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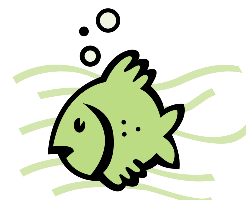
In This Issue:

A Fish Story — Essential Fatty Acid Requirements During Infancy



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Docosahexaenoic acid (DHA, 22:6n–3) has been the object of intense interest during the past several years because it is an important structural component in the cell membranes of brain, retina and other neural tissues, and studies have suggested that some infants may be dependent on an exogenous source of this compound for optimal development of visual acuity and cognitive function.[1,2] DHA is present in human milk[3], but it has not been added to infant formulas sold in North America. The purpose of this article is to briefly discuss the recent literature in this area and to consider implications it may have on the possible supplementation of infant formulas in North America.

Essential Fatty Acids

The n-3 and n-6 long-chain polyunsaturated fatty acids (LCPUFAs) are synthesized by the elongation and desaturation of their essential fatty acid (EFA) precursors. DHA is derived from alpha-linolenic acid (ALA, 18:3n–3) and arachidonic acid (AA, 20:4n–6) is synthesized from linoleic acid (LA, 18:2n–6). The LCPUFAs are precursors of eicosanoids and have a variety of other metabolic functions in addition to their role as structural components of membranes. Adequate amounts of LCPUFAs are synthesized from their precursors in young children and adults, but human infants may lack the capacity to do so.

Pre-term infants and DHA

There are several reasons why premature infants may require an exogenous source of DHA and/or AA.[4] The retina and brain accumulate DHA most rapidly during the third trimester of pregnancy and in early life. However, this accumulation is interrupted by premature delivery – at a time when the physiological need for DHA is likely to be greatest. Furthermore, the capacity for de novo synthesis of DHA and AA from their essential fatty acid precursors is not fully developed, and may not be sufficient to meet the high physiological demand. Finally, treatments provided in the neonatal intensive care unit such as drugs and oxygen therapy may have unknown consequences on essential fatty acid metabolism.

Recent intervention trials have suggested that preterm infants may benefit from the addition of LCPUFAs to the diet. Uauy and Hoffman reported that preterm infants fed formulas supplemented with a combination of soy and fish oil accumulated DHA in plasma and red blood cell lipids similar to breast fed babies.[2] Infants fed non-DHA supplemented formulas failed to achieve this level of incorporation despite the fact that its precursor (ALA) was present. In addition, visual acuity (as measured by the ERG threshold — the minimum amount of light required to elicit a given retinal response) was similar between breast fed infants and those fed DHA, but lower in infants fed ALA without preformed DHA.

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O'Connor et al. also found beneficial effects of supplementing premature infants with dietary LCPUFAs.[4] Premature infants (n=470) were fed formulas containing DHA and AA from a fish/fungal source and an egg triglyceride/fish source and compared to a control group fed formula without LCPUFAs. The fatty acid supplementation was initiated within 72 hours of the first enteral feeding and continued throughout the first year of life. DHA and AA supplementation resulted in improved visual acuity from four to six months corrected age (CA), increased motor development at one year CA among infants with birth weights ≤ 1250 g and greater vocabulary comprehension at 14 months CA compared to controls. The authors suggested that supplementing formulas for premature infants with AA and DHA is beneficial.

There are no officially established requirements for LCPUFAs in infants. A Recommended Dietary Allowance (RDA) has not been established, and the American Academy of Pediatrics has not published a statement on the essentiality of these compounds. However, adverse effects have not been reported in premature infants, and most clinical trials, including a recent meta-analysis[5], support the contention that premature infants are likely to benefit from a carefully balanced exogenous source of LCPUFAs.

Essential fatty acid requirements of full-term infants

The effect of LCPUFA supplementation on the development of full-term infants is more subtle than for premature infants, and intervention trials have yielded mixed results. At least four studies[6-9] have found positive results including improved developmental quotient, visual acuity and visual evoked potential while other studies have found no benefit.[10-13]

Jensen et al. have expressed caution regarding the feeding of LCPUFAs because diminished growth and delayed neurodevelopmental parameters have been observed in some fish oil-fed full term infants.[3] The effects in these infants were associated with reduced plasma and erythrocyte AA that may have resulted from a reduced capacity to synthesize AA from LA, and/or competitive effects exerted on AA from eicosapentaenoic acid (EPA, 20:5n-3) that is present at a high concentration in fish oil. Jensen et al. also observed slightly diminished growth at 120 days of age in full term infants fed formula with a low ratio of LA to ALA (4.8) in the *absence of exogenous LCPUFAs* compared to infants fed a similar formula with a high LA/ALA ratio of 44.[13] These studies emphasize the importance of a proper balance of *all* essential fatty acids in the infant diet.

Interpretation of these studies is complicated by a variety of factors:

- Different levels of DHA and/or AA have been used – lower levels would be more likely to yield negative results
- Different ratios of LA to ALA have been used — higher amounts of LA could limit the conversion of ALA to DHA by inhibiting the delta-6 desaturase
- Different sources of LCPUFAs have been used (e.g. fish oils, egg phospholipids, fungi/algae) – these sources vary in composition and may contain competitive compounds such as EPA
- Limited statistical power — most studies have followed only 20-30 infants per treatment
- Different methods for assessing visual and cognitive development have been used – these parameters are subject to wide ranges of variability within the normal infant population and are very difficult to measure
- Potential confounding variables are difficult to control for in small studies — examples include: sex; race; gestational age; birth weight; incidence of infection or illness; bilirubin levels in the first week of life; alcohol use in pregnancy; strenuous exercise during pregnancy; maternal parity; smoking; nutrition; weight; age and marital status

Given the nature of the data and the difficulty in making meaningful comparisons between studies, it seems clear that more information is needed in order to fully understand the factors that contribute to the requirement for LCPUFAs in term infants.

Infant formulas in North America

Human milk is unquestionably the preferred source of nutrients for babies, and has traditionally served as the gold standard for the design of infant formulas. Breast fed infants receive substantial amounts of LCPUFAs compared to babies fed commercial infant formulas currently available in North America. DHA/AA-containing infant formulas are widely available outside of North America for both term- and preterm infants. Furthermore, the U.S. Food and Drug Administration recently approved a generally recognized as safe (GRAS) notification authorizing the use of DHA and AA in pre- and full term infant formulas.[14] These observations suggest the strong possibility that commercial infant formulas containing added LCPUFAs will become available in the United States in the relatively near future. Health Canada has not approved LCPUFAs for use in infant formula, but will likely consider this issue as more data become available.

Summary

Long Chain Polyunsaturated Fatty Acids (DHA and AA) are vital for normal growth and development of the human infant. These compounds provide structural integrity to cell membranes and act as precursors for eicosanoids. The preponderance of existing data suggests that premature infants given an exogenous source of DHA are likely to experience improved cognitive and visual development compared to non-supplemented infants. Similar studies on full-term infants are less consistent, but the data are difficult to interpret. It seems likely that infant formulas fortified with DHA and/or AA are likely to become commercially available in the United States in the relatively near future.

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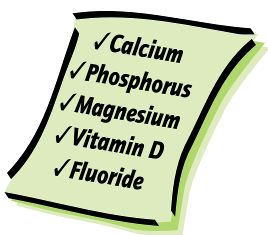
Dietary Reference Intakes: The Initial Report



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The first report of the Food and Nutrition Board's Dietary Reference Intakes deals with five nutrients that play a critical role in the development and maintenance of bone and other calcified tissues. The nutrients covered are: calcium, phosphorus, magnesium, vitamin D, and fluoride.[1] Following are some of the highlights from the report; the entire report can be viewed and purchased from the National Academy Press website, www.nap.edu.

Calcium

Uncertainties about the methods and values obtained from balance studies that form the basis of the desirable retention model, the lack of agreement between observational and experimental data, and the lack of longitudinal data led to the decision to set Adequate Intakes (AIs) rather than Estimated Average Requirements (EARs) for calcium (see Table 1 for a review of terms used in the new standards). The AI for infants 0-6 months of age is the estimated mean intake of calcium from human milk by healthy breastfed infants. Human milk plus solid food is the criterion used to determine the AI for infants aged 7-12 months, and extrapolation of data on the desirable calcium retention from 4-8 years of age is the criterion for infants aged 1-3 years.

Adverse effects of excess calcium intake occur primarily as a result of supplementation. Not enough data were available to establish a UL specific to infants aged 0-12 months. Despite the dearth of studies on the safety of excess calcium intake in toddlers, a UL was established due to the risk of depletion of zinc and iron in particular when calcium intake is excessive.

Table 1. Review of Terminology[1]

Estimated Average Requirement (EAR): The value for intake of a nutrient that is estimated to meet the requirement of 50 percent of individuals in a gender and age group.

Recommended Dietary Allowance (RDA): The average daily dietary intake level needed to meet the nutrient requirements of nearly all individuals in a gender and age group.

Adequate Intake (AI): The value used instead of the RDA if there is a lack of scientific evidence available to derive an EAR.

Tolerable Upper Intake Level (UL): The highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in a specified life stage group.

Phosphorus

Previous recommendations for phosphorus were linked with calcium, and the focus was on the Ca:P ratio of the diet. This approach has been questioned, and the report cites several problems with using a ratio to determine needs. In this report, the AI for phosphorus for infants aged 0-6 months reflects data on mean intakes of infants fed human milk. In addition, data on phosphorus balance, accretion and serum P_i were reviewed and considered as supportive evidence for the AI. For infants aged 7-12 months, the AI represents the average intake of phosphorus from human milk plus phosphorus obtained from infant foods. For children aged 1-3 years, an EAR was set based on rates of accretion of phosphorus in bone and soft tissue corrected for absorption efficiency and urinary losses using the factorial approach. The RDA was then determined from the EAR value.

The UL for phosphorus for infants aged 0-12 months was not possible to establish due to the lack of reports of adverse effects of high dietary phosphorus intake. A UL for toddlers was determined based on the *No Observed Adverse Effect Level (NOAEL)* for adults adjusted by an uncertainty factor that accounts for a potentially increased susceptibility due to a smaller body size.

Magnesium

As with calcium and phosphorus, the AI for magnesium for infants from birth through 6 months of age reflects the observed mean intake of infants fed mainly human milk. Magnesium from human milk and solid food was considered in determining the AI for infants 7-12 months of age. Magnesium balance data were used as the basis and then data were interpolated from other age groups to determine the EAR for children aged 1-3 years.

The UL is based on supplementary magnesium, because when ingested as a naturally occurring substance in foods, magnesium does not exert any harmful effects. It was not possible to set a UL for infants 0-12 months for supplementary magnesium because no toxicity data exist for this age group. Children aged 1-3 years were

> ***The UL is based on supplementary magnesium, because when ingested as a naturally occurring substance in foods, magnesium does not exert any harmful effects.***

assumed to be as susceptible to the osmotic effects of nonfood sources of magnesium as adults. The adult value was adjusted on a body-weight basis to derive the UL for children.

Vitamin D

The AI for infants aged 0-12 months is based on the lowest intake of vitamin D that is associated with the lower limit of normal serum 25(OH)D concentration. It assumes no vitamin D synthesis from sunlight exposure. Setting the recommendations for children aged 1-3 years was more complex. There are no data available to determine the amount of vitamin D required to prevent vitamin D deficiency in children in this age group. An AI rather than an EAR was set because sunlight exposure confounds the literature and intake data were not available to establish an EAR. The mean intake of vitamin D in older children and for children not exposed to adequate sunlight who showed no evidence of vitamin D deficiency and had normal 25(OH)D values was extrapolated for ages 1-3 and doubled. Therefore, for children aged 1-3 years, the recommended AI was set to cover the needs of all children, regardless of sunlight exposure.

The UL for infants was based on two studies. In the first, infants showed retarded linear growth when they received 45-112.5 µg/day vitamin D as supplements. In the second study, no effects on linear growth were observed when infants ingested 34.5-54.3 µg/day of dietary vitamin D from milk formulas. No specific data were available on excess intakes in children aged 1-3 years. As a result, and because toddlers have increased bone formation, the adult UL was considered appropriate.

Fluoride

In infants aged 0-6 months, fluoride intake is highly variable depending on whether or not the infant is breast or formula fed and if the formula is ready-to-feed or must be reconstituted. The AI is based on intake from human milk since the lower fluoride intake from this source does not seem to increase the risk of dental caries. A higher AI that is weight-based (0.05 mg/kg/day) is set for infants 7-12 months because it offers protection against dental caries with no known negative health effects. The same weight-based AI (0.05 mg/kg/day) is used for children aged 1-3 years, multiplied by a reference weight of 13 kg.

Based on data, an average chronic daily intake of fluoride of 0.10 mg/kg appears to be the level beyond which moderate enamel fluorosis appears in some children. This level was multiplied by an uncertainty factor of 1 since enamel fluorosis is a cosmetic and not a health effect. The resulting ULs were determined using reference weights based on data from NHANES III.

Table 2. Summary of Nutrient-Based Dietary Standards for Ca, P, Mg, vitamin D, and F[1]

Nutrient	0 – 6 Months	7 – 12 Months	1 – 3 Years
Calcium			
AI	210 mg/day	270 mg/day	500 mg/day
UL	Not Set	Not Set	2500 mg/day
Phosphorus			
AI	100 mg/day	275 mg/day	–
EAR	–	–	380 mg/day
RDA	–	–	460 mg/day
UL	Not Set*	Not Set*	3 g/day
Magnesium			
AI	30 mg/day	75 mg/day	–
EAR			65 mg/day
RDA			80 mg/day
UL	Not Set*	Not Set*	65 mg of **supplementary** magnesium
Vitamin D			
AI	5 µg/day	5 µg/day	5 µg/day
UL	25 µg/day	25 µg/day	50 µg/day
Fluoride			
AI	0.01 mg/day	0.5 mg/day	0.7 mg/day
UL	0.7 mg/day	0.9 mg/day	1.3 mg/day

*Source of intake should be from formula and food only

Reference

1. Standing Committee on Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academy Press, 1997.

Note: The Food and Nutrition Board of the Institute of Medicine, The National Academy of Sciences, recently released the fourth report in the series. Titled *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, the report can be viewed and purchased from the National Academy Press website, www.nap.edu.