Limited Effectiveness of Long-Chain Polyunsaturated Fatty Acids in Infant Formula

Is Universal Use of These Supplements Justified?

M. Jane Heinig, PhD, IBCLC
Jennifer Goldbronn, RD
Jennifer Bañuelos, MAS
UC Davis Human Lactation Center

CALIFORNIA WIC ASSOCIATION
WORKING FOR BETTER HEALTH

UCDAVIS
HUMAN LACTATION CENTER

April 2010

INTRODUCTION

FOR NEARLY A DECADE, infant formulas sold in the United States have included the long-chain polyunsaturated fatty acids (LC-PUFAs) arachidonic acid (ARA) and docosahexaenoic acid (DHA). Marketing materials for these products, aimed at health professionals and the public, claim that added LC-PUFAs are needed for optimal brain and visual development and that formulas supplemented with LC-PUFAs are superior to standard formulas. Since 2003, ARA and DHA have been included in formulas purchased by the USDA Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), resulting in higher food costs for the program.[1] Given that more than 9 million women, infants, and children[2] participate in WIC nationally, it is important that any factor that increases program costs be justified.

When a parent makes a decision about infant feeding, she or he is able to consider many factors, including the infant's unique needs. However, when program administrators make decisions about which formulas should be made available to WIC participants, they must identify the best and most cost-effective means to meet the requirements of thousands of participating infants. Money spent on formula represents a large portion of the WIC budget and strongly influences how many people the program may serve.[1] In the past, WIC formula costs have been reduced through the use of state-level or regional contracts that are negotiated with manufacturers. Under these agreements, the majority of the participating families within each region receive the same type of formula. However, the program has the flexibility to provide alternative formulas to infants with special medical needs to ensure their nutritional requirements are met. For example, families with infants born prematurely have access to formulas with more calories and nutrients than those fed to infants born at term.

According to 2004–2006 data, 57 to 68 percent of all infant formula sold in the United States was purchased through the WIC program.[1] It is no surprise, then, that any increase in the price of formula can result in a significant impact on program costs. For example, the net wholesale price for formula contracts in December 2008 were, on average, 73% higher (after adjustment for inflation) than prices negotiated in prior contracts.[1] These contract changes resulted in a $127 million increase in cost to the WIC program in just one year, an amount that could have been used to enroll more than 130,000 participants. Much of this cost increase has been attributed to the addition of higher-cost formulas supplemented with DHA and ARA to the December 2008 formula contracts.[1] Given that these formulas are more expensive than those previously offered and that the WIC program allows for flexibility in formula selection for at-risk infants, an important question arises: Does the research evidence support the inclusion of these additives to formulas offered to the *majority* of WIC infants?

DHA/ARA formulas contributed to $127 million in increased costs to the WIC program in one year.

The answer is no. Despite studies showing advantages of specific fatty acid additives for some populations of infants (including some preterm infants),[3] the current evidence related to LC-PUFAs *does not support* the need for their addition to the contract formulas offered to most WIC families. Although challenging, careful reviews of not only the safety, but also the *effectiveness* of formula additives are needed so that WIC administrators can make responsible and informed decisions about their formula contracts. Additional additives are likely to be made available in infant formulas over the next decade as infant-feeding research continues. Some of these new additives may prove to be beneficial for the majority of infants, others may not. Therefore, a process is needed to ensure that 1) all participating formula-feeding infants receive the formulas that best meet their needs, and 2) WIC does not incur unnecessary costs for additives or ingredients that provide no direct benefit to the majority of WIC infants.

FATTY ACIDS AND INFANT HEALTH

FATS, COMPRISED OF DIFFERENT TYPES of fatty acids, are a major component of every cell in the human body. Fatty acids are used primarily as a source of energy, but they also serve other important physiological roles.[4,5] While we do need different types of fatty acids to play various metabolic roles in our bodies, we are also capable of making most of the fatty acids needed to maintain health from "essential" fatty acids that can only be obtained from the foods we eat. DHA and ARA are not considered essential for most people. We are able to make DHA and ARA from the

essential fatty acids alpha-linolenic acid and linoleic acid, respectively. For many decades, all infant formulas have contained essential fatty acids in sufficient amounts to meet infants' needs. Newer, supplemented formulas also include *preformed* DHA and ARA made commercially.

Our bodies are capable of making most of the fatty acids needed to maintain health.

PHYSIOLOGY OF FATTY ACIDS

FATTY ACIDS ARE NAMED based on their structural characteristics, such as the number and types of chemical "bonds" they contain. These characteristics affect their actions in the body. DHA and ARA are both *polyunsaturated* fatty acids and they are considered to be "long-chain fatty acids" because they contain more than 18 carbons.

In human beings, the liver makes the majority of needed DHA and ARA from the essential fatty acids. Other cells in the body, such as some of those in the central nervous system, are also capable of converting essential fatty acids to ARA and DHA. This allows the body to maintain LC-PUFAs at relatively high levels in the brain.[4]

Synthesis of both ARA and DHA in the body is dependent on the presence of specific enzymes, and both of these fatty acids use some of the *same* enzymes for their metabolism. Consuming a diet excessive in one fatty acid may interfere with and limit the metabolism of the other. Therefore, a high dietary intake of DHA might suppress the metabolism of ARA. This possibility must be considered as increasing levels of DHA are added to formulas and other foods. A balance between the two fatty acids is important to maintain health.[5,6] Early studies of infant formulas supplemented with only DHA resulted in poor growth, initially thought to be associated with impairment of ARA metabolism, but this hypothesis has been disputed.[7] Regulatory authorities in many countries have created guidelines for the balance of fatty acids in infant formulas.[8,9] In the United States, however, the FDA requires only a minimum level of linoleic acid in infant formula, and currently does not provide recommendations for the balance of fatty acids.

FUNCTIONS OF FATTY ACIDS

Vision

DHA is found in high concentrations in the retina and makes up as much as 40% of total fatty acids in certain cells in the eye. DHA is needed for normal transmission of light (via the optic nerve) as an electrical signal to the brain, where the signal is interpreted as vision.[5,10]

The Central Nervous System

Nerve cells in the brain, retina, and other parts of the body transmit electrical currents that can send messages throughout the nervous system. ARA and DHA are two of the major LC-PUFAs in nerve tissue and are concentrated in the membranes of developing cells. LC-PUFAs play a role in normal brain function.[4] DHA may also be involved in the metabolism of two critical brain chemicals; dopamine and serotonin.[4] The roles of ARA and DHA in metabolism of these chemicals indicate that these fatty acids are important for normal activity in the brain and nervous system.[11]

Immunity

Special compounds called prostaglandins and leukotrienes are made from ARA. Prostaglandins are involved in regulation of blood pressure and smooth muscle function, and both prostaglandins and leukotrienes are involved in immune function.[5] Other ARA derivatives have been implicated in the prevention of cardiovascular disease, possibly because of their role in reducing inflammation.[12]

FATTY ACID REQUIREMENTS

ALL FATTY ACIDS CAN BE USED as a source of energy by the body when needed. Human infants obtain 50% of energy from dietary fat and fat stores. When energy is low, fatty acids (including essential fatty acids) may be used to provide needed calories. When the body has enough energy, some fatty acids will be used for calories, but a significant proportion of the essential fatty acids will be used for other functions. Only about 1% of the dietary energy for infants needs to come from essential fatty acids.[13,14] Currently, there are no requirements set for preformed DHA or ARA because they are not essential for most infants.[13]

Regulation of Fatty Acids

The amount of ARA made in the body appears to be closely controlled.[5] DHA is also regulated; however, DHA concentrations in the brain appear to vary more with differences in dietary intake than those of ARA. Internal regulation of these nutrients is important to keep babies healthy

despite differences in the amount and type of milk they consume.[4,13]

The absorption, transport, and use of most nutrients are regulated in babies' bodies to prevent imbalances and in some cases, direct harm from excessive amounts. These mechanisms work to improve the body's ability to obtain and use nutrients when there is deficiency and to eliminate excessive amounts when too much of any nutrient is consumed. Therefore, giving increasing amounts of nutrients (including DHA and ARA) will not result in unlimited increases in babies' bodies. Babies benefit from additional nutrients only when they have a *deficiency*.

Use of most common nutrients are regulated in babies' bodies.

Infants at Risk for Deficiency

The majority of infants are capable of producing their own LC-PUFAs from essential fatty acids, but for some infants, this process is not effective in meeting their needs. For example, some preterm or low birth weight infants may have low nutrient stores or higher energy needs compared to term infants. These infants would be more likely to benefit from higher intakes of preformed DHA and ARA than healthy term infants. Evidence from randomized controlled trials suggest that some subgroups of vulnerable infants may benefit from supplemented formulas.[7, 14-16]

STUDIES OF HEALTHY TERM INFANTS

Challenges in Interpreting Research

Over the last decade, DHA and ARA have been the focus of an enormous number of research studies. Apart from the challenges associated with reviewing so many studies, there are other factors that complicate the interpretation of this research. Differences in study design (sample sizes, outcomes, dietary interventions, etc.) and quality (methodology, analysis, attrition) must be considered when comparing outcomes. Researchers in the field have called for a more standardized approach.[17] Further, many of the tests used in the studies to detect differences in visual and cognitive function between feeding groups were never intended or validated to compare "good" with "better" infant function, nor to predict future cognitive ability. Rather, they were intended for use in detecting developmental delays or poor function in infancy. Marketing materials used to sell supplemented formulas may easily be interpreted as suggesting that future intelligence and artistic ability may be increased by intake of supplemented formulas despite a lack of evidence to support these claims.

Study Outcomes

When faced with enormous numbers of research studies, many medical professionals and policy-makers will turn to systematic literature reviews or special analyses of groups of studies to make decisions. One of the most famous and well-respected sources of scientific review is the Cochrane Library. Following rigorous guidelines for study selection and evaluation, Cochrane reviews have been written on thousands of health topics, including many related to infant feeding. Randomized-controlled trials are often selected for these reviews because they are considered to be the best source of objective evidence in experimental science.

In a 2008 Cochrane review, 14 randomized-controlled trials examining the effect of DHA/ARA supplements on term infants' visual and cognitive function were selected based on study quality.[18] The conclusion drawn by the reviewers was unequivocal: they reported that routine supplementation of formulas with LC-PUFAs to improve infant outcomes "could not be recommended based on current evidence." In a more recent review,[7] Makrides and colleagues also found little evidence to suggest that term infants benefit from supplemented formulas, even in studies with increasing amounts and duration of supplementation. The authors contend that preterm infants may benefit from these formulas because they do not receive as much DHA/ARA as would infants born at term. Other large, randomized controlled trials examining mental and motor development throughout the first year or beyond also found no consistent differences between supplemented and unsupplemented infants.[19-21]

Despite the lack of clear benefit of DHA and ARA supplemented formulas for term infants, researchers continue to conduct studies, some suggesting that higher amounts of DHA and ARA be given.[22] Studies using increasing doses of DHA and ARA are underway. However, a study examining the effect of high levels of LC-PUFAs (using higher concentrations than had been previously tested) among preterm infants failed to demonstrate beneficial effects.[23] In another study providing higher levels of DHA/ARA to term infants, differences in visual acuity occurred at some but not all of the study time points. Of greater interest was a *regional* difference in outcomes, with infants in some participating cit-

ies showing no response to the supplement while infants in another location did.[24] Researchers are also including additional outcomes, such as problem solving at various ages, in an effort to find potential benefits for these formulas. These efforts have also yielded mixed results.[25-27]

Several authors have suggested that intakes of LC-PUFAs must be high enough to achieve levels similar to breastfed infants before effects will be seen.[22,24] Use of supplemented formulas has been associated with changes in fatty acid concentrations in babies' bodies[28,29] but these differences have not resulted in similar changes in cognitive, visual, or motor function. Despite increases in circulating and tissue LC-PUFAs that occur after supplementation, no study has shown an advantage with the use of these supplemented formulas compared to breastfeeding on any visual or cognitive outcome, even when the studies were conducted among breastfeeding populations with low intake of DHA. These findings lend support to the position that term infants are able to make enough DHA and ARA to meet their needs from dietary essential fatty acids alone.

It appears, then, that despite marketing efforts indicating that all infants are likely to benefit from supplemented formulas, the current evidence shows that only a subgroup of infants is likely to need these formulas.

CONCLUSION

WITH SO MUCH RESEARCH already completed using LC-PUFAs in infant formulas, scientists have identified subgroups of infants who may benefit from these supplements. These infants should and do have access to formulas supplemented with DHA and ARA. However, these supplements are currently being marketed and sold for use with *the majority of* infants.

Logically, use of additives in primary WIC contract formulas should be supported by research evidence indicating that healthy term infants benefit from them, particularly if these formulas are more expensive than standard formulas. If the evidence does not support benefits of supplemented formulas for healthy term infants and states are required to use these formulas as the primary contract formula, WIC may be spending millions of dollars unnecessarily.

How did these additives come to be used in so many formulas? Marketing efforts for these formulas have been quite successful in convincing parents and the public that supplemented formulas will provide benefits to nearly all infants. Despite the lack of evidence justifying the use of supplemented formulas for healthy term infants, parents are willing to purchase these formulas "just in case" their infants might benefit from them. However, this thinking would be similar to all parents deciding to purchase prescription eyeglasses for their infants and young children "just in case" they might have vision problems. Most parents would believe it would be a waste of money to do so.

DHA and ARA supplemented formulas are likely to be followed by formulas with many types of additives. Given the potential for extra formula costs to significantly impact family and national budgets, it is important that an objective source of information be available to families and to administrators in the WIC program so that fully informed formula purchasing decisions can be made. Infant feeding experts should be called upon to review studies related both to the safety and *effectiveness* of all new additives intended for formulas that may be purchased by the WIC program. These periodic reviews could then be used to inform administrators' decisions about infant formula contracts and reduce unnecessary spending.

Summary of Findings

- ARA and DHA are necessary for normal brain and visual function.
- The WIC program currently purchases relatively expensive formulas supplemented with LC-PUFAs and distributes them to most infants participating in the program, including healthy full-term infants.
- Long-chain polyunsaturated fatty acids ARA and DHA may be obtained not only from dietary sources but also from body stores and from conversion of essential fatty acids in the body. Therefore, DHA and ARA are not considered essential for most human beings; that is, *dietary* sources of these fatty acids are not necessarily needed to maintain health.
- Research on DHA and ARA formulas has been going on for more than a decade. Millions of dollars have been spent and thousands of children have participated in these studies. To date, there is no evidence that supports that the *majority* of infants need these formulas nor is there evidence that infants given formulas with any amount of DHA or ARA have advantages over breastfed infants.

REFERENCES

1. Oliveira V, Davis D, Smallwood D (2010). Rising infant formula costs to the WIC program: Recent trends in rebates and wholesale prices. ERR-93, U.S. Department of Agriculture, Economic Research Service.
2. FNS National Level Annual Summary http://www.fns.usda.gov/pd/wisummary.htm Accessed 2/18/10.
3. Simmer K, Schulzke SM, Patole S (2008). Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev.* 23:CD000375.
4. Larque E, Demmelmair H, Koletzko B (2002). Perinatal supply and metabolism of long-chain polyunsaturated fatty acids: Importance for the early development of the nervous system. *Ann NY Acad Sci.* 967:299-310.
5. Carlson SE (2001). Docosahexaenoic acid and arachidonic acid in infant development. *Semin Neonatol.* 6:437-449.
6. El-Badry AM, Graf R, Clavien PA (2007). Omega 3 – Omega 6: What is right for the liver? *J Hepatol.* 47:718-725.
7. Makrides M, Smithers LG, Gibson RA (2010). Role of long-chain polyunsaturated fatty acids in neurodevelopment and growth. *Nestle Nutr Inst Workshop Ser Pediatr Pgm.* 65:123-136.
8. European Union Commission (2006). Commission directive 2006/141/EC on infant formulae and follow-on formulae and amending Directive 1999/21/EC, *Official Journal of the European Union*, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:401:0001:0033:EN:PDF
9. Koletzko B, et al. (2005). Global Standard for the composition of infant formula: Recommendations of an ESPGHAN Coordinated International Expert Group. *J Pediatr Gastroent Nutr* 41:584-599.
10. Jeffrey B, Weisinger H, Neuringer M, et al. (2001). The role of docosahexaenoic acid in retinal function. *Lipids.* 36:859-871.
11. Uauy R, Hoffman D, Peirano P, et al. (2001). Essential fatty acids in visual and brain development. *Lipids.* 36:885-895.
12. Forsyth JS (2009). Do LCPUFAs influence cardiovascular function in early childhood. In Koletzko, B.; Decsi, T.; Molnár, D.; Hunty, A. (Eds.), *Early Nutrition Programming and Health Outcomes in Later Life: Obesity and Beyond.* N.Y.: Springer. pp. 59-63.
13. Institute of Medicine (2002). *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids.* Washington, D.C.: National Academies Press.
14. Giovannini M (2001). Overview: Conditionally essential nutrients: Long-chain polyunsaturated fatty acids. In Newburg, D. (Ed.), Bioactive Components of Milk. N.Y.: Plenum. *Advances in Experimental Medicine and Biology* Vol. 501:351-355.
15. Smithers LG, Gibson RA, McPhee A. et al. (2008). Effect of long-chain polyunsaturated fatty acid supplementation of preterm infants on disease risk and neurodevelopment: A systematic review of randomized controlled trials. *Am J Clin Nutr.* 87:912-920.
16. Makrides M, Gibson RA, McPhee AJ et al. (2009). Neurodevelopment outcomes of preterm infants fed high-dose docosahexaenoic acid: A randomized controlled trial. *JAMA.* 301:175-182.
17. Cheatham CL, Colombo J, Carlson SE (2006). n-3 Fatty acids and cognitive and visual acuity development: Methodological and conceptual considerations. *Am J Clin Nutr.* 83:1458S-1466S.
18. Simmer K, Patole SK, Rao SC (2008). Longchain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database Syst Rev.* 23:CD000376.
19. Beyerlein A, Hadders-Algra M, Kennedy K et al. (2010). Infant formula supplementation with long-chain polyunsaturated acids has no effect on Bayley developmental scores at 18 months of age—IPD meta-analysis of 4 large clinical trials. *J Pediatr Gastroent Nutr* 50:79-84.
20. Agostoni C, Zucotti GV, Radaelli G et al. (2009). Docosohexaenoic acid supplementation and time at achievement of gross motor milestones in health infants: A randomized, prospective, double-blind, placebo-controlled trial. *Am J Clin Nutr.* 89:64-70.
21. Auestad N, Scott DT, Janowsky JS et al. (2003). Visual, cognitive, and language assessments at 39 months: A follow-up study of children fed formulas containing long-chain polyunsaturated fatty acids to 1 year of age. *Pediatrics.* 112:e177-e183.
22. Hoffman DR, Boettcher JA, Diersen-Schade DA (2009). Toward optimizing vision and cognition in term infants by dietary docosahexaenoic and arachidonic acid supplementation: A review of randomized controlled trials. *Prostaglandins, Leukotrienes, and Essential Fatty Acids.* 81:151-158.
23. Smithers LG, Collins CT, Simmonds LA et al. (2010). Feeding preterm infants milk with a higher dose of docosahexaenoic acid than that used in current practice does not influence language or behavior in early childhood: A follow-up study of a randomized controlled trial. *Am J Clin Nutr.* 10.3945/accn.2009.28603.
24. Birch EE, Carlson SE, Hoffman DR et al. (2010). The DIAMOND study: A double-masked, randomized controlled clinical trial of the maturation of infant visual acuity as a function of the dietary level of docosahexaenoic acid. *Am J Clin Nutr.* doi: 10.3945/ajcn.2009.28557.
25. Drover JR, Hoffman DR, Castaneda YS, et al. (2009). Three randomized controlled trials of early long-chain polyunsaturated fatty acid supplementation on means-end problem solving in nine-month-olds. *Child Dev.* 80:1376-1385.
26. Willatts P, Forsyth JS, Dimodugno MK et al. (1998) Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet.* 35: 688-691.
27. Willatts P, Forsyth JS, Dimodugno MK et al. (1998). Influence of long-chain polyunsaturated fatty acids on infant cognitive function. *Lipids.* 233:973-980.
28. Hoffman DR, Wheaton DK, James KJ et al. (2006). Docosohexaenoic acid in red blood cells of term infants receiing two levels of long-chain polyunsaturated fatty acids. *J Pediatr Gastroenterol Nutr* 42:287-292.
29. Schwartz J, Dube K, Sichert-Hellert W, et al. (2009). Modification of dietary polyunsaturated fatty acids via complementary food enhances n-3 long-chain polyunsaturated fatty acid synthesis in healthy infants: A double blinded randomized controlled trial. *Arch Dis Child.* 94:876-882.

CALIFORNIA WIC ASSOCIATION
WORKING FOR BETTER HEALTH

April 2010

California WIC Association
1107 Ninth Street, Suite 625
Sacramento, CA 95814
916/448-2280 www.calwic.org

UCDAVIS
HUMAN LACTATION CENTER

UC Davis Human Lactation Center
One Shields Avenue
Davis, California 95616
530 754-5364
http://lactation.ucdavis.edu

Funding generously provided by

The California Endowment