International Society for the Study of Fatty Acids and Lipids 2018 Symposium: Arachidonic and Docosahexaenoic Acids in Infant Development

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At the 13th Congress of the International Society for the Study of Fatty Acids and Lipids, Las Vegas, NV, USA, May 27–31, 2018, a satellite symposium addressed the topic, “Arachidonic and Docosahexaenoic Acids in Infant Development.” Drs. Norman Salem, Jr. and Susan Carlson co-chaired the sessions featuring 5 international leaders in this research area. The following report summarizes the presentations.

Newly Discovered Elovonoids in Vision and Cognition

Elovonoids are novel lipid mediators synthesized from very long-chain (VLC) omega-3 (n-3) polyunsaturated fatty acids (PUFA), particularly docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA), by the elongase enzyme ELOVL4. This enzyme is expressed in photoreceptor cells, neurons in several brain regions, and other tissues [1–3]. ELOVL4 generates 32- and 34-carbon n-3 VLC-PUFA from which 2 elovonoids were synthesized and characterized in the laboratory of Nicolas Bazan, Louisiana State University Neuroscience Center of Excellence, USA [2]. Unlike neuroprotectins derived from DHA, elovonoids are synthesized from n-3 VLC-PUFA

that are derived from chains of phospholipids and sphingolipids.

Mutations in the *ELOVL4* gene result in juvenile macular degeneration, impaired neural development, neuronal dysfunction, hyper-excitability, and seizures [4, 5]. The enzyme is also necessary for neonatal survival [6].

At a symposium held in conjunction with the 13th Congress of the International Society for the Study of Fatty Acids and Lipids, Las Vegas, NV, USA, May 27–31, 2018, Bazan presented recent data from his laboratory on the discovery of elovonoids. Mixed cultures of cerebral cortex or hippocampal neuronal cells that were deprived of oxygen and glucose for 90 min and then treated with N32 or N34 elovonoids showed increased cell survival after 12 h. Similarly, these cells exhibited neuroprotection when stressed by exposure to N-methyl-D-aspartate, which exerts excitotoxicity [2]. Elovonoids clearly protected against neuronal cell death by decreasing apoptotic nuclei induced by N-methyl-D-aspartate or oxygen/glucose deprivation.

In an animal model of ischemic stroke, elovonoid treatment reduced the volumes of the ischemic core (area of severe ischemia), penumbra (ischemic but viable tissue), and total lesion volume [2]. In related stroke experiments, elovonoid-treated animals exhibited less infarction

tion, improved blood vessel integrity and reduced disruption of the neurovascular unit, a mixed group of cells whose coordinated activity regulates central nervous system homeostasis [7].

Retinal pigment epithelial cells also produce elovonoids, which are active during retinal development and also have pro-survival and pro-homeostatic activities under oxidative stress [1]. Jun et al. [1] showed that they upregulate the production of several protective proteins during oxidative stress, such as sirtuin, prohibitin, and the anti-apoptotic proteins Bcl2 and Bcl-xL. These and other protective activities uncovered by the Bazan's group have direct implications for juvenile macular degeneration and other neurological conditions associated with mutations in *ELOVL4*.

In an unpublished work, Bazan described data showing that elovonoids counteract the cell damage inflicted by the abnormal protein amyloid-beta in retinal pigment epithelial cells, photoreceptor outer segments, and extracellular deposits known as Drusen [8–10]. Other studies demonstrated the rescue of mouse retinal pigment epithelial cells damaged by amyloid-beta, protected as a result of the elovonoid-induced downregulation of senescence genes or age-related macular degeneration genes.

In summary, Bazan's laboratory discovered that elovonoids: (1) induce neuronal and retinal cell survival under oxidative stress in cultured cells; (2) have neuroprotective effects in experimental models of disease, such as ischemic stroke and traumatic brain injury; (3) counteract amyloid-beta peptide-induced cell damage that occurs in age-related macular degeneration and Alzheimer's disease; (4) enhance the abundance of pro-homeostatic proteins and decrease the abundance of proteins engaged in cell damage; (5) are active during retina and brain development; (6) may modulate transcriptome architecture to induce neuronal cell survival and regulate developmental neurogenesis.

Arachidonic and DHA in Infant Development

Many studies have documented the importance of the n-6 and n-3 long chain polyunsaturated fatty acid (LCPUFA), specifically arachidonic acid (ARA) and DHA, in the structure and function of the brain and retina [11, 12]. These LCPUFA are actively and selectively transported across the placenta to the developing fetus [13, 14] and are incorporated much more effectively than for their 18-carbon precursors [15, 16]. Physical, bio-

chemical, and functional effects of n-3 LCPUFA-deficient diets have been amply described [17, 18].

Changes in brain function are also related to maternal and infant diets [19, 20], but the activities of individual n-3 PUFA remain poorly defined. It has been demonstrated, however, that provision of alpha-linolenic acid (ALA) as the main source of n-3 PUFA during pregnancy does not promote neonatal DHA status [15, 21]. The function and interactions of n-6 fatty acids have not been fully described although linoleic acid (LA) is considered a negligible source of brain ARA in the rat when preformed ARA is available [22].

To investigate the interaction between ARA and EPA or DHA during growth and development Toru Moriguchi et al. [23], Azabu University, Japan, studied hand-reared, delta-6 desaturase (*FADS2* gene) knockout mice fed artificial formula containing different levels of ARA and DHA. This mutation eliminates the conversion of LA and ALA to their LCPUFA products, thereby preventing the in vivo production of ARA, EPA, and DHA [24]. Studies entailed 5 groups of knockout mice and 2 control groups fed artificial milk as previously described [12] containing 27% mixed fats with or without 1.2% ARA, EPA, or DHA, or 1.2% ARA + 1.2% DHA or 1.2% ARA + 1.2% EPA with a wild-type control and a knockout control receiving 17.4% LA and 4.1% ALA as the sole PUFAs. Animals were reared for 3 weeks and then weaned. At that time mice consumed a solid diet with each additional LCPUFA increased from 1.2 to 2.0% of total fatty acids for 6 more weeks. At 9 weeks of age, mice were evaluated for motor activity and coordination using the Morris water maze and the Rota-rod test. The investigators determined brain fatty acid composition at 11 weeks.

Presenting the findings from this study, Moriguchi reported that the knockout control animals weighed 30% less than the wild-type controls [12]. Those fed ARA or ARA in combination with EPA or DHA had body weights that did not differ from the wild-type controls. Water maze results also demonstrated the longest latency, that is, poorest results in the knockout controls without LCPUFA compared with all other groups. In contrast, all groups consuming DHA with or without ARA were not different from the wild-type controls, while those consuming ARA had latencies longer than those of the wild-type controls, but not as long as the latencies of knockout controls without LCPUFA.

In the motor coordination study examining the time until the animal falls off an accelerating rotating rod, the researchers compared the duration to the wild-type control, which had the longest duration [12]. The shortest

time was seen in the knockout controls and animals consuming only ARA. The longest duration occurred in the animals fed ARA and DHA, which was not different from the wild-type controls. The duration of the ARA and EPA group was less than the ARA and DHA group, although the difference did not reach statistical significance.

Moriguchi presented images of the small intestine that revealed hemorrhagic lesions and dark stools in 6 of the 7 mice fed DHA-only diets at 6 weeks of age. Forty percent of the knockout control mice did not survive until 11 weeks. Intestines appeared normal in all the knockout mice consuming ARA plus DHA or EPA and in those fed only EPA. Moriguchi speculated that very low levels of ARA contributed to the impaired mucosal development they observed.

When the team examined total brain weights, knockout controls exhibited significantly lower weight than the wild-type controls. Brain weights did not differ from the wild-type controls in animals consuming all ARA diets and those with only EPA. But the DHA-only mice had the lowest brain weight, even though the difference from the control did not reach statistical significance. The researchers concluded that ARA alone was sufficient to restore brain weight to control levels. In terms of PUFA composition of the hippocampus, provision of ARA and ARA + DHA restored hippocampus LCPUFA levels to those of the wild-type controls. The addition of EPA with or without ARA did not affect DHA levels, but addition of ARA lowered levels of brain DHA relative to the wild-type controls or groups with ARA+DHA. Only the diet with both DHA and ARA restored hippocampus LCPUFA levels to that of the wild-type controls.

In order to study the interaction between ARA and DHA further, Moriguchi's team carried out a 5-week pilot study using knockout mice reared artificially as described above using the same control diet and 3 treatment diets containing 0.3% DHA, 0.3% DHA + 0.3% ARA, and 0.7% ARA + 0.3% DHA as a percent of total fatty acids. The investigators assessed whole brain fatty acid composition at 5 weeks of age. As expected, the total PUFA, ARA, and DHA content of the knockout control animals was markedly decreased. All groups consuming DHA showed increased levels of whole brain DHA compared with the knockout controls, while the 2 groups consuming ARA and DHA also had levels of these fatty acids comparable to the wild-type control mice. In animals fed twice as much ARA as DHA, these LCPUFA levels were indistinguishable from the wild-type control mice.

Moriguchi concluded from these studies that (1) ARA was essential for normal growth during lactation and ear-

ly development; supplementation of delta-6 desaturase knockout mice with only ARA or only DHA was insufficient for normal development; (2) only the combination of ARA + DHA was able to improve the motor and coordination dysfunction observed in animals unable to synthesize these LCPUFA; (3) preliminary data suggest that the optimum ratio of ARA:DHA to restore brain PUFA distribution in these knockout animals was 2:1; (4) addition of DHA only can lead to antagonism of brain ARA levels and very low peripheral levels of ARA, which were associated with hemorrhagic stools. These observations question the safety for human infants of such formulas.

Early Life Exposure to DHA and ARA Results in Long-Term Differences in Brain Function

Clinical trials of the supplementation of mothers during pregnancy or lactation with DHA with or without ARA on neurodevelopmental outcomes in the offspring have yielded mixed results [25–28]. Differences in study design, age at assessment and the use of global measurements of neurocognitive function have contributed to discrepancies among the data [29]. Studies of infants consuming diets differing in LCPUFAs have also reported inconsistent outcomes on various neurodevelopmental assessments at different ages [30–32]. Discussing some of these studies, Kathleen Gustafson, University of Kansas Medical Center, Kansas City, MO, USA, presented some of the key findings from the DIAMOND study on neurodevelopmental outcomes in infants who consumed 3 different levels of DHA in the presence of a constant amount of ARA [33].

In this randomized, double-blind, clinical trial, 122 healthy term infants (37–42 weeks gestation) consumed from birth 1 of 4 cow's milk infant formulas containing 0.32, 0.64 or 0.96% total fatty acids from DHA plus 0.64% ARA for 12 months [30]. The control group consumed unsupplemented formula. At the ages of 4, 6, and 9 months the investigators measured the sustained attention of infants defined as the time spent actually looking at a stimulus, in this case, a static color image of an adult face. Sustained attention has been strongly linked to active information processing in human infants [34]. Across all ages, infants consuming either 0.32 or 0.64% DHA had significantly greater sustained attention than the control group. Attention in the 0.94% DHA group did not differ from that in the control or the other 2 groups.

The investigators conducted another series of age-appropriate cognitive assessments when the children were

18–72 months of age [31]. Statistically significant positive outcomes were associated with 0.32 and 0.64% DHA intakes on the Dimensional Change Card Sort task [35] and with 0.64 and 0.96% DHA levels for the Stroop task [31], although several assessments were unaffected by LCPUFA intake.

After 4 months of age, children are better able to sustain attention, filter information, implement rules and suppress or delay an anticipated response. In cognitive tests where the correct response is no response, as in the no-go phase of a go/no-go test, brain electrical activity provides a way to assess inhibitory control [36]. One such measure is the event-related potential (ERP) [37]. Although few studies have examined the effects of LCPUFA supplementation on neurodevelopmental outcomes, Gustafson's group used ERP measures to assess inhibitory control in the same LCPUFA-supplemented children at 5.5 years of age. ERP signals were also combined during times of temporary stability to reflect synchronized activation known as microstates [38]. Differences in microstates are believed to represent different experimental conditions or time sequences [39], with successive microstates representing certain information processing steps. The researchers expected to see differences in ERP and microstate measures between the LCPUFA-supplemented and control groups. Data from the various treatment groups were combined because differences among treatments were not significant.

LCPUFA-supplemented children scored higher on executive function tasks compared with unsupplemented control children, as reflected in their brain electrophysiology. Supplemented children had a faster reaction time compared with controls, with boys faster than girls. There were no group differences in the accuracy of the responses. The most striking differences occurred in contrasting conditions, especially when children had to suppress a response in the no-go part of the go/no-go test.

Three ERP measurements taken at different brain areas were assessed by amplitude and latency of response, both of which were larger for the no-go portion of the go/no-go test than the go portion. These differences were greater for the LCPUFA-supplemented children, particularly in measurements reflecting visual processing and attention, possibly suggesting enhanced cognitive processing [40]. Similarly, the greater amplitude observed in response to the no-go part of the test could be construed as reflecting more mature forms of inhibition control. These responses are consistent with those reported by others [41, 42]. The authors suggest that their results from the ERP analyses are consistent with previous data from the

same cohort in which LCPUFA-supplemented children outperformed controls in executive function tasks involving learning rules and inhibition tasks [31]. They are also consistent with results from functional brain imaging studies in 8–10-year-old boys with low DHA status [43] and non-human primates consuming a life-long n-3 LCPUFA diet [44].

The investigators observed activation of a larger synchronized neuronal network in the LCPUFA children compared with controls using microstate analysis. The microstate reflecting the no-go condition was significantly longer in the supplemented children than in the controls, perhaps suggesting inequality between the 2 groups under conditions requiring inhibition.

Gustafson concluded that (1) LCPUFA-supplemented children have better inhibition control of learned actions compared with unsupplemented children; (2) ERP findings support previous observations suggesting that LCPUFA supplementation has a programming effect during a critical period of human development; (3) multimodal brain imaging results suggest a long-term benefit of early life DHA and ARA supplementation for attention and inhibition systems 8 years after supplementation ends.

LCPUFA in Infant Formula: Clinical Results and Future Directions

The ideal source of nutrition for infants is human milk from a well-nourished mother, but an appropriate substitute must be available if necessary. Thus, the challenge for infant formula is to provide the nutrient composition that most closely resembles the growth and developmental results achieved with human milk. In his examination of this challenge, Eric Lien, University of Illinois, Urbana, IL, USA, focused on the addition of DHA and ARA to infant formula for term infants. Breast milk contains on average approximately 1.5 times as much ARA as DHA [45]. DHA concentration is dependent on dietary intake, while ARA concentration is less so. During the first 6 months of life a breast-fed infant accrues twice as much DHA in brain as a formula-fed infant not consuming DHA [46]. Central nervous system DHA levels are sensitive to dietary DHA intake, but ARA levels are less so, suggesting tighter regulation of ARA [47]. Synthesis of DHA and ARA from their 18-carbon precursors is limited, so that preformed DHA and ARA are needed to meet the developing infant's needs [48, 49].

DHA concentrates in the brain and nervous system, particularly in photoreceptor outer rod segments where

it is tightly conserved. In the first 6 months of life, DHA accumulates mostly in the brain and lean tissue, but accretion is significantly reduced in infants not receiving dietary DHA [46]. The fact that DHA is important for brain and visual acuity development in infancy was demonstrated clearly in rhesus monkeys more than 30 years ago [17] and in human infants consuming DHA-supplemented infant formula [33]. Recent studies have focused on visual and nervous system development [50], fundamental neuroprotective mechanisms at the cellular and molecular level [1], and various retinal disorders [51].

A review of the early RCTs conducted in term infants consuming formula with various levels of DHA and ARA suggested that formula with DHA levels close to 0.32% total fatty acids found in breast milk [45] resulted in improved visual development compared with lower levels of DHA [52]. A more recent review recommended that infant formula provide 100 mg DHA/day and 140 mg ARA/day for the first months of life, with 100 mg DHA/day continuing for the second 6 months of life [53].

Results of DHA- and ARA-supplemented infant formula on cognitive outcomes have been mixed, but several methodological issues precluded firm conclusions [54]. In particular, assessments of global development, such as the Bayley Scales of Infant Development [55] appear insufficiently sensitive to different types of cognitive function and are of limited use, especially after 18 months of age [56]. Evaluation tools designed for more specific aspects of cognition, for example, memory and attention, provide more detailed insights into childhood cognitive development over several years.

A US cohort enrolled 122 term infants who consumed cow's milk formula containing 0.0, 0.32, 0.64 or 0.96% total fatty acids as DHA for 12 months after birth. All DHA-supplemented infants also consumed 0.64% ARA, while control infants received no LCPUFA [30]. Infants were evaluated at 4, 6, and 9 months of age for sustained attention and peak look duration. Infants consuming 0.32 or 0.64% LCPUFA had longer sustained attention compared with control infants, and those consuming 0.96% LCPUFA did not differ from the 2 lower DHA groups. The investigators conducted a follow-up evaluation of 81 children at 18 months and 6 years of age [31]. In addition to Bayley Scales of Infant Development at 18 months, they included 1 or more of 8 other cognitive assessments at 6-month intervals until age 4, and annually thereafter until age 6 years.

LCPUFA supplementation affected some, but not all, measures of cognitive function in preschool children.

Measures of attention, rule learning and implementation, that is, Stroop scores and Dimensional Change Card Sort, were significantly higher in the combined supplementation groups than in the controls [30, 31]. At ages 4 and 5, scores on verbal ability, for example, Peabody Picture Vocabulary and Wechsler Intelligence Scale, were higher in LCPUFA-supplemented children, but assessments of spatial memory, simple inhibition or advanced problem-solving did not differ. It is not surprising that a specific class of dietary nutrients (LCPUFAs) may influence some, but not all, aspects of cognitive development. The results were limited by the small sample sizes, but were consistent with other studies of maternal LCPUFA supplementation [26, 57].

Infants consuming formula with DHA and ARA have more desirable immune responses as assessed by markers of immune function, for example, cytokines, T-cell types and health outcomes, compared with infants fed formula without LCPUFA. Clinical studies demonstrate that consuming formula with DHA and ARA contributes to the development of a more mature immune system [58, 59], improves immune responses to dietary allergens [60], may reduce the risk of allergic diseases in the first year of life [61], and may reduce the risk of upper respiratory infections and diarrhea [33, 62].

Lien also touched on the effect of polymorphisms in the *FADS 1* and *FADS 2* genes, which affect the production of enzymes that convert LA and ALA to their LCPUFA derivatives, primarily ARA, EPA, and DHA. *FADS* genotypes may account for up to 28% of the variability in serum fatty acid levels [63]. Polymorphisms in these genes may interact with dietary LCPUFA [64, 65] affecting LCPUFA concentrations in breast milk, erythrocyte membranes, liver lipids, and other tissues. They have also been linked to the development of intelligence in children, coronary artery disease, acute myocardial infarction, allergic diseases, and other conditions [66] and could have implications for child health [67]. The inclusion of *FADS* gene polymorphisms should be considered in the assessment of future clinical trial results.

Lien emphasized the importance of including both DHA and ARA in infant formulas. Not only is ARA found in relatively constant amounts in human breast milk worldwide [45], ARA is transferred to the fetus from the mother, accumulates in brain in the first 6 months of life, and diminishes in brain with high intakes of DHA without ARA [68–70]. Although the production of formula with added DHA but no ARA has been suggested [71], experts have raised strong objections to this possibility [56, 70, 72].

Eyeing the future, Lien observed that the importance of ARA and DHA in infant formula continues to evolve. In addition to their established functions in vision and cognition, LCPUFA involvement in immune function and illness warrants further investigation and the effects of various *FADS* gene polymorphisms need to be better understood.

Interaction of Infant Diet and *FADS* Gene Polymorphisms on Cognition and Allergy: Policy Implications

Dietary consumption of LCPUFAs and the endogenous conversion of their 18-C precursors LA and ALA to LCPUFA are the main determinants of tissue LCPUFA levels. Rates of precursor conversion are very low in humans [15] and are affected by genetic polymorphisms in the genes affecting the synthesis of LCPUFA [73]. The 2 most important gene clusters affecting LCPUFA production encode enzymes for fatty acid desaturation (*FADS1*, *FADS2*, *FADS3*) and elongation (*ELOVL2*). Several single nucleotide polymorphisms (SNPs) in these genes, especially the *FADS* gene cluster, have been identified and studied in the context of LCPUFA [74, 75]. The effects of these polymorphisms may be associated with several health risks, including cognition and allergies in infants and children, adult obesity [76], cardiovascular disease risk [77], and low-density lipoprotein levels [78].

Dietary intake and tissue PUFA concentrations have been linked to many health outcomes, but results have often been inconsistent, especially in the areas of child cognition and allergies [67]. A relevant question is whether and to what extent genetic background and gene polymorphisms modulate responses to diet [66]. An early study in 700 adults showed that certain SNPs associated with *FADS1* and *FADS2* genes were strongly associated with lower levels of ARA and higher levels of LA in serum phospholipids and that carriers of these rare variants had a lower prevalence of allergic rhinitis and atopic eczema [75]. *FADS1* and *FADS2* SNPs are often associated with higher levels of n-6 precursors but have weaker effects on n-3 PUFAs [79, 80]. These studies have been replicated in plasma and adipose tissue [81], erythrocyte membranes [82], breast milk [80], and other tissues [83], with the strongest associations reported in genome-wide association studies [84].

The effect of *FADS* gene polymorphisms on DHA in blood or tissues has been less well studied. Women who were homozygous (2 copies) for a minor *FADS* allele had

lower proportions of DHA and ARA in plasma phospholipids and breast milk compared with carriers of the major allele [73, 85, 86]. Only women with the major allele increased breast milk DHA by consuming fish or fish oil [85]. To what extent hormones might have affected the observations is unknown, but estrogen affects LCPUFA metabolism [87, 88].

Associations between *FADS* gene polymorphisms and allergic diseases are inconsistent. Schaeffer reported associations of some of these variants with a lower prevalence of allergic rhinitis and atopic eczema in German adults [75]. Similarly, Rzehak et al. [74] reported a lower prevalence of eczema in a German cohort of 2-year-old children but not in Dutch children included in the same study. In neither cohort were blood PUFA levels linked to the risk of eczema. Infants exclusively breastfed for more than 5 months who carried at least 1 minor *FADS* gene polymorphism had a significantly reduced risk of physician-diagnosed asthma up to 10 years of age [89]. However, duration of breastfeeding had no effect on risk of asthma in those without these polymorphisms.

Barman et al. [90] examined the association between *FADS* gene polymorphisms and the development of allergy in a Swedish birth cohort sampled at birth and 13 years of age. They, too, observed a lower proportion of ARA in cord and adolescent serum in carriers of the gene variants. Investigators assessed allergic responses by questionnaire and genetic polymorphisms in participants who had blood samples from birth and at age 13 years. Atopic eczema or respiratory allergy were the only atopic diseases observed. Carriers of either of 2 *FADS* gene polymorphisms had approximately half the risk of atopic eczema at 13 years of age compared with participants having 2 major alleles, but the risk of respiratory allergy was not associated with the gene variants. Although the investigators also examined 2 variants of the *ELOVL2* gene, neither was associated with allergy risk. The authors suggested that the risk of other allergic diseases might be more closely associated with n-3 LCPUFA, which are less affected by *FADS* polymorphisms.

Koletzko et al. concluded by noting that breastfeeding provides both ARA and DHA [91], which compensates for low LCPUFA synthesis in carriers of some *FADS* gene polymorphisms. Infants with gene-linked low ARA synthesis consuming formula without additional ARA might be at greater risk of asthma, eczema, or other allergic diseases and possibly suboptimal cognitive development [67, 92]. In light of the suggestion that infant formula be supplemented only with DHA and not ARA [71], such formula would ill serve the needs of developing infants,

especially as *FADS* gene polymorphisms may affect approximately 30% of the European population [67]. He observed that formula with DHA and no ARA resulted in decreased ARA levels in erythrocytes [93] and poorer verbal IQ scores compared with infants receiving DHA and ARA [94]. ARA has different functions from DHA and is the principal unsaturated fatty acid in the inner cell membrane lipids of heart, vascular epithelium, and many other organs where it participates in diverse cellular functions [72]. He supported the conclusions of others that ARA plus DHA should be included in infant formula [68, 70].

Conclusion

Research presented at this symposium reinforced the importance of LCPUFA in infant diets and showed the continuing evolution of this field with the newly discovered elovanoids, derived from VLC n-3 PUFA. These novel lipid mediators are active during retina and brain development and have several neuronal and retinal cell survival properties. While the importance of DHA for fetal and infant brain and retinal structure and function is widely accepted, it has become clearer that ARA is also essential for normal growth and development during lactation and early childhood. More advanced measures of brain function and childhood behavior support the involvement of both DHA and ARA during critical periods

of early human development that may extend into late childhood. Further, infants consuming formula with both DHA and ARA have improved immune responses and a lower risk of some allergic diseases and upper respiratory infections.

Infants carrying certain *FADS* gene polymorphisms affecting LCPUFA synthesis may have higher levels of LCPUFA precursors, particularly LA, and lower levels of LCPUFAs, including ARA. These alterations have been associated with a lower incidence of asthma and atopic eczema but also with possible detriments to cognitive function. Together, these diverse studies and much previous research indicate that both DHA and ARA are necessary additions to infant formula when breast milk is unavailable.

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Authors Contribution

The principal author was J.A.N. and N.S. reviewed and edited all drafts. Both authors approved of the final version and have agreed to be fully accountable for its contents.

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