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# Beyond Building Better Brains: Bridging the Docosahexaenoic acid (DHA) Gap of Prematurity

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## Abstract

Long chain polyunsaturated fatty acids (LCPUFA) including docosahexaenoic acid (DHA), are essential for normal vision and neurodevelopment. DHA accretion *in utero* occurs primarily in the last trimester of pregnancy to support rapid growth and brain development. Premature infants, born before this process is complete, are relatively deficient in this essential fatty acid. Very low birth weight (VLBW) infants remain deficient for a long period of time due to ineffective conversion from precursor fatty acids, lower fat stores, and a limited nutritional provision of DHA after birth. In addition to long- term visual and neurodevelopmental risks, VLBW infants have significant morbidity and mortality from diseases specific to premature birth, including bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP). There is increasing evidence that DHA has protective benefits against these disease states. The aim of this article is to identify the unique needs of premature infants, review the current recommendations for LCPUFA provision in infants, and discuss the caveats and innovative new ways to overcome the DHA deficiency through postnatal supplementation, with the long term goal of improving morbidity and mortality in this at risk population.



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**Conflict of Interest**

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**Keywords**

Docosahexaenoic Acid; DHA; Long Chain Polyunsaturated Acids; LCPUFA; Prematurity; Neonatal Nutrition; Bronchopulmonary Dysplasia; BPD; Necrotizing Enterocolitis; NEC; Retinopathy of Prematurity; ROP

## Introduction

Long chain polyunsaturated fatty acids (LCPUFA) including docosahexaenoic acid (DHA) and arachidonic acid (ARA), are essential for normal growth, vision, neurodevelopment and overall health. *In utero* LCPUFA accretion occurs primarily during the last trimester of pregnancy, when maternal levels are high and growth and brain development are rapid. Premature infants born before this process is complete are relatively deficient in DHA, the most variable of these essential LCPUFAs.(1) Additionally, DHA status in very low birth weight infants (VLBWs) remains low due to inadequate fat stores, ineffective conversion from precursor fatty acids and a limited nutritional supply.(2) Evidence demonstrates that LCPUFA supplementation improves neurodevelopmental and visual outcomes in this high risk population.(3–15) New evidence is emerging to suggest that the benefits of DHA supplementation extend beyond the brain. *In vitro*, animal model, and a few human studies demonstrate a role for improved LCPUFA provision in prevention of diseases specific to premature infants, including bronchopulmonary dysplasia (BPD)(11, 16–22), necrotizing enterocolitis (NEC)(23–27), and retinopathy of prematurity (ROP).(28–34) The purpose of this review article is to encourage further discussion about the recommended provision of DHA specifically for premature infants and the need for further study of specific dose, timing, safety and benefits in this high risk population.

## The Role of Essential LCPUFAs

Essential LCPUFAs are important components of the phospholipid bi-layer of cell membranes, contributing to structural integrity and function throughout the body. *In vitro* and animal studies demonstrate their many functions. In the brain and retina, they have highly specialized functional roles making them important for normal signal transduction, neurotransmission and neurogenesis. In tissues throughout the body, they are released from membranes by phospholipases for conversion to important hormones, eicosanoids, lipoxins and resolvins that mediate inflammation, immune function, platelet aggregation and lipid homeostasis. They also serve as local signaling molecules and transcription regulators of genes involved in inflammation, development and metabolism. Their ubiquitous arrangement and multifaceted functionality make LCPUFAs extremely important for normal growth, development, and overall health.

Humans can synthesize saturated and monounsaturated FAs but lack the enzymes required to synthesize omega-3 and omega-6 LCPUFAs *de novo.* Thus, they are essential and must be taken in through diet. DHA and ARA (22- and 20-carbon LCPUFAs, respectively) may be obtained directly through the diet – oily fish for DHA, meat and eggs for ARA - or from their 18-carbon precursor FAs, α-linolenic acid (ALA) and linoleic acid (LA).(Figure 1.) The most common essential FA found in the Westernized diet is LA, an omega-6 FA

abundant in vegetable oils, nuts and seeds. LA can be converted to the ARA, also an omega-6 FA. ARA is found throughout the body in phospholipid membranes and upon activation serves as a precursor to prostaglandins, thromboxane and leukotrienes. The nutritionally less abundant omega-3 FA precursor is ALA, found in flaxseed, canola, walnuts and soy. ALA can be converted to eicosapentaenoic acid (EPA) and DHA, but only in small amounts. These omega-3 LCPUFAs are rapidly and preferentially incorporated into cell membranes where they serve important functional and structural roles in the brain and retina and have anti-inflammatory and metabolic signaling functions in other tissues. An appropriate balance of these pathways is necessary for normal immune function and clotting, however, in excess leads to inflammation.

The omega-6 and omega-3 FA families are not interchangeable, making intake from both groups essential. Additionally, the conversion to ARA and DHA from their respective precursors is through the same rate limiting and inefficient desaturase enzyme in the liver. Due to the pervasive lack of omega-3 in the typical Western diet, there is an increasing dietary imbalance of omega-6 to omega-3 LCPUFA which can induce a pro-inflammatory state, attributing to multiple disease states. In a DHA deficit, the specialized phospholipid membranes in the retina and brain can become replaced with substitute FAs altering function which may affect memory, attention and visual processing. Unfortunately, a typical Westernized diet contains an abundance of omega-6 with very little omega-3 FAs, driving this imbalance bias.

## The DHA Gap of Prematurity

Because DHA cannot be synthesized *de novo*, the developing fetus is dependent on a maternal source. Most DHA accumulation occurs during the third trimester of pregnancy when growth and brain development are rapid.(35) Hormonal changes during pregnancy induce a hyperlipidemic state, increasing the availability of all circulating lipids; estrogen further increases conversion of precursor ALA to DHA, sustaining preferential uptake. FA transport across the placenta is both passive and active. Passive transport is directly dependent on maternal blood levels, while active transport occurs through FA transport proteins which are up-regulated during pregnancy to preferentially transport LCPUFAs to the fetal blood stream.

Infants born before this process is complete have interruption in normal LCPUFA accretion. Indeed, preterm infants have lower DHA levels than their term peers.(1) Furthermore, in very preterm infants (<28 weeks gestation) this deficit persists or worsens due to decreased adipose stores, a limited ability to convert precursor ALA to DHA and poor nutritional provision of preformed LCPUFA.(16) Relying on dietary intake to overcome this deficit is not plausible because this population often does not reach full enteral feedings until after several weeks of age, forcing them to rely heavily on parenteral nutrition early in life. Commercially available intravenous lipid emulsions provide essential precursor FAs only, rather than preformed DHA. This formulation may be sufficient to avoid essential FA deficiency in adults, but is inadequate to maintain DHA levels in very low birth weight (VLBW) infants due to decreased desaturase conversion and increased demands during rapid growth and neurodevelopment. These factors are unique to premature infants and

contribute to persistently low DHA levels, especially if complications of prematurity or illness further delay the advancement of feedings.

Even after full enteral feedings are reached, nutritional options available in the neonatal intensive care unit (NICU) provide extremely variable daily allowances of DHA that do not account for the relative deficits of premature infants. Calculated DHA provision for various neonatal diets is summarized in Table 1. Mother's own milk is the recommended diet for all infants and provides both ARA and DHA. However, there is a wide variation in DHA content (from 0.06–1.4%) based on regional, individual dietary and lactation differences.(36, 37) Milk from lactating mothers who deliver prematurely is higher in DHA than those who deliver at term.(38) Various human milk fortifiers that are routinely added to support the needs of premature infants also affect LCPUFA provision.(39) Alternatives to mother's own milk include donor human milk and commercially available infant formula. Donor human milk is a source of LCPUFA. Pasteurization does not alter DHA concentrations (40) however, the overall fat content is typically lower (41) and DHA provision is variable between banks and may be very low.(40) Infant formula is now routinely supplemented with DHA at levels similar to the world-wide average breast milk levels (0.2–0.35 wt:wt%) and ARA at higher levels (0.4–0.6 wt:wt%). Despite supplementation, neither breast milk, nor formula, which offers a calculated range of 3–23 mg/day after full feedings are reached, can match the estimated uterine accretion rate of 42–75 mg/day of DHA.(2, 4, 35) Additionally, only 80% of DHA given enterally is absorbed in the intestine,(2) and feeding practices in the NICU may further decrease DHA provision. Continuous drip feedings through a gavage tube markedly decreases fat provision,(42) presumably as lipids adhere to the plastic tubing. Given these factors, enteral doses may need to be closer to 65 mg/d which approximates 1–1.5 wt:wt% of FAs in human milk or formula to meet the needs of premature infants.(2) For these reasons, a critical reevaluation of the proper dose and mechanism of delivery to overcome the "DHA gap of prematurity" is critical to support the normal health and development of this at risk population.(3–6, 8, 11)

## The DHA Gap, Vision and Neurodevelopment

In 1992, Lucas reported findings that breastfed infants had a higher IQ than formula fed infants, which stimulated much interest in the importance of nutrition for visual and cognitive development.(43) Agostoni found a correlation between the fat content in breast milk and improved neurodevelopment at 12 months of age.(1) At the time, DHA was one important nutrient found in breast milk, but not formula, and animal studies supported the important structural and functional role in vision and brain development. A flurry of formula supplementation studies followed for term and then preterm babies. Findings from these studies support, but do not demonstrate a conclusive benefit from LCPUFA supplementation for term infants.(44) As expected from current knowledge about the "DHA gap of prematurity", subsets of premature infants demonstrate improvements in visual and neurodevelopmental outcomes.(3–5, 8, 10, 11, 13) Study results are mixed and dependent upon diet variability, regional differences, dose, timing, and sensitivity of outcome measurements for each particular study as illustrated in Table 2 and 3. Overall most experts in the field support the need to adequately remedy the DHA deficit in this most at-risk population.

Studying DHA related neurodevelopmental outcomes in infants is fraught with difficulty. Short term outcomes have typically been measured by the Bayley's Scales of Infant Development (BSID) including the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). This is a well standardized and validated test of overall infant development that is frequently utilized in neonatal follow up clinics. However, critics suggest this test may not be a sensitive indicator of hippocampal or specific learning dysfunction including difficulty with perceptual organization, distractibility, processing speed and inattention at school age, which are common in very premature infants (45) and are improved with increased DHA status.(13, 46) Similarly, visual acuity tests that are administered at a very young age (ranging from Teller cards to Visual Evoked Potentials (VEP), have similar sensitivity and specificity variability. Testing at school age may be a better indicator but is costly and often associated with loss to follow up, confounding and bias factors that may be introduced after infancy.

Although meta-analysis does not conclusively demonstrate a significant effect of LCPUFA formula supplementation on infant cognition (47), this conclusion should be cautiously considered, especially for premature infants. Combining the results of various formula supplementation studies is fraught with limitations because of dose-related variability that was inadvertently introduced with timing and administration methods. Although there were many well-performed, randomized controlled trials, LCPUFA provision in intervention formulas was variable between the studies (DHA 0.2–1.0% of total FAs). Many studies were designed to provide the amount of DHA found in world-wide term human milk (0.32%). As previously discussed, this amount may meet the needs of healthy, full-term babies but cannot begin to meet the deficit seen in very premature infants. Indeed, preterm human milk typically has higher DHA content then term human milk to support the infant's needs.(38) Additionally, DHA supplementation through formula is reliant on enteral intake which is widely variable in very premature infants. In our institution, the average length of time for an infant born at ≤28 weeks gestation to reach full enteral feedings is 29.5 days (Range: 14–42 days). Thus, the length of time that VLBWs receive little to no enteral, preformed DHA, may introduce significant bias. Breastfeeding introduces even more confounding because extremely variable levels of DHA are present in human milk dependent on regional, dietary, lactation and storage factors.(36, 39) Many of the formula supplementation studies allowed breast feeding even in the "control group" that was getting non-supplemented formula, and breast milk FA levels are rarely reported in such studies. In fact, the most convincing study demonstrating DHA related improvements in both the MDI and PDI required that 80% or more of the infant's diet be either supplemented or non-supplemented formula rather than breast milk.(3) Thus, with formula supplementation studies, "dosing" is difficult to accurately ascertain, and the provision may have been too low and started too late for the preterm population.

Despite limitations, some significant visual and neurodevelopmental benefits have been demonstrated from improved DHA provision in preterm infants (3–5, 8–11, 13) especially using more specific learning assessment tools or higher and more reliable supplementation methods. Tanaka, et al. demonstrated that breastfed premature infants had significantly higher DHA blood levels that directly correlated to improved attention, impulsivity and processing speed at 5 years of age.(48) Henriksen, et al showed that VLBW infants

supplemented with 32 mg DHA and 31 mg ARA in addition to DHA containing breast milk (0.7%) led to better problem solving and recognition memory by event-related potentials at 6 months of age. (4) Further follow up of this cohort revealed improved attention at 20 months of age.(13) Although formula supplementation studies have been less convincing (12, 47) because of the aforementioned limitations, subsets of premature infants fed formula with added DHA and ARA had better neurocognitive function, visual attention, visual evoked response time and visual acuity than premature infants fed non-supplemented formula (3, 5–8, 10–12) and effects persisted later in life.(9)

## The DHA Gap and Additional Health Risks of Prematurity

The beneficial effects of DHA may go well beyond building better brains. VLBW infants are at a unique risk for inflammatory mediated diseases that dramatically increase the morbidity and mortality of prematurity. There is growing evidence that DHA supplementation decreases the incidence and severity of several health risks including NEC, BPD and ROP. The optimal balance of LCPUFAs may also decrease the risk of late onset sepsis (16) and in animal models may improve bone health.(49)

**Necrotizing Enterocolitis (NEC)** is an inflammatory bowel disease that threatens the life and long-term health of 5–10% of VLBW infants. NEC carries a 15–30% mortality for these tiny infants and those who survive are at risk for recurrent strictures and bowel obstruction, mal absorption, failure to thrive from short bowel syndrome, parenteral nutrition associated liver disease and central line infections. In a randomized controlled trial, Carlson showed that premature infants who were fed DHA supplemented formula had a decreased incidence of NEC compared to peers who were fed unsupplemented formula.(27) Although this was not a primary outcome measure of the study, it sparked interest in the mechanism for protection. Since that time, multiple animal models of NEC have demonstrated LCPUFA modulated reduction in both incidence and severity of bowel disease through multiple pathways associated with intestinal inflammation and necrosis.(23–26) The protective effects of DHA are multifactorial. Local cell membrane phospholipids play a structural role in protecting the integrity of intestinal cells and alterations in LCPUFA content is important in bacterial translocation and intracellular fluid shifts associated with cell stress signaling that initiates NEC.(23) LCPUFAs in phospholipid membranes also serve as precursor molecules for eicosanoid production; they are integral in modulating inflammatory cell signaling, gene expression and transcription of key regulators in inflammatory and endotoxin translocation.(23–26) Despite promising animal studies, results are mixed and meta-analyses in humans have not confirmed the protective benefit of DHA against NEC. In part, this may also be due to limited sample sizes, variable timing and dosing of DHA supplementation and similar confounding as described above.(12) Overall, evidence is increasing to support the benefits of DHA in NEC protection.

**Bronchopulmonary dysplasia (BPD)** is a significant lung disease that complicates prematurity due to arrested alveolarization in developing lungs exposed to mechanical ventilation, oxygen, and other inflammatory mediators before normal development is complete. BPD, as defined by an ongoing oxygen requirement at 36 weeks adjusted gestational age, affects up to 32% of premature babies and 50% of VLBW infants. Many

animal studies reveal mechanisms by which omega-3 LCPUFA may protect against chronic inflammatory lung disease in premature infants.(17–22) In addition to previously mentioned anti-inflammatory mechanisms, additional protective properties in the lung are mediated through the PPAR pathways, of which DHA is a known ligand.(17, 19, 21) PPAR agonists accelerate lung maturation and prevent hyperoxia induced lung injury by stimulating development of Type II, surfactant producing pneumocytes and vasoproliferation in the lung.(21) Transgenic mice able to convert omega-6 to omega-3 LCPUFAs have markedly decreased endotoxin-induced lung inflammation.(22) Similarly, omega-3 LCPUFA supplementation reduces endotoxin- and *Pseudomonas*-induced lung injury through modification of both pro- and anti-inflammatory molecules related to BPD.(17, 18) These anti-inflammatory properties are associated with improved bacterial clearance, reduced lung injury, and increased survival after infection.(17) Even structural alveolar changes found in hyperoxia exposed and intrauterine growth restricted (IUGR) mouse pups are diminished through maternal supplementation with DHA.(19, 20) This evidence suggests beneficial DHA modulation of early lung development despite stressors known to induce defective alveolarization that translates to less BPD in premature infants.

A retrospective analysis by Martin demonstrated that premature infants less than 30 weeks GA with reduced blood DHA levels had a 2.5 fold increased risk of chronic lung disease.(16) Furthermore, a blinded, multi-center, controlled trial randomized premature infants to receive “standard” (through routine feeding) or “high dose” DHA with breast milk concentrations of ≥ 1 wt:wt% of total FA content (through maternal supplementation with 500 mg DHA-rich tuna oil capsules). Overall, VLBW infants weighing <1250 g at birth, and all preterm male infants (including those over 1250 g at birth), who received the “high dose” DHA feedings had significantly less BPD.(50) Finding additional innovative ways to administer DHA to infants on early mechanical ventilation or oxygen exposure during critical periods of pulmonary development may further reduce lung disease in this at risk population.

**Retinopathy of Prematurity (ROP)**, caused by abnormal vascular development of the retina, is the leading cause of visual impairment and blindness in premature infants. There are various factors that precipitate ROP at two critical stages of retinal development. Premature infants are born into a state of relative hyperoxia compared to fetuses still developing *in utero*. This oxidative stress down regulates vascular endothelial growth factor which can precipitate obliteration of the developing microvasculature in the retina. Eventually, this down regulation of vessels, alongside increasing metabolic demand causes a relative hypoxic state with overcompensation of angiogenic hormones and a second phase of rapid neovascularization. The abnormal vascular growth in this second stage may invade the vitreous placing traction on the retina.

DHA supplementation decreases the severity of ROP in VLBW infants.(29) The retina contains the highest concentration of DHA of all tissues, where it incites cytoprotective, angiogenic regulation and neuroprotective mechanisms.(28) Maternal supplementation with omega-3 LCPUFA demonstrates a decrease in both the primary oxygen-induced vaso-obliteration and the secondary neovascularization abnormalities associated with oxygen induced retinopathy in nursing mouse pups.(31, 32) Preventative effects are, in part,

mediated through increased production of neuroprotectins and resolvins which diminish the vasoconstrictive effects of thromboxane A2 (a platelet ARA metabolite) and modulate excessive neovascularization in the second stage of ROP development.(30) Recent studies translate the protective effects of omega-3 LCPUFAs against ROP in VLBW infants.(29, 33, 34) Two recent prospective, randomized trials showed that premature infants weighing less than 1250 g who received intravenous fish-oil containing emulsion rather than a conventional parenteral lipid source in the first days of life had a lower incidence (34) and significantly decreased severity of ROP.(33)

## Current Dietary Provision of DHA for Infants

The dietary provision of lipids for infants is extremely important due to the rapid growth and development that occurs during the first year of life. Breast milk is the optimal nutrition for all infants and contains all essential FAs, including preformed DHA. Because DHA levels found in human milk are dependent upon maternal intake and blood levels, the current consensus by experts in the field is that pregnant and lactating women should receive at least 200 mg/day of DHA through diet or a safe alternative supplement.(51) This recommendation is supported by the World Association of Perinatal Medicine, the Early Nutrition Academy, and the Child Health Foundation. The consensus group also recommends that if formula is substituted, it should contain between 0.2–0.5% of total FAs as DHA and an equal or greater amount of ARA to support infant growth and development. (51) Many formula supplementation studies show that LCPUFA blood levels do not reach those of breastfed infants with the addition of precursor FAs alone (i.e., ALA and LA)(52), and the addition of only DHA and not ARA to formulas may be associated with a decreased growth rate.(3)

Recommendations by the Child Health Foundation task force established the importance of dietary LCPUFA provision for infants and prompted the addition of DHA and ARA to commercialized infant formulas. However, the optimal daily DHA intake is yet unknown. Using the average breast milk content as the standard dietary provision of LCPUFA for all infants is problematic because DHA content in human milk varies a great deal. A meta-analysis including 65 studies and 2474 women around the world found the mean level of DHA to be 0.32 + 0.22% (range: 0.06–1.4%, median 0.26%)(36). Studies demonstrate that DHA concentration varies with maternal dietary fish intake (37), socioeconomic status (53) and dietary supplementation.(54) LCPUFA levels also vary with duration of breastfeeding (55), freezing/storage (56) and between preterm and term milk (38). Overall, US women tend to have DHA levels below the world wide mean, presumably due to their typically low fish intake.(36) Additionally, breast milk is designed to meet the needs of a normal term infant, but may not account for needs at earlier developmental time points or to make up for relative deficiencies noted in newborns at-risk for deficiency (premature, small for gestational age, infants born to diabetic mothers).(1, 2, 57, 58)

## Overcoming the DHA Gap of Prematurity

Currently, LCPUFAs are provided to premature infants through infant formula or human milk fortifier supplements. This content appears to meet the routine needs of term infants,

but is not adequate to remedy the DHA deficit found in premature infants. This may be the reason outcome studies show more conclusive benefit with DHA provision at a higher range or supplementation in addition to dietary sources.(4, 11) Formulas supplemented with an algal DHA source have been shown to be safe and well-tolerated, but a higher DHA dose (>0.32%) may be necessary to correct the relative deficiency and to optimize the benefits for VLBW infants.

A relatively new strategy for increasing DHA provision to premature infants is through its addition to commercialized human milk fortifiers used to increase calories, protein and mineral content of human milk and meet the needs of VLBW infants. Until 34 to 35 weeks gestation, when babies develop a coordinated suck and swallow, they are typically given enteral feedings through a feeding tube. Until that time, mothers pump and freeze their milk which is then thawed and fortified with human milk fortifier for feedings. With the growing focus on DHA, some fortifiers have now added DHA in an attempt to meet the needs of VLBW infants. This unique dosing method provides a higher daily DHA dose, but still requires establishment of full enteral feedings and is not uniform due to widely variable DHA levels in mother's milk that may be further altered by freezing and storing.

To date, no DHA supplementation study has attempted to "normalize" the DHA status of preterm infants throughout the critical first weeks of postnatal development (i.e., achieve levels found in term babies). The route and dose provided through either infant formula or breast milk with fortifier relies on the variable ability of the infant's gastrointestinal system to handle full enteral feedings. Thus, this approach is unreliable for providing sufficient DHA for catch up. Many VLBWs are not fed completely by enteral route for several weeks or longer, and routinely available intravenous lipids do not contain preformed omega-3 FAs. Due to these factors, the average accumulation of DHA during the first month of life in a very preterm infant is roughly 50% of the expected *in utero* accretion.(2) New parenteral products are being developed to provide improved LCPUFA balance by IV route until full enteral provision can be accomplished. Investigated results of parenteral interventions are highly anticipated. An alternative approach could be the direct enteral provision of DHA, independent of diet. This potentially cost-effective method would allow early intervention even before the infant reaches full feedings or fortification. Daily enteral dosing can be easily adjusted, is independent of the need for invasive intravenous access and may be continued beyond parenteral nutrition needs. Although there may be benefits to either parenteral or enteral supplementation, careful evaluation of potential adverse consequences or unintended alterations to the balance of the omega-6: omega-3 ratio will be required.

The need for supplemental DHA in the premature infant is clear. VLBW infants rapidly become and remain DHA deficient for an extended period of time due to ineffective conversion from precursor fatty acids, lower fat stores, and a limited nutritional provision of DHA after birth. Optimizing LCPUFA provision postnatally may not only improve vision and neurodevelopment in VLBW infants, but may also reduce the morbidity and mortality from BPD, NEC, and ROP.

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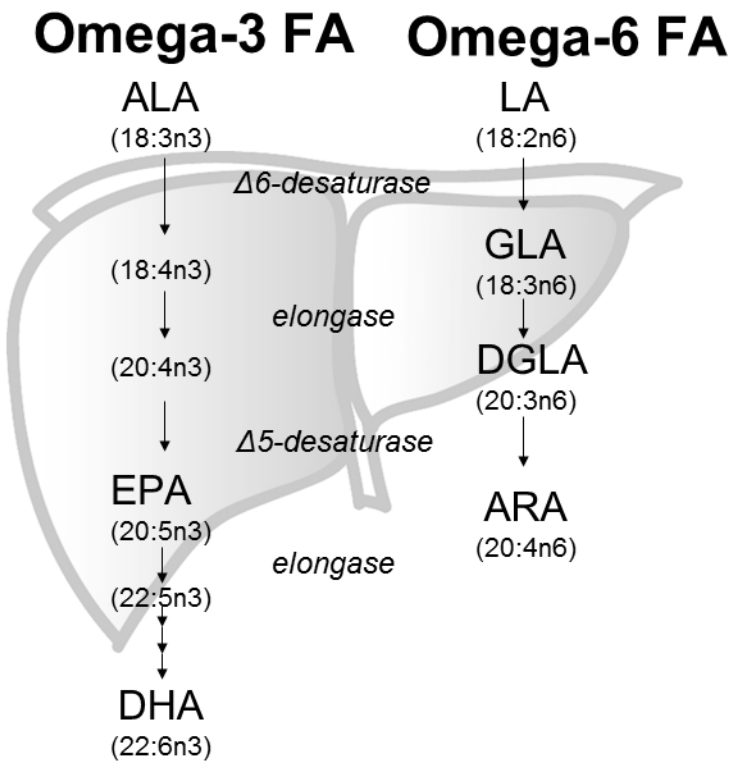


LA, linoleic acid; GLA, ɣ-linolenic acid; DGLA, di-homo- ɣ-linolenic acid; ARA, arachidonic acid
ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

**Figure 1.**

Omega-3 and Omega-6 long-chain polyunsaturated fatty acid synthesis from precursor essential fatty acids.

## Table 1

DHA Provision from Various Neonatal Nutrition Options and estimated *in utero* accretion*

| ***In utero* accretion*** | **42 mg/d** | | | |
|---|---|---|---|---|
| | **20 kcal/oz** | **22 kcal/oz** | **24 kcal/oz** | **26 kcal/oz** |
| **Worldwide human milk**** (w/unsupplemented HMF fortifier) | 23.0 mg/d | 21.0 mg/d | 19.2 mg/d | 17.7 mg/d |
| **North American human milk**** (w/unsupplemented HMF fortifier) | 10.1 mg/d | 9.2 mg/d | 8.4 mg/d | 7.7 mg/d |
| **Pasteurized donor human milk**† (w/unsupplemented HMF fortifier) | 4.2 mg/d | 3.8 mg/d | 3.4 mg/d | 3.2 mg/d |
| **DHA supplemented liquid HMF**‡ | 0 mg/d | 8.2 mg/d additional | 13.8 mg/d additional | NA |
| **Term formula**⁄ | 17.7 mg/d | NA | NA | NA |
| **Preterm formula**⁄ | NA | 19.7 mg/d | 20.4 mg/d | NA |

HMF, human milk fortifier; DHA, docosahexaenoic acid; NA, not applicable

The calculated daily DHA provision is based on nutritional provision at a full feeding goal of 120 kcal/kg/d which is 180 ml/kg/d of 20 kcal/oz, 164 ml/kg/d of 22 kcal/oz, 150 ml/kg/d of 24 kcal/oz or 138 ml/kg/d of 26 kcal/oz nutrition. Estimated provision does not account for intestinal absorption (80%) or continuous drip feedings which further decreases availability.(2, 42)

* Peak *in utero* accretion rate in the last 5 weeks of pregnancy.(35)

** Based on an average of 4 g/100 ml fat content, a worldwide mean DHA content of 0.32 wt:wt% and a North American mean DHA content of 0.14 wt:wt% in mother's own milk.(36)

† Based on lower fat content of 3.2 g/100 ml (41) and mean DHA content of 0.073%(40) in pasteurized donor human milk of Midwestern mothers.

‡ Enfamil Human Milk Fortifier Acidified Liquid® has 3 mg DHA per 5 ml vial to be mixed 1 vial with 50 ml of human milk to make 55 ml of 22 kcal/oz feeding (3 mg/DHA) or 2 vials with 50 ml of human milk to make 60 ml of 24 kcal/oz feeding (6 mg DHA).

⁄ Term formula represented by Enfamil Lipil®, Preterm formula 22 kcal/oz by Enfacare Lipil® and 24 kcal/oz preterm formula by Special Care Formula® as ready to feed product.

## Table 2

DHA intervention studies and neurodevelopmental outcomes in premature infants

| Reference | Intervention | Population | Outcome |
|---|---|---|---|
| O'Connor-2001 (5)<br>n=470 | 0.3% DHA to term<br>0.2% to 1 year | GA:<33 weeks<br>BW: 750–1800 g | 9 points higher on PDI in <1250 g at 12 months |
| Fewtrell-2004 (8)<br>n=238 | 0.5% to 9 months | GA 25–34 weeks<br>BW:<2000 g | 9 points higher MDI in boys at 18 months |
| Isaacs-2011 (9)<br>n=107 | Ongoing follow up at 10 years | | Improved verbal IQ*, full scale IQ*, vocabulary*, similarity* and word- pair learning scores‡ in formula fed only infants |
| Fang-2005 (10)<br>n=28 | 0.05% DHA for 25 weeks | GA: 30–37 weeks | 7 point higher MDI and 4 point higher PDI at 6 months<br>11 point higher MDI and 8 point higher PDI at 12 months |
| Clandinin-2005 (3)<br>n=361 | 0.3% to 12 months | GA:<36 weeks | 7 points higher PDI<br>5–10 points higher MDI at 18 months |
| Makrides-2009 (11)<br>n=657 | 1% to term vs. 0.3% | GA:<33 weeks | 4–5 points higher MDI in <1250 g and all girls |
| Smithers-2010 (12)<br>n=128/125 | Ongoing follow up at 26 mo/3–5 yr | | No difference in communication (MCDI) at 26 mo. or behavior (SDQ and STSC) by 3–5 years |
| Henriksen-2008 (4)<br>n=141 | 32 mg DHA and 31 mg ARA/100 ml breast milk per day for average 63 days | BW:<1500 g receiving breast milk (mother's or donor) | Improved Ages and Stages problem solving scores at 6 months |
| Westerburg-2011 (13)<br>n=92 | Ongoing follow up at 20 mo | | Improved free-play Duration of Focused Attention & Summary Attention Rating Score at 20 months |
| Van Wezel-Meijler-2002 (14)<br>n=42 | 0.34% DHA/0.68% ARA | GA: <34 weeks<br>BW: <1750 g receiving formula only | No difference in MRI myelination scores at 3 and 6 mo. or MDI/PDI at 3, 6, 12 and 24 months |
| Carlson-1996 (6)<br>n=59 | 0.2% DHA/0.6% ARA for 2 months | BW: 747 g-1245 g | Improved visual attention at 12 months by the Fagan Test of Infant Intelligence |

DHA, Docosahexaenoic acid; ARA, Arachidonic acid; GA, Gestational age; BW, Birth weight; IQ, Intelligence quotient; PDI, Bayley's Scale of Infant Development – Psychomotor Developmental Index; MDI, Bayley Scale of Infant Development – Mental Developmental Index; MCDI, MacArthur Communicative Development Inventory; SDQ, Strengths and Difficulties Questionnaire; STSC, Short Temperament Scale for Children

*Wechsler Abbreviated Scale of Intelligence

‡Children's Memory Scale (CMS) word paired scores, a test of hippocampal function

## Table 3

DHA intervention studies and visual outcomes in premature infants

| Reference | Intervention | Population | Visual Test | Outcome |
|---|---|---|---|---|
| Birch-1992 (7) n=73 | 1% DHA for 4 months | BW:1000–1500 g | ERG/VEP Teller cards | ERG and VEP better at 3 weeks, VEP improved at 4 months |
| O'Connor-2001 (5) n=470 | 0.3% DHA to term 0.2% to 1 year | GA: <33 weeks BW: 750–1800 g | VEP Teller cards | VEP better at 6 months |
| Carlson-1993 (15) n=67 | 0.5% DHA | BW: 725–1400 g | Teller cards | Better at 2 and 4, but not different at 6,9,12 months |
| Carlson-1993 (15) n=67 | 0.2% DHA, 0.3% EPA | BW: 748–1398 g | Teller cards | Better at 2 and 4, but not different at 6,9,12 months |

DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid; GA, Gestational age; BW, Birth weight; ERG, Electroretinography; VEP, Visual Evoked Potential