td>
</tr>
<tr>
<td>Meat-based</td>
<td>Cow milk sensitivity</td>
<td>Beef hearts</td>
<td>4.0</td>
<td>16</td>
<td>Sesame oil Beef heart fat</td>
<td>4.8</td>
<td>47</td>
<td>Tapioca starch and sucrose</td>
<td>9</td>
<td>37</td>
</tr>
</tbody>
</table>

(revised 3/5/80)
IX. LITERATURE CITED


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