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Dietary Docosahexaenoic Acid and Arachidonic Acid in Early Life: What Is the Best Evidence for Policymakers?

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Keywords

Arachidonic acid · Docosahexaenoic acid · Global dietary policies · Infants · Young children

Abstract

Background: A wealth of information on the functional roles of docosahexaenoic acid (DHA) and arachidonic acid (ARA) from cellular, animal, and human studies is available. Yet, there remains a lack of cohesion in policymaking for recommended dietary intakes of DHA and ARA in early life. This is predominantly driven by inconsistent findings from a relatively small number of randomised clinical trials (RCTs), which vary in design, methodology, and outcome measures, all of which were conducted in high-income countries. It is proposed that this selective evidence base may not fully represent the biological importance of DHA and ARA during early and later life and the aim of this paper is to consider a more inclusive and pragmatic approach to evidence assess-

ment of DHA and ARA requirements in infants and young children, which will allow policymaking to reflect the marked diversity of need worldwide. **Summary:** Data from clinical RCTs is considered in the context of the extensive evidence from experimental, animal and human observational studies. Although the RCT data shows evidence of beneficial effects on visual function and in specific cognitive domains, early methodological approaches do not reflect current thinking and this undermines the strength of evidence. An outline of a framework for an inclusive and pragmatic approach to policy development on dietary DHA and ARA in early life is described. **Conclusion:** High-quality RCTs that will determine long-term health outcomes in appropriate real-world settings need to be undertaken. In the meantime, a collective pragmatic approach to evidence assessment, may allow public health policymakers to make comprehensive reasoned judgements on the merits, costs, and expediency of dietary DHA and ARA interventions.

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Introduction

Although the importance of fatty acids for human health and well-being was initially recognised almost 90 years ago [1, 2], it is during the last 3 decades that there has been considerable interest to understand the roles of long chain polyunsaturated fatty acids (LCPUFAs) in infant growth and development [3–7]. The seminal work of Manuela Martinez showing the rapid accretion of docosahexaenoic acid (DHA) and arachidonic acid (ARA) by the infant brain during the first 1,000 days of life [8], was the driver for many scientists, clinical researchers, nutritionists, developmental psychologists and epidemiologists to contribute to this important research domain.

Although there is now a wealth of information on the functional roles of DHA and ARA from cellular, animal and human studies, there remains a lack of cohesion in policymaking on dietary intakes of DHA and ARA in early life [9–11]. This predominantly relates to inconsistent findings from a small number of randomised clinical trials (RCTs). RCTs in infants born at term have been the subject of 4 Cochrane systematic reviews [12–15]. These have each concluded that routine supplementation of full-term infant formula with LCPUFAs cannot be recommended at this time [12–15]. Although the included RCTs have been rigorously reviewed, they vary considerably in design, methodology and outcome measures, and were all conducted in high-income countries. This selective evidence base may not fully represent the biological importance of DHA and ARA during early and later life, and consequently, current national and international policies may not adequately serve the needs of all infants and children at a time of rapid growth and development.

The aim of this paper is to examine the need for a more inclusive and pragmatic approach to evidence assessment and policymaking, which will be more sensitive to the DHA and ARA requirements of all children worldwide.

Grading the Strength of Evidence when Assessing Health Care Interventions

Cochrane reviews are undertaken using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for rating quality of evidence and grading strength of recommendations in systematic reviews [16]. The GRADE approach results in an assessment of the quality of a body of evidence according to one

of four grades – High: confident that the true effect lies close to the estimate of effect; Moderate: The true effect is likely to be close to the estimate of effect but may be substantially different; Low: The true effect may be substantially different from the estimate of effect; and Very low: The true effect is likely to be substantially different from the estimated effect. Key elements of studies that may influence the strength of evidence include design and methods, dose-response associations, magnitude of effect, attrition rates and risk of bias that may decrease or increase the observed effect and the estimated overall health gain within the target population.

RCTs are generally viewed as high-grade evidence. However, this can be altered if assessment demonstrates that there are study limitations based on how the RCTs were conducted and whether there are weaknesses in key domains, for example, sample size and attrition [17–19]. In contrast, observational studies are generally assumed to provide evidence of lower grade because of the higher risk of bias attributable to lack of randomization and inability of investigators to control for known or unknown confounding factors. However, the strength of the evidence base for observational studies may be raised by methodological qualities such as large sample size and robust long-term data [17–19]. With these potential changes in strength of evidence, it is important that evidence from all research sources is included in the assessment process, and this is particularly relevant in public health interventions.

Early Dietary Intake of DHA and ARA – What Is the Evidence of Health Benefit from RCTs?

The objective of the Cochrane reviews was to assess whether supplementation of formula milk with LCPUFAs is both safe and beneficial for full-term infants, while focusing on effects on visual function, neurodevelopment and physical growth [12–15].

In each of the reviews, only randomised and quasi-RCTs were eligible for inclusion, and the studies selected for review compared infant formula enriched with DHA plus ARA or DHA alone, with infant formula that was devoid of these fatty acids. The LCPUFA supplements could be from any source including fish oil, egg triglycerides or algal oils. Eligibility for inclusion required the following criteria – infants were ≥ 37 weeks of gestation at birth; study formula was commenced within 2 weeks after birth; study formula was the only source of milk from the time of randomisation until at least 8 weeks of

age; and a minimum of 3 months follow-up data on clinical outcomes of interest were available for analysis. Types of outcome measures included visual acuity (measured using either Tellers cards or visual evoked potentials), neurodevelopmental outcomes (General Quotient, Intelligent Quotient and other measures of cognitive functions), and physical growth (weight, length and head circumference).

The initial review in 2001 [12], included a final selection of 9 studies and in the most recent review [15], 31 studies were identified as potentially eligible, but following evaluation, only 15 were included. The final selection of studies emerged from the GRADE system of rating quality of evidence and grading strength of recommendations in systematic reviews [16]. The reasons for exclusion of 16 studies from the final analysis were – infants also received breast milk, late introduction of intervention formula or the formula contained other nutrients of interest, only laboratory outcomes were measured, study was not blind or methods were not clear.

In the most recent review [15], it was noted that there were no new cohorts since 2011, although there had been further follow-up of the previous cohorts. Therefore, with almost all the studies having been included in the previous reviews, it is not surprising that the conclusions in the 2017 review were in keeping with those of previous reviews. It was concluded that the majority of the RCTs did not show beneficial effects of LCPUFA supplementation on the neurodevelopmental outcomes of term infants, that the beneficial effects on visual acuity had not been consistently demonstrated, and finally, that routine supplementation of term infant milk formula with LCPUFA cannot be recommended [15]. The reviewers did not express any concern regarding the safety of supplementation of infant formulas with DHA and ARA. However, data on high-dose intervention is limited and Colombo and colleagues have indicated that sustained attention may be attenuated with DHA concentrations that are 3 times that of breast milk [20].

Although the studies had been rigorously assessed from a design and methodology perspective, they are a small disparate group of studies, demonstrating marked variation in intervention source of fatty acids (egg phospholipid, algae, and fish oil), dose and duration of intervention, unknown levels of DHA and ARA intake from complementary foods, differences in age at assessment, and a diverse range of assessments (Table 1). With this level of heterogeneity, it is difficult to draw an overriding view on the health benefits of LCPUFAs in early life. However, several studies did show evidence of beneficial

effects on visual function, especially where there was a combination of high dose and longer intervention duration, and in specific cognitive domains including problem solving and attention control (Table 1).

The heterogeneity in the design and methodology used in the RCTs can be partly explained by the fact that the studies were undertaken over a period lasting 2 decades and included the first RCTs of LCPUFAs undertaken in newborn infants. Understandably, the initial designs and methods reflect a high level of caution and are not representative of current thinking on dose and duration of the intervention, and choice of assessments [17]. None of the studies allowed for the effects of fatty acid desaturase genotype on fatty acid status, and although current evidence indicates that the impact on ARA levels, and to a lesser extent DHA, is limited compared to dietary intake, this variable should be considered in future studies [21]. It is also surprising that DHA and ARA status of the participants was not routinely measured in several of the included studies at the time of recruitment and assessment to confirm differences in status between intervention and control groups. Moreover, all the studies included in the review were undertaken in high-income countries, and on reflection it is very likely that many of the participants were not DHA or ARA deficient [18]. This would clearly attenuate the effects of the intervention and importantly, would conceal potential beneficial effects in infants with low LCPUFA status.

It is important that researchers and policymakers distinguish between the appraisal of evidence and the process of making policy [19]. The comment by the Cochrane reviewers that supplementation cannot be recommended based on this RCT data is an appraisal of the evidence based on their systematic review. However, public health interventions are intended to promote or protect health in communities or populations, and therefore policymaking has a broader perspective, which includes reducing inequality and protecting the most vulnerable [19]. The deficiencies in the reviewed RCTs that have been reported [17] should not only provide learning for researchers and future RCTs but also provide a marker for policymakers as they determine which evidence will provide the best policy on dietary LCPUFAs for vulnerable infants and young children worldwide.

If new RCTs, which will address past methodological issues and are conducted in appropriate real-world settings, are now commenced, definitive long-term data on health outcomes will not be available for several years. This presents a dilemma for public health policymakers –

Table 1. Studies included in the Cochrane review 2017 [15] – listing researchers, intervention and duration, outcome measures and age at assessment

Researcher, year	Intervention	Sample, n	Duration	Outcome measure	Age at assessment (* indicates beneficial effect in vision or cognition)
Agostoni et al. [64], 1995	DHA (0.3%) and ARA (0.44%)	60	4 months	Neurodevelopment (Brunet-Lezine test)	4, 12 and 24 months*
Auestad et al. [65], 1997	DHA (0.13%) and ARA (0.45%) DHA alone (0.2%)	134	4 months exclusive and milk for 12 months	Growth Visual function (VEP, Teller Cards) neurodevelopment (BSID, Stanford-Binet IQ) Language (McArthur communicative development inventory)	Growth at 1, 2, 4, 6, 9 and 12 months. Visual acuity at 2, 4, 6, 9, 12 and 39 months. Neurodevelopment at 1 and 3 years. Language development at 14 months and 3 years
Auestad et al. [66], 2001	DHA (0.13%) and ARA (0.45%)	404	4 months exclusive and milk for 12 months	Visual function (VEP, Teller Cards) Neurodevelopment (BSID) language (McArthur communicative development inventory)	Growth at 1, 2, 4, 6, 9 and 12 months. Visual acuity at 2, 4, 6 and 12 months. Fagan test of infant intelligence at 6 and 9 months, infant development at 6 and 12 months. Language development at 9 and 14 months. Parental reporting of infant temperament at 6 and 12 Months
Ben et al. [67], 2004	LCPUFA content of the formula was not clear	121	up to 6 months of age	Growth Neurodevelopment	Growth and neurodevelopmental outcomes at 3 and 6 months of age
Birch et al. [68], 1998	DHA (0.36%) and ARA (0.72%).	79	until 17 weeks of age	Growth Visual function (VEP) Neurodevelopment (BSID)	Growth and visual acuity at 6, 17, 26, 39 and 52 weeks. Infant development at 18 months*
Birch et al. [69], 2005	DHA (0.36%) and ARA (0.72%)	103	up to 52 weeks of age	Growth Visual function (VEP)	Growth, and visual acuity at 6, 17, 26, 39 and 52 weeks*
Birch et al. [70], 2010	DHA (0.32%) and ARA (0.64%). 4 groups: control (0% DHA), 0.32% DHA, 0.64% DHA, 0.96% DHA. For Cochrane review, the 0.32% DHA chosen as the intervention arm.	170	up to 1 year of age	Growth Visual function (VEP) Cognitive function, attention control	Visual acuity at 12 months. Quality of attention, heart rate, age-appropriate standardised and specific cognitive tests (18 months to 6 years every 6-monthly), growth until 6 years of age, school readiness and receptive vocabulary*
Bouwstra et al. [71], 2005	DHA (0.3%) and ARA (0.45%)	315	2 months	Growth Neurodevelopment (Hempel and BSID) Growth	Neurodevelopmental assessment and growth, cardiovascular, cognitive and behavioural assessments at 9 years
Carlson et al. [72], 1996	DHA (0.10%) and ARA (0.43%)	39	1 year	Visual function (Teller cards)	Visual acuity at 2, 4, 6, 9, and 12 months*
Lapillonne et al. [73], 2000	DHA (0.31%).	24	4 months	Growth	Weight, length and head circumference at 2 and 4 months of age
Lucas et al. [74], 1999	DHA (0.32%) and ARA (0.30%)	309	6 months	Growth Neurodevelopment (BSID) gastrointestinal tolerance	Neurodevelopment at 18 months Growth and gastrointestinal tolerance at 6, 9 and 18 months

Table 1. (continued)

Researcher, year	Intervention	Sample, n	Duration	Outcome measure	Age at assessment (* indicates beneficial effect in vision or cognition)
Makrides et al. [75], 1995	DHA (0.35%)	32	up to 30 weeks of life	Visual function (VEP) Neuro-development	Vision at 16 and 30 weeks*
Makrides et al. [76], 1999	DHA (0.34%) and ARA (0.34%) DHA alone (0.34%)	83	4 months.	Growth, neurodevelopment (BSID), Visual function (VEP)	Growth at 6, 16 and 34 weeks and at 1 and 2 years of age. Neurodevelopment at 1 and 2 years
Morris et al. [77], 2000	DHA (0.2%) and ARA (0.4%).	109	12 weeks	Growth	Growth at 6 weeks, 3 months, 6 months and 1 year
Willatts et al. [78], 1998	DHA (0.15% to 0.25%) and ARA (0.3% to 0.4%).	72	4 months	Cognitive function intelligence	Infant cognition by a means-end problem-solving test at 10 months. Assessments of intelligence quotient (IQ), attention control (Day-Night Test) and speed of processing on Matching Familiar Figures Test (MFFT) in 6-year infants*

do they simply wait for RCT data to become available, or do they endeavour to protect the interests of infants and young children, especially those living in medium- and low-income countries, by assessing the broader evidence base and develop policies that are based on broad reasoned judgement?

What Do Experimental and Animal Studies Tell Us about DHA and ARA in Early Life?

The n-3 LCPUFAs influence cellular membrane structure and function [3–7], and DHA is especially important in the brain and retina, where it rapidly accumulates during the early years of life [8]. DHA is also the precursor of potent lipid mediators called resolvins and protectins, which play crucial roles in the prevention or treatment of common chronic diseases that may lead to significant morbidity and mortality. The n-6 LCPUFAs, particularly ARA, are widely distributed throughout human cells and tissues [6]. In addition to the central nervous system where ARA plays an essential structural and functional role, ARA is also a metabolic requirement for all cells as a precursor for eicosanoids that modulate a variety of biological processes, particularly those relating to cerebral, cardiovascular and immune function [6].

To assess the level of interest in experimental and animal research relating to DHA, an audit of all papers published on Medline over a 12-month period (January 1, 2016 to December 31, 2016) was undertaken [22]. The search terms included (“docosahexaenoic acids” [MeSH Terms] OR (“docosahexaenoic” [All Fields] AND “acids” [All Fields]) OR “docosahexaenoic acids” [All Fields] OR (“docosahexaenoic” [All Fields] AND “acid” [All Fields]) OR “docosahexaenoic acid” [All Fields]) AND (“animals” [MeSH Terms:noexp] OR animal [All Fields]) AND 2016 [Date – Publication]. This search of a single research database identified 95 publications during the 12-month search period, with 45 classified as primary scientific research, 20 human studies, observational and RCT studies, 27 reviews, and 3 studies that were considered not relevant.

During the 12-month period, there were 45 publications providing original scientific research on the role and function of DHA with a focus on cellular metabolism or effects on specific organ tissue, with studies relating to brain and immune function being most prevalent. The research findings confirmed that DHA is metabolically relevant at all stages of the human life course, and that DHA and its derivatives interact at multiple levels, including cell

membrane composition, metabolism, signal transduction and amplification and gene expression. The relationship of DHA to different biological systems throughout the human life course, underlines the importance of taking a whole life perspective when considering the dietary needs for DHA and other LCPUFAs in early life.

The number of papers relating LCPUFAs to immune function reflects the increasing evidence that a chronic low-grade inflammatory state is a pathological feature of a wide range of chronic conditions, including the metabolic syndrome, nonalcoholic fatty liver disease, type 2 diabetes mellitus, and cardiovascular disease. There is emerging information on novel mechanisms of action by dietary fatty acids of different classes influencing inflammatory processes, some acting through proinflammatory and others through anti-inflammatory or inflammation-resolving mechanisms [23, 24]. Moreover, the balance between DHA and ARA is considered to have important immunomodulatory roles during the postnatal period when the immune system is rapidly developing; intervention studies have demonstrated improvement in many markers of immune function in infants fed formula supplemented with ARA and DHA compared with unsupplemented formula, and this is associated with beneficial health outcomes including reduction in the risk of developing allergic and atopic disease early in life [25].

The MEDLINE search identified 27 review articles, 18 referring to animal and human studies and 9 were exclusively related to human studies. A common theme was that outcome measures were more consistent in animal intervention studies, and translating this evidence to health outcomes in humans has been challenging. This discrepancy between animal and human data may partially relate to variance in methodology. In animal studies, the duration of dietary intervention is significantly longer than in human intervention studies, when adjusted for the respective life expectancies. The average age at which mice attain puberty is 42 days, which is frequently the duration of nutritional interventions in mice, including recent DHA studies [26]. There are no known human RCTs where the dietary intervention was initiated at birth and continued until puberty. The original rat studies by George and Mildred Burr showed that it was several months of total exclusion of fatty acids before the rats showed obvious clinical signs of essential fatty acid deficiency [2]. It may be that longer duration of intervention in humans will demonstrate later programming effects. Data from the Cochrane review shows that in the majority of the RCTs involving DHA and ARA supplementation, the duration of supplementation was 4 months,

which is approximately 2–3 days in the life of a mouse [27]. There are specific domains that may be sufficiently sensitive to DHA and ARA and produce effects within a relatively short period of intervention, but an expectation that global neurodevelopment will be influenced by 4 months of supplementation is probably unrealistic.

What Do Observational Studies Tell Us About DHA and ARA in Early Life?

The MEDLINE search also identified 20 observational studies. Observational studies may represent a more feasible study design for evaluating public health interventions than RCTs [19]. While RCTs (notably cluster RCTs) can be designed to evaluate even complex public health programs, often they are not feasible because of logistic or resource constraints. Even a carefully planned study such as the Promotion of Breastfeeding Intervention Trial, which was described as the largest RCT of human lactation, and was led by 2 international research teams from Canada and England, and conducted in a country that is structured and organised, the cluster randomisation model was undermined by the unexpected withdrawal of 3 clusters. This led to an imbalance in the randomisation model and the analysis needed to include adjustments for potential confounding variables, as is done in observational studies [28]. With the scientific, logistic, and financial pressures in conducting long-term RCTs, it may be constructive to pragmatically balance the need for a robust study design with the need for evidence that is inclusive and relevant to the needs of the target population. Under these circumstances, an observational study may not only be informative but also perceived as being low risk, cost effective and scientifically appropriate.

There have been several interesting observational studies that investigated the relationships between dietary or circulating n-3 LCPUFAs and all-cause mortality, and these have recently been assessed by a systematic review and meta-analysis that included 11 prospective observational studies [29]. The studies included 371,965 participants from general populations and considered 31,185 death events. From this analysis, the dose-response indicated that for each 0.3 g/day increment in n-3 LCPUFA intake, there was an associated 6% lower risk of all-cause mortality and for each 1% increment in the proportions of circulating DHA and EPA in total fatty acids in blood there was an associated 21 and 20% decreased risk of all-cause mortality respec-

tively. Moderate to high heterogeneity was observed across the analysis, but the authors concluded that the findings suggest that both dietary and circulating LCPUFA are inversely associated with all-cause mortality [29].

Hibbeln et al. [30] utilized data from the Food and Agriculture Organisation (FAOSTAT) [35] to measure n-3 LCPUFA dietary intake in 38 predominantly developed countries and related that data to age-adjusted mortality due to cardiovascular disease, coronary heart disease, and stroke. They determined that the greatest protection was provided by a total n-3 LCPUFA dietary intake of 750 mg/day, which most closely correlated with the dietary intake of the Japanese population. They commented that Japan is a modern industrialized society with a large population and well-documented rates of illnesses and nutrient intakes. Low rates of cardiovascular disease have been consistently reported in Japan, despite high rates of smoking and hypertension [34]. Moreover, when the Japanese move to the United States and consume a diet low in n-3 LCPUFAs, the risk of cardiovascular disease increases, suggesting that the protective effect is not genetic [31].

In a multinational study, published mathematics test scores from the Program for International Student Assessment of the Organization for Economic Cooperation and Development, which is a single test that is administered in a consistent way to 15-year-old students in 59 countries, were related to national data on maternal milk DHA levels in 28 high- and medium-income countries from both the Northern and Southern Hemispheres [32]. The findings showed a strong correlation between breast milk DHA levels and cognitive performance in the mathematics test with the observed association remaining highly significant after controlling for national wealth, investment in education and macronutrient intake.

Although observational studies tend to raise further research questions, multinational observation studies that, for example, relate early life dietary intake of DHA (and other LCPUFAs) to later life health outcomes, merit consideration by public health policymakers.

What Is the Best Evidence for Public Health Policymakers?

To increase the value of health care services, many countries have established programs or independent agencies that inform health care decision-making

through systematic reviews of healthcare interventions, for example, the National Institute for Health and Clinical Excellence in the United Kingdom [33] and in the United States, the Agency for Healthcare Research and Quality created the Effective Health Care (EHC) Program in 2005 [34]. A key element of the EHC program, is the Comparative Effectiveness Review, the aim of which is to determine how the relative benefits and harms of a range of options compare, rather than to answer a narrow question on whether a single therapy is safe and effective [35–38]. As noted in the Cochrane reviews of LCPUFAs, it is not unusual for the number of RCTs that are available to provide direct comparisons to be relatively small, and there is then a risk that the body of evidence is insufficient to draw robust conclusions about comparative benefits and harms. It is also noted that in the 2017 review [15], there were no new cohorts since 2011. Under these circumstances, there is a need to seek a more wide-ranging opinion from the research literature, including evidence from experimental studies, placebo-controlled trials, and observational studies.

In the consideration of observational studies by Comparative Effectiveness Reviews, it is emphasised that systematic reviewers should answer 2 specific questions – first, are there gaps in the RCT evidence to satisfactorily address the review questions that are under consideration? And second, will observational studies provide valid and useful information to address these key questions? [35, 38]. It is clearly stated that there is no a priori reason to exclude observational studies from research questions on health benefit, but they should be evaluated on the same criteria used to evaluate the inclusion of RCT data, namely, whether the observational study results address the key question and whether the observational data are likely to be valid.

It is also noted that in relation to applicability of evidence, and the relevance to the target population and setting, observational studies may be particularly insightful [35–38], and therefore, they may be particularly relevant in public health interventions that focus on promoting or protecting health at community and national levels. The public health considerations of a specific health issue within a population will generally include – the perceived magnitude and importance of the problem, the potential effectiveness and harms of an intervention, the feasibility of its implementation, and its political and public acceptability [19]. Decision-making around dietary LCPUFAs in early life is an important public health issue, and for informed policy de-

cision-making, a broader examination of the literature may allow the process to progress from research evidence to policy implementation in a timelier manner.

Is There Evidence of Inadequate Dietary Intakes of DHA and ARA in Early Life?

The World Health Organisation (WHO) recommends that mothers worldwide exclusively breastfeed infants for the child's first 6 months to achieve optimal growth, development and health. Thereafter, they should be given nutritious complementary foods and continue breastfeeding up to the age of 2 years or beyond [39]. It is recognised that additional nutrient dense complementary foods (liquid and solid) are required following the exclusive breastfeeding period to prevent under-nutrition and stunting in the childhood population [40].

Human milk is a complex dynamic bioactive fluid which, in addition to containing essential nutrients for normal growth and development, has several compositional components that make it unique. Unlike infant formula, which is standardised within a very narrow range of composition, human milk composition is dynamic, and varies during a feeding, diurnally, during the period of lactation, and between mothers and populations [41]. A potent example of human milk uniqueness is the consistent presence of significant quantities of DHA and ARA [42, 43] and this contrasts with the trace amounts that may be found in cow's milk, goat milk, soya milk and rice milk [44]. The level of availability of DHA and ARA in human milk, as opposed to that in other animal and plant milks, is highly indicative of their essentiality for human infants. Moreover, there are documented mechanisms that actively transport DHA and ARA through the placenta from the mother to the fetus during pregnancy [45] and for DHA and ARA to be released from maternal lipid stores and transported to the breast during lactation [46]. These evolutionary mechanisms enhance the delivery of DHA and ARA to the fetus during the prenatal period and to the infant post birth. Endogenous synthesis of DHA and ARA is limited in infants [47] and therefore the infant is dependent upon dietary sources of both DHA and ARA.

Amounts of DHA and ARA in human milk tend to vary by maternal diet and nutritional status [42, 43]. Based on data from 65 studies of milk from 2,474 women, the mean concentration of ARA (% fatty acids by weight) was 0.47% (range 0.24–1.0%) and the mean con-

centration of DHA was 0.32% (range 0.06–1.4%). The levels of DHA were particularly low in populations with the greatest poverty – 0.06% DHA in Pakistan, Northern Sudan, and 0.10% DHA in Southern Sudan [42]. Applying the WHO recommendation on exclusive breast feeding for 6 months, it is estimated that at 6 months, infants will be receiving approximately 171 mg/day of ARA and 111 mg/day of DHA, based on a breast milk intake of 854 mL/day [48] and the reported mean concentrations of DHA and ARA in human milk [42]. An infant receiving a formula without supplemented DHA and ARA will clearly have zero consumption from milk feeds during this time and it has been shown that these infants not only have lower blood levels of DHA [49], but the accretion of both DHA and ARA in the brain is significantly lower in infants fed a formula that is devoid of these fatty acids [49, 50].

Complementary foods tend to have low concentrations of DHA and ARA and this is evident in both high- and low-income countries [51–54]. In low-income countries, it is common practice for weaning infants to receive the food from the family bowl, which is most commonly of plant origin and will have low ARA and DHA content. In a recent publication, the dietary intake of ARA and DHA at the population level was strongly related to the economic status of the country [55]. The analysis was based on food consumption data originally collected by the Food and Agriculture Organisation (FAO) [56] and by applying food composition tables, the per capita dietary intakes of DHA and ARA were estimated for 175 countries worldwide, with 47 classified as developed and 128 as developing. This analysis demonstrated that per capita intakes of both fatty acids varied significantly in relation to the gross national income of the country, with low-income countries having intakes of DHA and ARA, which were only 20–25% of that of high income countries. The 28 countries in the lowest income category had per capita median DHA and ARA intakes of 47 and 43 mg/day, respectively, and this group represents a total population of nearly 740 million people. There was considerable regional variation with lowest intakes for both ARA and DHA being in Sub-Saharan Africa and Southern, Western and Central Asia [55].

Estimates were also made of DHA and ARA intakes during the age period of 6–36 months [57]. This analysis estimated intakes of DHA and ARA from breast milk and complementary foods using published data on median duration of breast feeding, mean concentration of DHA and ARA in breast milk, and mean intakes of breast milk.

The dietary intakes of DHA and ARA in infants and young children aged 6–36 months from 76 developing countries (17 upper middle income, 34 lower middle income, and 25 low income) were 48.8 and 63.7 mg/day respectively. The contribution of DHA and ARA intake from complementary foods was directly related to the gross national income of the country and the intakes of DHA and ARA from complementary foods following the discontinuation of breast feeding for the 76 countries were 14.6 and 17.9 mg/day, respectively, and in the lowest income countries, intakes fell to 9.6 and 8.9 mg/day respectively. The DHA and ARA intake from complementary foods was exceptionally low in the poorest resource countries, especially Nepal (DHA 0.7 mg/day; ARA 1.1 mg/day), Ethiopia (DHA 1.1 mg/day; ARA 3.8 mg/day), and Rwanda (DHA 1.8 mg/day; ARA 1.7 mg/day) [57, 58].

This evidence, which was based on data originally collected by the FAO, shows that many millions of infants and young children, especially the most vulnerable living in low-income countries have a dietary intake of DHA and ARA, which is significantly low compared to current international recommendations. The FAO has provided specific recommendations on dietary intakes of DHA in infants and young children stating that from 0–6 months the daily requirement is 0.1–0.18%E of DHA (equivalent to a mean of 102 mg/day); for 6–24 months, DHA requirement is 10–12 mg/kg bodyweight (equivalent to 70–120 mg/day); for 2–4 years, DHA and EPA 100–150 mg/day, with DHA and EPA increasing to 200–250 mg/day at age 6–10 years [10]. In 2013, the European Food Safety Authority recommended an adequate intake of 100 mg/day DHA for older infants (>6 months of age) and young children below the age of 24 months [59] and in 2014, European Food Safety Authority determined adequate nutrient intakes of LCPUFA from birth to the age of 24 months as 100 mg DHA/day [9]. There are few explicit dietary recommendations for ARA. However, an expert advisory group recommended that during the first months of life, infants should receive 140 mg ARA/day [60]. A study in Belgium noted that in children 2.5–3 years of age, the DHA intake was 45 mg/day and for ARA 17 mg/day, indicating that intake in this high-income country, was significantly below recommended levels [61]. Codex Alimentarius has identified DHA as an optional ingredient for infant formulas and stated that if DHA is added to infant formula, a guidance upper level should be 0.5% fatty acids, the ARA content should reach at least the same concentration as DHA; and the content of eicosapentaenoic

acid that can occur in sources of LCPUFA, should not exceed the content of DHA. National authorities may deviate from the above conditions, as appropriate for the nutritional needs [62]

The consequences of an inadequate intake of DHA and ARA, and other key nutrients, are preventable. Researchers, healthcare workers, policymakers, and other key actors need to consider the level of evidence required and decide what actions are appropriate for this strength of evidence. The transferability of the evidence into practice requires a weighing of multiple factors such as the perceived magnitude and importance of the problem, the potential effectiveness and harms of the intervention, the feasibility of its implementation, its political acceptability and the public demand for action [19]. Although different interest groups may advocate for competing recommendations based on the same evidence, it is critical that the dietary needs of the most vulnerable infants are at the center of the discussion. Progress will require a pragmatic approach, which may become incremental, as future evidence becomes available. To reach an agreement on the balance between the level of evidence and the measures required to address the need, a framework consisting of key questions is proposed (Appendix).

Conclusions

Relating early life nutritional interventions to later life health outcomes is always going to be challenging and all research methods will have their limitations. There is a real concern that inconsistency in RCTs of LCPUFA supplementation may be misinterpreted as indicating that low dietary intake of DHA and ARA will be of no consequence to even the most vulnerable infants. Recent evidence indicates that a high proportion of the global childhood population may be at risk of LCPUFA deficiency in early life [55, 57, 58].

It is important that the body of research available to policymakers reflects the socio-economic, cultural, dietetic and genetic diversity of the populations being considered, and that studies are inclusive and focus on those individuals and communities that are at greatest risk. In some settings, observational studies may represent the most feasible and appropriate study designs for identifying at-risk populations and evaluating public health interventions.

With the first 1,000 days of life being a critical period for normal growth and development, a key objective of an incremental pragmatic approach to dietary DHA and

ARA in early life should be to establish an LCPUFA safety net for the most vulnerable infants worldwide. This can be achieved by ensuring that levels of DHA and ARA in infant formulas, follow-on formulas, and complementary foods reflect published data on median levels of DHA and ARA in breast milk.

Appendix

An Evaluation Framework for a Pragmatic Approach to Policy Issues on Dietary DHA and ARA in Early Life

Why Is a Pragmatic Approach Being Considered?

A key principle of the EHC Program is that the questions that are being addressed in reviews must be answered at a time when decision makers need the information. The slow and unpredictable translation of research into practice has been linked to the assertion that the evidence base should be developed through traditional explanatory models and efficacy designs rather than be the product of more pragmatic methodologies. Pragmatic models such as those adopted by the EHC have evolved to identify benefits and potential harm and to address practical issues that may provide momentum to the translation of research evidence to effective implementation.

The distinction between the appraisal of research evidence and the process of making policy is particularly important when considering what question(s) needs to be answered. From a research perspective, the Cochrane review asked the question – Is DHA and ARA supplementation of infant formulas beneficial and safe? A public health policy question that views the issue from a population perspective could be – Should measures be taken to ensure that at-risk infants and young children receive food sources that will adequately complement their current low DHA (and ARA) intakes? Clearly these questions are not mutually exclusive, if the evidence from the first question indicated that there was no evidence of benefit and that the intervention was potentially harmful, public health policymakers would reject their policy proposal. However, as there is some evidence of benefit, there is no evidence of harm, and there is non-RCT evidence indicating that inadequate dietary intake of DHA and ARA in early and late life has potentially serious health consequences, the pragmatic public health question has merit and justifies consideration.

What Is the Driver for this Public Health Policy Question?

The main complementary food source for DHA is oily fish and for ARA meat, poultry and eggs. Any child who has a diet that is low in marine and animal foods will become deficient in these fatty acids. Recent published evidence indicates that dietary intakes of DHA and ARA in infants and young children aged 6–36 months are significantly lower than current recommendations, especially in low income countries [55, 57, 58]. From a policy perspective, the issue meets the principal objectives of public health policies which are to improve population health, avoid harm and reduce health inequality.

What Is the Magnitude of the Issue?

The WHO has stated that childhood stunting is one of the most significant impediments to human development globally, affecting approximately 162 million children under the age of 5 years. It is

a largely irreversible outcome of inadequate nutrition and repeated bouts of infection, during the first 1,000 days of a child's life. Inadequate provision of complementary foods, especially animal foods, is a key factor in the development of acute malnutrition, stunting and mortality. With low intakes of marine and animal food, (and therefore low intakes of DHA and ARA), being associated with stunting, DHA and ARA food sources or supplements need to be made available to infants and young children who are at greatest risk [55, 57, 58]. If current trends continue, projections indicate that 127 million children under the age of 5 years will be stunted in 2025 [63]. WHO global recommendations on complementary feeding encourage consumption of healthy, diversified diets, including high-quality, nutrient-rich, animal source food during the period 6–23 months [40].

What Is the Evidence to Support a Pragmatic Dietary DHA and ARA Intervention in Early Life?

There is lack of consistency in the evidence from RCTs and this is related to weaknesses in design and methodologies, especially in early studies. Although there is evidence of benefit in vision and some specific aspects of cognition, there are learning points for new-quality RCTs that need to be conducted in appropriate settings. While the outcome of these studies is awaited (and this may be in several years), it is important to consider other supporting evidence that is emerging from experimental, animal, and observational data, including the immunomodulatory roles of DHA and ARA in early life, when the immune system is rapidly developing. A pragmatic approach that is based on the totality of evidence can begin to constructively address the inadequate dietary intake of DHA and ARA in the at-risk infant and child population.

What Is the Intervention, How Will It Be Implemented, and How Will Outcomes Be Measured?

The main objective of the intervention will be to increase the availability of DHA and ARA food sources and relevant nutritional products for at-risk populations, and this should be part of a wider initiative to promote effective coordination and collaboration through integrated, multisectoral action, supported by effective governance of food systems at all levels, and facilitated by high-level political support. Maintaining the momentum of growth in agricultural productivity will be crucial in the coming decades with a stronger focus on nutrient-dense foods such as fruits, vegetables, legumes and animal-source foods. These actions need to be supported by nutrition, health, and education institutions, industry and other professional and voluntary organisations. Food sources for DHA and ARA, and specific nutritional products are currently widely available in high-income populations and this availability now needs to extend to countries in greatest need. Inherent within the pragmatic approach is a flexibility that will allow opportunities for local teams and communities to have local ownership of the policy and investigation of the effects of implementation, and be able to make refinements to the process, based on intermittent evaluation and real-time and real-world data.

Is This a Cost-Effective Solution?

Malnutrition imposes unacceptably high costs on society in human and economic terms. Recent research showed that investing US\$1.2 billion annually in micronutrient supplements, food forti-

fication and biofortification of staple crops for 5 years would generate annual benefits of US\$15.3 billion, a benefit-to-cost ratio of almost 13–1, and this would result in better health, fewer deaths and increased future earnings [6]. Child and maternal malnutrition is the largest nutrition health burden in the world.

Disclosure Statement

Professor Stewart Forsyth undertakes consultancy work for DSM, a producer of nutritional ingredients including DHA and ARA. Professor Philip Calder is an advisor to DSM, Danone/Nu-

tricia, FrieslandCampina, Cargill and Smartfish and has received speaking honoraria from DSM, Danone and Abbott Nutrition. Professor Francis Zotor, Dr. Paul Amuna, and Professor Barbara Meyer have no conflict of interest to declare. Professor Bruce Holub serves on the Scientific Advisory Board for a Canadian supplement company (Jamieson) and on the Scientific Advisory Panel for Nutritional Fundamentals for Health. He is also on the Advisory Council for the Seafood Nutrition Partnership in the United States. He has given lectures to medical groups with financial support from Mead Johnson (Canada). He serves as Scientific Director for the DHA Omega-3 Institute (a not-for-profit research and educational group) based at the University of Guelph Research Park.

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