


## What's in the Bottle? A Review of Infant Formulas

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### Abstract

Infant formulas are designed to be a substitute for breast milk. Since they are sole source of nutrition for growing and developing infants, they are highly regulated by the government. All ingredients in infant formulas must be considered “generally recognized as safe.” Manufacturers are continually modifying their products to make them more like breast milk. Functional ingredients added to infant formula include long-chain polyunsaturated fatty acids, nucleotides, prebiotics, and probiotics. The most common breast milk substitutes are standard cow’s milk–based term infant formulas, which include subcategories of organic and breast milk supplementation, and come in standard dilutions of 19 or 20 calories per ounce. In addition to standard cow’s milk–based term infant formulas, there is a line of term infant formulas marketed for signs and symptoms of intolerance. These products include modifications in lactose content, partially hydrolyzed protein, added probiotics, or added rice starch. There are also specialized formulas for medical conditions such as prematurity, gastrointestinal disorders, allergy, disorders of fat metabolism, and renal insufficiency. Infants on specialty formulas should be monitored closely by medical professionals. Formulas come in ready-to-feed, liquid concentrate, and powder forms. Each offers advantages and disadvantages. Each step in the formula mixing process or each manipulation required for the feeding is another opportunity to introduce bacteria to the formula. There are guidelines for preparing formula in institutions. Standard dilution and mixing instructions are different for each formula, so individual recipes are needed. Caregivers should also be educated on proper hygiene when preparing formula at home. (*Nutr Clin Pract*.XXXX;xx:xx-xx)

### Keywords

infant formulas; infant nutrition; pediatric nutrition; enteral nutrition

The Federal Food, Drug, and Cosmetic Act (FDCA) defines an infant formula as “a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.”<sup>1</sup> By definition, a formula is a substitution for human milk, which is the optimal source of nutrition for an infant. Since human milk is the gold standard, the first true infant formulas were formulated to match the macronutrient composition of human milk using cow’s milk.<sup>2</sup> Breastfeeding promotes gastrointestinal (GI) development, immune support, and neurodevelopment that infant formulas cannot and may never be able to provide.<sup>3</sup> Even with the latest modifications and functional ingredients, infant formulas lack hormones, immunoglobulins, enzymes, and live cells that are in human milk.<sup>4</sup>

The American Academy of Pediatrics (AAP) supports the World Health Organization’s recommendation that human milk should be sole source of nutrition for healthy term infants birth to 6 months of age.<sup>3</sup> A mother may not breastfeed or pump or might begin supplementing with formula for many reasons, such as health and social or cultural reasons, or she may not be able to breastfeed or pump because of medical reasons, such as a medication she must take or because the baby has a medical need for a specialized formula.<sup>5</sup> In any situation, a mother should be encouraged and supported in her feeding plan for her infant.<sup>4</sup> Even with strong recommendations from professional organizations and healthcare professionals to breastfeed or

provide expressed breast milk to infants, by 2 months of age, most infants will have been fed some infant formula.<sup>6</sup>

Before the first infant formula was developed, an infant whose mother was not able to breastfeed was fed by a wet nurse. When wet nurses fell out of favor, infants were fed unmodified animal milks from donkeys, goats, mares, and cows, with cow’s milk being the most readily available. Physicians quickly discovered that infants fed these unmodified milks were prone to dehydration and had higher death rates than breastfed infants.<sup>2</sup> This issue seems to have come full circle with contemporary parents developing their own formula recipes using unmodified animal milks to provide “organic” or “natural” foods to their infants. These practices are dangerous and should be discouraged. The AAP recommends that nonformula milk or milk substitutes be avoided in infants <12 months

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of age because these products are not adequate in some nutrients and may have excesses of other nutrients.<sup>4,7</sup> The formulas that are available on the market are designed to meet the specific needs of infants, have been shown to support normal growth and development, and are well tolerated.<sup>2</sup>

The AAP Committee on Nutrition makes recommendations for the vitamin and mineral levels for infant formulas. The first recommendation was made in 1967, and they have been periodically reviewed and revised since then.<sup>2</sup> With the help of the AAP Committee on Nutrition, there are established levels for 29 nutrients and maximum levels established for 9 nutrients in infant formulas.<sup>8</sup> Due to the decreased bioavailability of nutrients in infant formula compared with human milk, infant formulas have higher concentrations of nutrients.<sup>4</sup> The Infant Formula Act of 1980 (revised 1986), an amendment to the federal FDCA, was developed in response to soy formula being produced with inadequate chloride. This resulted in metabolic acidosis and death in several infants.<sup>9</sup> This act gave the Food and Drug Administration (FDA) responsibility for monitoring the manufacture of infant formulas.<sup>10</sup> If an infant formula is formulated to meet the specific nutrition needs for a certain medical condition, then the formula is considered “exempt.” Exempt formulas are monitored and regulated with the same high standards that nonexempt formulas are but must meet the criteria for the specific medical condition for which it was modified (ie, prematurity).

## Functional Ingredients in Infant Formulas

All ingredients used in the manufacturing of infant formulas whether exempt or nonexempt must be “generally recognized as safe.”<sup>1</sup> In an effort to design infant formulas to be more like breast milk, formula manufacturers are adding ingredients such as long-chain polyunsaturated fatty acids, nucleotides, prebiotics, and probiotics to their formulas.

Long-chain polyunsaturated fatty acids docosahexaenoic acid (DHA) and arachidonic acid (ARA) play a key role in neural tissue structure and function, cell membrane structure, and cognitive development.<sup>11</sup> DHA rapidly accumulates in brain tissue during the first 2 years of life, but levels of accumulation are dependent on dietary DHA intake. DHA can be synthesized from the essential fatty acid  $\alpha$ -linolenic acid, but the conversion process is low (estimated <4%).<sup>12</sup> ARA is synthesized from the essential fatty acid linoleic acid. Most infant formulas are now supplemented with DHA and ARA, and supplementation has been shown to increase DHA in the brain.<sup>13</sup> More research is needed to determine if there is a significant benefit to added DHA and ARA.

Nucleotides are integral in almost all biological processes in the body. These nonprotein nitrogenous compounds are considered “conditionally essential” in infancy due to increased need for nucleic acid synthesis during periods of rapid growth, immunosuppression, decreased protein intake, or gut injury.<sup>14</sup> They play a key role in cell signaling and energy metabolism, are a structural component of coenzymes and precursors of nucleic acids, and help with regulation of protein homeostasis.<sup>5</sup>

Nucleotide supplementation promotes growth, benefits the GI tract and immune functions, and enhances mucosal recovery after intestinal injury.<sup>15</sup>

Prebiotics are indigestible carbohydrates that stimulate favorable activity of indigenous probiotic bacteria. Probiotics are live microorganisms that alter host microflora and interfere with adherence of pathogenic bacteria. Together they have positive effects on mucosal immune system development.<sup>16</sup> Breast milk contains a probiotic bacteria not found in standard infant formula. Breast milk probiotics enhance both passive and active infant immunity. To mimic the positive influence of intestinal microbiota activity supplied by breast milk, probiotics are added to formula by some manufacturers.<sup>17</sup>

There are many different infant formulas on the market today, and each formula has a unique composition and indication.<sup>5,7</sup> Even within the same category of formula, each manufacturer has a similar but different product. See Table 1 for general information on formula types. Infant formula is marketed directly to parents and because of the large number of different products, healthcare professionals are not always familiar with all of the individual product characteristics.<sup>6,18</sup> This review discusses each category of infant formula but not information about specific products. For information about a specific product, visit the manufacturer website. See Table 2 for manufacturers’ websites.

## Standard Cow’s Milk–Based Term Infant Formula

The most commonly used infant formula if an infant is not breastfed is a standard cow’s milk–based term infant formula. This is usually the first choice of parents and first recommendation from pediatricians.<sup>7</sup> These formulas are designed to be similar in composition to breast milk and are shown to support normal growth and development of the healthy term infant. One brand is not superior to another, yet each manufacturer has a unique formulation for its products.<sup>6,19</sup> All products are iron fortified to prevent iron-deficiency anemia<sup>20</sup> and contain added DHA and ARA. Standard dilution for standard cow’s milk–based infant formulas is 19 or 20 calories per ounce (0.64 or 0.67 calories/mL).

Several standard cow’s milk–based term infant formulas on the market are labeled “organic.” The Organic Foods Production Act regulated by the U.S. Department of Agriculture must be met to label a product organic. Animals must be fed organic food and must be free of added growth hormones or antibiotics. Plants must be grown with approved pesticides.<sup>21</sup> It should be noted that there are no documented health benefits to using organic infant formulas. When organic milk is compared with conventionally produced milk, there are no significant differences in macronutrient composition, quality, or safety of the products. There is also no difference in hormone levels.<sup>22</sup> In addition, all milk is evaluated for the presence of antibiotics.<sup>22</sup> These formulas still meet all the standards of the Infant Formula Act.

Another subcategory of standard cow’s milk–based term infant formulas is “for breastfeeding supplementation.” Each of

**Table 1.** General Formula Information.

| Category of Formula           | Standard Dilution, kcal/oz | Approximate Grams/100 mL |      |         | Possible Sources  |  |   | Condition/Population   |
|-------------------------------|----------------------------|--------------------------|------|---------|---|--|---|--|
|                               |                            | CHO                      | Fat  | Protein | CHO   | Fat  | Protein   |  |
| Added rice starch             | 20                         | 7.4                      | 3.4  | 1.7     | Lactose, rice starch, maltodextrin, corn syrup solids   | Palm olein, soy, coconut, high oleic sunflower, DHA, ARA   | Nonfat milk   | Not recommended for preterm infant. Ten times thicker than standard formula prior to ingesting. Viscosity increases with stomach acid contact.         |
| Amino acid                    | 20                         | ~7                       | ~3   | ~2      | Corn syrup solids, maltodextrin, tapioca starch   | MCTs, soybean, coconut, high oleic sunflower or safflower, high 2-palmitic vegetable oil, DHA, ARA | 100% free amino acids   | Hypoallergenic. For intact protein intolerance, malabsorption, severe food allergies, GI tract impairment  |
| Extensively hydrolyzed        | 20                         | ~7                       | ~4   | ~2      | Corn syrup solids, dextrose, modified cornstarch, sucrose, tapioca starch, corn maltodextrin, lactose | MCTs, soy, corn, safflower, high oleic vegetable oil, palm oleic, sunflower, DHA, ARA              | Casein hydrolysate with added amino acids, enzymatically hydrolyzed whey, extensively hydrolyzed casein | Extensively hydrolyzed for malabsorption disorders, short gut, cystic fibrosis, milk protein allergy, intractable diarrhea. Also available in 24 kcal. |
| Fat modified                  | 30                         | 10                       | 5.4  | 3.5     | Corn syrup solids   | 84% MCTs, soy oil, DHA, ARA  | Calcium caseinates, sodium caseinates   | For chylothorax, LCHAD deficiency  |
| Human milk preterm            | 20                         | 6.6                      | 3.9  | 1.4     | Lactose   | Human milk   | Whey/casein   |  |
| Human milk term               | 20                         | 8                        | 3.5  | 0.9     | Lactose   | Human milk   | Whey/casein   |  |
| Premature                     | 20–30                      | ~7–8                     | ~4   | ~2      | Corn syrup solids, maltodextrin, lactose  | MCTs, high oleic, soy, coconut oil, safflower oil, DHA, ARA  | Whey, casein, nonfat milk, whey protein concentrate, enzymatically hydrolyzed whey protein isolates     | Premature infants: hospital use only   |
| Premature discharge           | 22                         | 7.7                      | 3.9  | 2.1     | Corn syrup solids, maltodextrin, lactose  | MCTs, high oleic, soy, coconut oil, DHA, ARA   | Whey, casein, nonfat milk, whey protein concentrate   | Premature infants  |
| Reduced lactose, lactose free | 20                         | ~7.2                     | ~3.7 | ~1.4    | Corn syrup solids, sucrose, rice starch   | High oleic safflower, soy, coconut, DHA, ARA   | Milk protein isolate, partially hydrolyzed nonfat milk concentrate, whey protein concentrate            |  |
| Reduced mineral               | 20                         | 6.9                      | 3.8  | 1.5     | Lactose   | Coconut, corn, soy, high oleic safflower oil   | Whey protein concentrate, sodium caseinate  | Low renal solute load  |
| Soy                           | 20                         | 7.5                      | 3.4  | 1.7     | Corn maltodextrin, sucrose, corn syrup solids   | Palm olein, soy, coconut, high oleic safflower, DHA, ARA   | Hydrolyzed or nonhydrolyzed soy protein isolate   |  |
| Standard                      | 19–20                      | ~7.5                     | ~3.5 | ~1.5    | Lactose, galactooligosaccharide   | Palm olein, soy, coconut, high oleic sunflower, safflower oil, DHA, ARA                            | Nonfat milk concentrate, whey protein concentrate   | Standard   |

ARA, arachidonic acid; CHO, carbohydrate; DHA, docosahexaenoic acid; GI, gastrointestinal; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; MCT, medium-chain triglyceride.

**Table 2.** Infant Formulas and Manufacturer Websites.

| Product  | Manufacturer         | City, State                    | Website                     |
|--|----------------------|--------------------------------|-----------------------------|
| Bright Beginnings, Parent's Choice, Other Store Brands | Perrigo Nutritionals | Dublin, Ireland<br>Allegan, MI | www.perrigonutritionals.com |
| Earth's Best   | Earth's Best         | Boulder, CO                    | www.earthsbest.com          |
| Enfamil  | Mead Johnson         | Glenview, IL                   | www.meadjohnson.com         |
| Gerber Good Start                                      | Nestle               | Florham Park, NJ               | www.medical.gerber.com      |
| Honest Co. Organic                                     | Honest Co. Organic   | Santa Monica, CA               | www.honest.com              |
| Neocate  | Nutricia             | Gaithersburg, MD               | www.nutricia-na.com         |
| Similac  | Abbott               | Abbott Park, IL                | www.abbottnutrition.com     |

the 3 major formula manufacturers have made a modification to their standard term product to market it for breast milk supplementation. There is limited documentation that these formulas provide any significant benefit over using the standard cow's milk-based term infant formula to supplement breastfeeding.<sup>23</sup>

Previously, the standard dilution for term infant formulas across all categories was 20 calories per ounce (0.67 calories/mL) and ~1.4 g protein per 100 mL. Some term infant formulas now have a standard dilution of 19 calories per ounce (0.64 calories/mL) and ~1.3 g protein per 100 mL in an effort to be closer to breast milk, which has an average composition of 0.65 calories/mL and ~1.3 g protein per 100 mL. The Infant Formula Act does not have a requirement for calorie density, and these formulas meet the nutrient requirements for a term infant formula.<sup>24</sup> The thought behind this change in term infant formulas was to prevent obesity in formula-fed infants, yet there is limited documentation to show any specific benefit to this change.<sup>24,25</sup> Also, infants both formula fed and breastfed self-regulate intake.<sup>25</sup> This difference in calorie concentration may be significant when working with infants who may have higher calorie needs due to a medical condition.

### Term Infant Formulas for Signs and Symptoms of Intolerance

There is an entire category of term infant formulas marketed for infant colic, fussiness, and perceived GI issues.<sup>7,18,26</sup> Marketing claims are regulated by Regulatory Affairs of the FDA but do not require premarketing approval or scientific evidence to support the marketing claim. Instead, the claims must be "truthful and not misleading."<sup>18</sup> After seeing these marketing claims, parents may perceive their infants to have increased fussiness, colic, or gassiness and attribute it to the formula.<sup>18</sup> Formula modifications in this category include partially hydrolyzed protein (either casein and whey or 100% whey protein) with reduced lactose or lactose-free and/or added probiotics, or added rice starch. Standard dilution for these products is 19 or 20 calories per ounce (0.64 or 0.67 calories/mL).

Cow's milk protein intolerance occurs in 5%–15% of infants and a true allergy in 2%–7.5% of the population. Partially hydrolyzed cow's milk protein formula has been shown to alleviate feeding intolerance such as fussiness and gas. It is not

considered hypoallergenic, but instead, partially hydrolyzed protein is considered more easily digested, with reduced transit time, and lessens the potential of large protein molecules to permeate the intestines, resulting in GI distress.<sup>27</sup> Atopic disease is often associated with intolerance to cow's milk protein. Currently, there is no evidence partially hydrolyzed cow's milk protein formula can prevent atopic disease.<sup>28</sup>

Lactose is the primary carbohydrate in cow's milk and breast milk and the major source of the energy needed to fuel growth in infants. Reduced-lactose formula contains cow's milk protein, but the main source of carbohydrate is either brown rice syrup or corn syrup solids. Lactose intolerance occurs when the amount of lactase is inadequate, resulting in the inability to digest lactose properly.<sup>29</sup> Congenital lactase deficiency is a rare condition, and since breast milk contains lactose, babies are born with adequate lactase.<sup>30</sup> Temporary lactose deficiency can occur following acute gastroenteritis. Reduced-lactose and lactose-free formulas can shorten the course of diarrhea but is not indicated unless the infant is malnourished or at risk of malnutrition.<sup>19</sup> In most cases of transient lactose intolerance due to gastroenteritis, it is recommended to stay on breast milk or whatever formula the infant was on prior to the illness. Reduced-lactose or lactose-free formula made from cow's milk protein is not intended for infants with galactosemia.

Gastroesophageal reflux is often regarded as a significant problem and a primary reason for parents to seek formulas promoted to reduce reflux symptoms. Associated symptoms may include coughing and gagging during feeding and perceived pain such as irritability, crying, and fussiness. Volume, caloric density, nutrient composition, viscosity, pH, and osmolality all influence reflux and therefore dietary modifications are the most common remedy for reflux.<sup>31</sup> One common dietary modification is increasing the viscosity by adding dry rice cereal to the formula. Adding dry rice cereal to standard infant formula displaces nutrients, increases caloric intake, and slows gastric emptying time, further promoting reflux.<sup>5,31</sup> There are formulas available that replace some of the carbohydrate in the formula with rice starch to provide increased viscosity, which further thickens in the acidic environment of the stomach. Infants with uncomplicated gastroesophageal reflux may experience reduction in regurgitation and choking/coughing associated with these formulas.<sup>31</sup>

Despite limited applications, soy protein-based formulas may account for nearly 25% of the formula market in the United

States. Soy protein-based formula is whey, casein, and lactose free, since it is a plant-based formula. The soy protein isolate is supplemented with amino acids so that it meets the requirements for infant growth. The carbohydrate sources vary by manufacturer and can include corn maltodextrin, corn syrup solids, and sucrose. The fat content is derived from vegetable oil with added DHA and ARA.<sup>30</sup> Soy-based protein formulas are recommended for infants with galactosemia, hereditary lactase deficiency, and those who wish to provide a vegetarian-based diet.<sup>4</sup>

Currently, there is no conclusive evidence that dietary soy isoflavones have adverse effects on development, reproduction, or endocrine function.<sup>30</sup> Soy protein-based formulas are not recommended for premature infants and are not designed to meet the specific needs of the premature infant.<sup>32</sup> Previous formulations have been associated with increased incidence of osteopenia. Inadequate evidence exists regarding osteopenia risk in current formulations.<sup>33</sup> Soy formulas are no less allergenic than cow's milk protein-based formulas and are not indicated for the treatment of cow's milk protein allergy because 10%–14% of infants with cow's milk protein allergy will also react to soy protein.<sup>30,34</sup>

### Specialized Infant Formulas

Another category of infant formulas includes formulas designed to meet the specific needs of a disease or medical condition. These exempt formulas include premature infant, premature discharge, extensively hydrolyzed protein, amino acid-based, carbohydrate-free, fat-modified, and low-mineral formulas. Standard dilution differs by category, and in some cases, the product is designed so the calorie concentration can be easily manipulated.

Premature infant formulas are available for hospital use primarily, although one company now supplies one of the formulas in its line of premature formulas through retail. These formulas are designed to meet the needs of premature and low-birth-weight infants (specifically infants born <1500 g). These formulas are cow's milk protein based. The protein is intact and whey predominant, with one product that is partially hydrolyzed whey. The carbohydrate source is lactose with some glucose polymers, and some of the fat are medium-chain triglycerides (MCTs).<sup>32</sup> The micronutrient composition provides more calcium and phosphorus as needed to support growth similar to intrauterine growth and bone accretion. These formulas are available in ready-to-feed nurser bottles at various calorie concentrations, including 20 calories per ounce (0.67 calories/mL), 24 calories per ounce (0.8 calories/mL), and 30 calories per ounce (1 calorie/mL). There are also high-protein options available.

When approaching discharge from the hospital, premature infants not being breastfed or being fed breast milk are often transitioned to a premature discharge formula. These formulas are cow's milk based and have higher amounts of calcium and phosphorus in them. The standard dilution for these formulas is 22 calories per ounce (0.72 calories/mL), which is higher than term infant formulas. In theory, the additional nutrients and calorie concentration should provide added benefit to the premature infant, but a Cochran review concluded that there is not

sufficient evidence that premature discharge formulas provide any benefit over term infant formulas.<sup>35</sup>

Extensively hydrolyzed cow's milk protein formulas, specifically casein and/or whey, are subjected to chemical or enzymatic hydrolysis to reduce molecular weight. The hydrolysis process results in small peptides and amino acids. These formulas are considered hypoallergenic according to FDA standards and are less likely to cause an allergic reaction. Extensively hydrolyzed cow's milk protein formulas are also effective in reducing the risk of allergies.<sup>36</sup> Fatty acids are supplied by long-chain triglycerides, varying amounts of MCTs, and polyunsaturated vegetable oils.<sup>5</sup> Extensively hydrolyzed cow's milk protein formulas are recommended for infants intolerant to cow's milk and soy proteins and those with significant malabsorption due to GI or hepatobiliary disease.<sup>37</sup> Extensively hydrolyzed protein formulas are less palatable and more costly compared with standard formulas.<sup>5</sup>

Amino acid-based formulas contain 100% free amino acids. These formulas are specifically formulated for infants whose symptoms of hypersensitivity persist on extensively hydrolyzed cow's milk protein.<sup>38</sup> If an extensively hydrolyzed protein formula is effective, there is no added benefit to using an amino acid formula.<sup>39</sup> Amino acid-based formulas are indicated for dietary management of protein maldigestion, malabsorption, GI tract impairment, short bowel syndrome, severe food allergies, and eosinophilic GI disorders.<sup>5,39</sup>

Carbohydrate-free formulas contain either soy protein or hydrolyzed cow's milk protein as the protein source.<sup>5</sup> These formulas are designed for the management of carbohydrate metabolism disorders and carbohydrate malabsorption issues<sup>40</sup> and allow the physician or other healthcare professional to choose the appropriate carbohydrate source for the individual patient.<sup>5</sup>

Reduced- and modified-fat formulas are indicated for conditions of fat malabsorption, decreased bile salts, chylothorax, defective lymphatic transport of fat, and long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Since a good portion of the fat in these formulas is provided as MCTs and the malabsorptive conditions in which they are used, patients using these formulas may be at risk for essential fatty acid deficiency and should be monitored closely by a medical professional.<sup>23</sup>

One reduced-mineral formula on the market is used primarily in infants and toddlers with calcium disorders and renal insufficiency. The mineral level is similar to that of human milk and lower in phosphorus, potassium, and iron. Infants diagnosed with Williams syndrome, neonatal hyperparathyroidism, and osteopetrosis may also require a reduced-mineral formulation.<sup>5</sup> Iron supplementation may need to be considered, and infants on this formula should be monitored by a medical professional.

### Mixing Infant Formula

Infant formulas come in 3 forms: ready to feed, liquid concentrate, and powder. Each form offers advantages and disadvantages. See Table 3 for information on the forms of infant formulas. Of the 3 forms, the liquid products (ready to feed,

**Table 3.** Forms of Infant Formula.

| Type of Formula    | Standard Mixing                                     | Advantages   | Disadvantages   |
|--------------------|---|--|---|
| Ready to feed      | No mixing required                                  | Decreased risk of contamination due to decreased manipulation<br>Considered commercially sterile | Most expensive form   |
| Liquid concentrate | 1:1 ratio concentrate to water                      | Considered commercially sterile<br>Calorie concentration of final product can be manipulated     | Can only make a large batch that must be used within 24 hours of mixing |
| Powder             | 2 ounces of water to 1 scoop of powder <sup>a</sup> | Least expensive form<br>Can make only what is needed for one feeding or a large batch            | Not sterile   |

<sup>a</sup>Check label: some specialty products may have different mixing instructions for standard dilution.

liquid concentrate) are considered commercially sterile and are the preferred forms to be used in institutions.<sup>41</sup> The powder form of formula is not sterile and has been the cause of *Enterobacter sakazakii* infection in infants.<sup>42</sup> Powder forms of infant formula should only be used in institutions if liquid forms of the formula are not available.<sup>10</sup> Even though the powder is not sterile, it is safe and many infants have consumed formula made from powder.

It is recommended that purified water be used to mix infant formula in institutions. The reasons are that the water is sterile and solute free.<sup>41</sup> If the water is not purified, it must be sterile. The water should be chilled before mixing the concentrate or powder into it. Chilled water is recommended so that the holding temperature of the prepared formula can be reached quickly, limiting the time the formula is at an optimal temperature for bacterial growth.<sup>10</sup> If sterile water is needed for preparing formula at home, municipal tap or bottled water should be brought to a rolling boil for 1–2 minutes and covered with a sterile cover and cooled.<sup>10</sup> Chemically softened water should not be used to mix formula.<sup>10,41</sup> It is also recommended that powder formula be prepared just before feeding to minimize risk of contamination.<sup>43</sup>

Each step in the formula preparation process is an opportunity for bacterial contamination, and so is each manipulation of the prepared product (eg, transferring from the storage container to the feeding bottle or tube feeding bag).<sup>41</sup> There are guidelines established for proper procedures and equipment needed when mixing formula in institutions.<sup>10,41</sup> In addition, caregivers who will be preparing formula for their infant at home need to be educated on the importance of a clean work area and utensils when preparing infant formula and clean containers and feeding devices.<sup>44</sup>

Both liquid concentrate and powder formula can be mixed to higher than standard calorie dilutions if deemed medically appropriate. The standard calorie concentration for undiluted liquid formula concentrate is 40 calories per ounce, but there is no standard for the container. One manufacturer sells concentrate in a 12.1-ounce container while the others sell their products in a 13-ounce container. There is no standard for powder formula, with each manufacturer and formula having different size scoops, standard mixing instructions, and standard calorie concentrations. Mixing instructions differ from one formula to another, with some requiring a packed measure and others with an unlevelled scoop. With all of these differences, it is important

to develop recipes specific to each formula, and these recipes need to be updated with each formula modification as the standard instructions may change.<sup>43</sup>

In some medical conditions, increased calorie concentration may be necessary. This can be accomplished by using powder or concentrate and using less water to mix the formula or by adding a modular product. When concentrating calories higher than 24 calories per ounce, potential renal solute load needs to be considered because a high potential renal solute load can result in more rapid dehydration.<sup>45</sup> Usually, modular products have a lesser impact on potential renal solute load because they may have less of the contributing nutrients, such as protein, sodium, chloride, potassium, and phosphorus, but may not be the best option since it may result in deficient intake of a desired nutrient. Infants on an infant formula mixed to higher than standard calorie concentration should be monitored by a medical professional.

## Summary

Manufacturing and nutrient content of infant formulas are highly regulated to provide adequate nutrition for the quickly growing and developing infant who is not breastfed or who does not receive all breast milk. There are many different infant formulas on the market, and products can vary significantly within a category. Because marketing practices of infant formula companies are not as highly regulated, it can be confusing for parents and practitioners. Many formula changes are made because of perceived intolerances. There are also specialized formulas for use in specific medical conditions, including prematurity, GI disorders, allergies, altered fat metabolism, and renal insufficiency. When using any of these specialized formulas or when concentrating any formula to a calorie concentration above the standard, close monitoring by a medical professional is warranted.

Standard calorie concentration can vary among products as well as mixing instructions, so attention should be given to the specific formula and individual recipes, and instructions should be created. The type of water used to reconstitute powder and concentrate formula is important, and guidelines are available for safe formula mixing practices in institutions. Care should be given to educating caregivers on hygienic formula mixing practices at home.

## Statement of Authorship

K. Green Corkins and T. Shurley contributed to the conception/design of the review, contributed to the review of literature, drafted the manuscript, critically revised the manuscript, and agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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