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Review article

ARA or no ARA in infant formulae, that is the question

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ABSTRACT

Recently, the European Commission issued a Delegated Regulation updating the compositional and information requirements for infant and follow-on formulae that are to be applied at the latest in February 2021. This new regulation changes the status of docosahexaenoic acid (DHA) from an optional ingredient to a mandatory nutrient in these formulae at levels between 20 and 50 mg/100 kcal (0.5–1% of fatty acids). By contrast, arachidonic acid (ARA) becomes an optional nutrient. Following publication of the new regulation, global scientific experts have expressed concerns regarding the potential health risks of new infant formulae containing only DHA, especially at levels higher than those in breast milk and infant formulae marketed to date. Both DHA and ARA play a crucial role in infant development. First, breast milk, the gold standard for infant feeding, contains both DHA and ARA. Second, during development, the conversion of linoleic acid into ARA through desaturation steps is not sufficient to meet nutritional needs, especially in carriers of newly identified genetic variants in fatty acid desaturases, which weaken the biosynthetic production of ARA. Third, circulating levels of DHA and ARA in breastfed infants can only be matched with the addition of both fatty acids to formulae. And fourth, most studies performed to date have demonstrated that important physiological and developmental endpoints are sensitive to the ratio of dietary ARA:DHA. The precautionary principle applies when implementing the new EU regulation for infant and follow-on formulae. As a consequence, given the vulnerability of developing infants as well as the absence of conclusive evidence that formulae with at least 20 mg DHA/100 kcal, but no ARA, are safe and suitable to support the growth and development of infants similar to their breastfed peers, it remains necessary to still market formulas containing both ARA and DHA until proved otherwise.

1. Introduction

Nutritional deficiencies during the first 1000 days of life have a long-lasting impact on health status [1]. With hundreds to thousands of well-absorbed and metabolized nutrients and bioactive molecules, breast milk (BM) is tailored to promote optimal growth and development in infants as well as to protect them against infections and nutritional deficiencies [2]. Thus, exclusive breastfeeding remains the gold standard source of nutrition for at least the first 6 months of life [3]. Among lipids contained in BM, the long-chain polyunsaturated fatty acids (LCPUFA) arachidonic acid (ARA; 20:4n-6) and docosahexaenoic acid (DHA; 22:6n-3) are one of the key factors necessary for infants to thrive [4]. A significant number of infants in Europe are not breastfed for 6 months and need to be fed a formula [3]. In France, only 23% of infants are still at least partially breastfed at the age 6 months [3]. The composition of formulae is regulated and aims to provide healthy term infants with nutrients and sometimes functional components that support growth and development as close as possible to what is observed in breastfed infants. When considering the composition of lipids in infant formulae, the latter have to provide infants with enough energy and a well-balanced fatty acids content. Questions remain about optimal fatty acids composition. Several expert panels and food authorities have evaluated the optimal intakes of DHA and ARA in infancy and early childhood. In 2010, the joint report by The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) sets adequate intakes for DHA as 0.1–0.18% (~40–130 mg/day) and ARA as 0.2–0.3% (~80–215 mg/day) of energy between 0 and 6 months. Beyond 6 months, 10–12 mg/kg/

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day of DHA should meet infant needs [5]. The European Food Safety Authority (EFSA), on its end, considers that 100 mg DHA/day and 140 mg ARA/day are adequate for the majority of children until the age of 6 months, and then 100 mg DHA/day until 24 months of age [6]. However, until recently, these recommendations had not been translated into a mandatory addition of DHA and ARA in infant formulae, neither at the global level by the Codex Alimentarius [7] nor by the European Union [8]. In 2014, the EFSA issued a scientific opinion on the essential composition of infant and follow-on formulae stating that all of them should contain amounts of 20–50 mg DHA/100 kcal, while concomitant addition of ARA was not needed [9]. Elaborating on the basis of this EFSA opinion, the Commission Delegated Regulation (EU) 2016/127 that defines the latest compositional criteria for infant and follow-on formulae now mandates addition of DHA in the exact levels recommended by the EFSA, while the addition of ARA remains optional. This new regulation will be fully effective as of February 22, 2020 for regular infant and follow-on formulae and as of February 21, 2021 for those manufactured from protein hydrolysates [10].

Following the publication of the EFSA opinion of 2014 and the adoption of the new EU regulation, several global scientific experts have expressed concerns regarding the potential risks of new infant formulae containing only DHA, but no ARA [11–13]. The current review will weigh in the pro and con arguments with regard to adding ARA to healthy term infant formula in the presence of DHA in the light of currently available data regarding the biological roles and interactions between both LCPUFAs.

2. DHA and ARA: general features

DHA and ARA belong to LCPUFAs defined as unsaturated fatty acids with 20–24 carbons. LCPUFAs are grouped into two main families, omega 6 (n-6) and omega 3 (n-3), depending on the position of the first double bond from the methyl end group of the fatty acid. The parent fatty acids of these families, linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA, 18:3n-3), are essential fatty acids since humans cannot synthesize them and therefore they must be provided by the diet. LA and ALA are converted to longer chain, more highly unsaturated, through successive enzymatic chain elongation and desaturation steps (Fig. 1). LA is the precursor of ARA, and ALA that of eicosapentaenoic acid (EPA, 20:5n-3), and through further enzyme actions of DHA. The chain elongation/desaturation enzymes act on both n-3 and n-6 fatty acids leading to a competition between substrates for these enzymes [14].

DHA is mainly present in brain cell membranes where it concentrates in phospholipids of the prefrontal cortex (30–40% of fatty acids), which is important for association and short-term memory, and the photoreceptors of the retina where it ensures quality of vision [15]. ARA, while also present in the brain, is more widely distributed than DHA in the body. ARA is the principle unsaturated fatty acid in the heart, muscle, vascular endothelium, T-lymphocytes, adrenal, kidneys, liver, and the placenta [15]. DHA and ARA influence membrane structure and function, cell signaling and communication, lipid mediator production, and gene expression. ARA is specifically the precursor of eicosanoids that modulate a variety of biological processes in almost every tissue [15]. In early life, eicosanoids, among many other roles, modulate the release of somatostatin, play a key role in vasculature development and function, and promote an optimal immune system and tolerance development. In the first year of life, infants go through a period of immune immaturity during which they are more susceptible to infections. This early period, which is the most important period of T-cell differentiation and tolerance development to environmental

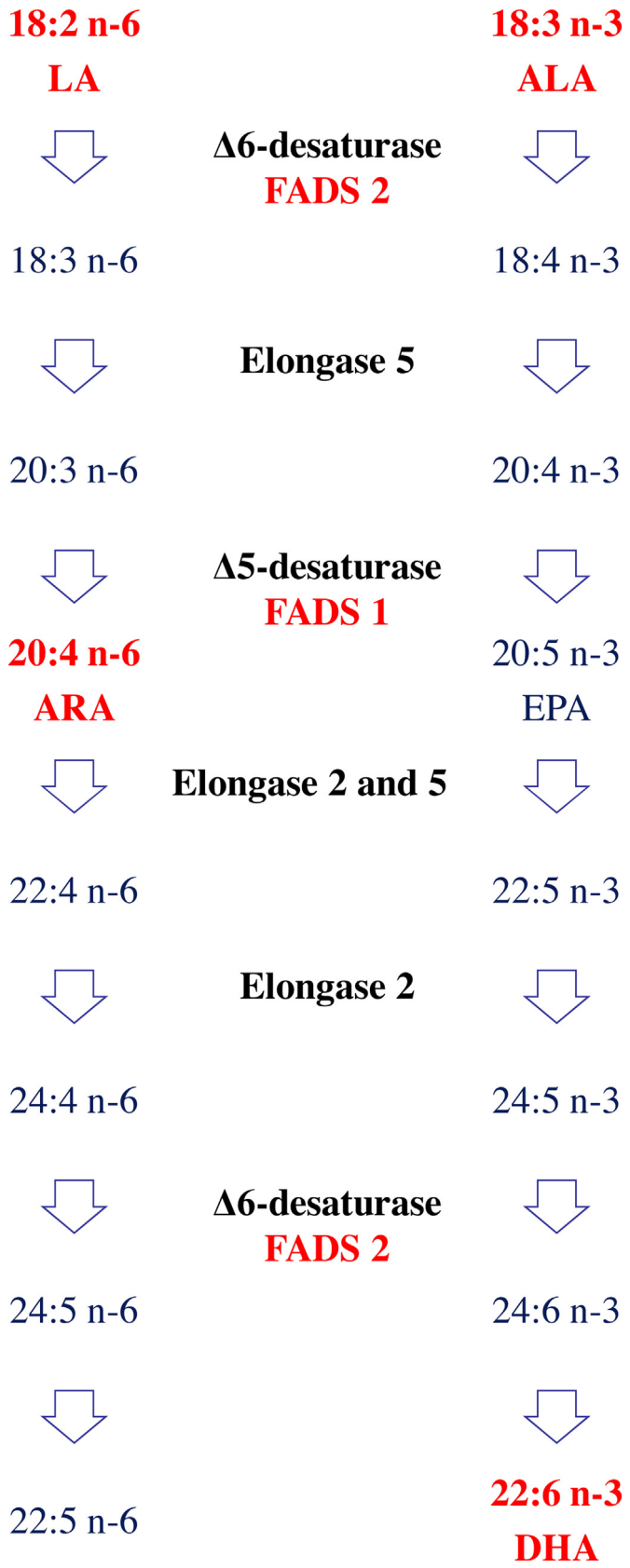

Fig. 1. Long-chain polyunsaturated fatty acid synthesis through successive enzymatic chain elongation and desaturation steps. LA: linoleic acid; ALA: α-linolenic acid; ARA: arachidonic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid. FADS 1 and 2: fatty acid desaturase 1 and 2 genes encoding Δ5-desaturase and Δ6-desaturase, respectively.

and dietary antigens, is characterized by a rapid increase in the content of ARA in the thymus [15,16]. Thus, ARA has an immunoregulatory role and might therefore participate in the prevention of infections and allergic diseases. However, clinical trials are still necessary to demonstrate that formulae supplemented with ARA have these properties in healthy term infants.

3. Should infant formula contain ARA when DHA is added? Cons

Different studies undertaken to monitor growth and brain development, especially visual acuity, have led to the conclusion that ARA addition to infant formulae does not offer any benefit to these outcomes.

With regard to growth, longitudinal or randomized controlled trials (RCT) performed with formulae containing DHA alone could not find evidence that growth parameters (weight, height, head circumference) were altered in full-term infants in either a positive or a negative way, although erythrocyte membrane ARA concentrations were found to be lower in the groups consuming the supplemented formula when compared with the control formulae devoid of DHA [17,18]. The recent opinion issued by the EFSA supporting no need for ARA addition to infant formulae was based on these studies [9]. The most recent meta-analysis concludes that LCPUFA supplementation of infant formulae, whether with DHA alone or with added ARA, supports a growth similar to the one of infants either breastfed or even fed an unsupplemented formula [19].

In the brain, during the last trimester of pregnancy and through the first 5 years of life, DHA and ARA undergo a rapid accretion with ARA absolute content reaching levels higher than those of DHA in the first 2 years [20]. Well-balanced incorporation of LCPUFAs is critical for an optimal brain development since they both play a key role in neurogenesis and synaptogenesis [21,22]. Studies in baboons receiving formulae enriched with various levels of DHA and ARA showed that levels of DHA are clearly responsive to dietary supply, while ARA levels are not [23]. Consistent with animal studies, autopsy studies in sudden infant death syndrome cases found a greater proportion of DHA in the brain cortex of breastfed infants relative to the ones who were fed with formulae devoid of LCPUFAs. Cortex DHA increased in breastfed infants (but not in formula-fed infants) with age. By contrast, accretion of ARA was dependent only on age but not on diet [24]. These results from animal and human studies led to the conclusion that brain DHA content mainly relies on dietary supply, while brain ARA is not affected, suggesting a tighter regulation at the level of incorporation or utilization [23,24]. It is noteworthy that the brain has a specific active desaturation/elongation system that converts LA to ARA [15].

The most widely accepted developmental effect of LCPUFAs in the infant and young child brain is certainly the improvement of vision development. RCTs assessing the effect of LCPUFA supplementation on visual acuity indicate that a beneficial effect, when observed, is likely associated with DHA only. Birch and colleagues found that infants who received a formula supplemented with DHA alone for the first 4 months of life had a visual maturation similar to that of their breastfed counterparts at 12 months of age when compared with the unsupplemented control group. The beneficial effect was sustained until 4 years of age but its persistence beyond this age remains to be demonstrated. The addition of ARA to DHA in amounts allowing an ARA/DHA ratio close to the one in BM did not add any further benefit but neither represented a health harm [25,26]. Based on these results, in 2009, the EFSA allowed the claim that DHA contributes to the visual development of infants from birth to 12 months as long as the formula contained at least 0.3% of total fatty acids as DHA [27].

The previous findings suggest that DHA supplementation alone does not affect growth and could promote an optimal brain development.

4. Should infant formula contain ARA when DHA is added? Pros

Despite the aforementioned evidence, a great deal of observations and research works support the concomitant addition of ARA with DHA. The following arguments underscore the numerous physiological roles played by ARA, which are definitely thought-provoking when the question of adding ARA or not to infant formulae is raised.

4.1. Breast milk contains both ARA and DHA

BM composition is the gold standard for feeding full-term infants. There is a robust consistency between thousands of milk samples from across the planet in the amounts of ARA in BM, while DHA is more variable but always present. The ARA concentration is greater than DHA in most BM worldwide and the ARA/DHA ratio can be as high as 2:1. The latest update on the BM LCPUFA content reported worldwide mean levels of DHA and ARA of 0.37% (SD 0.11) and 0.55% (SD 0.14) of total fatty acids, respectively [28]. One can note that French BM ARA and DHA contents were among the lowest worldwide. The BM DHA levels from women with accessibility to marine foods were significantly higher, with lower ARA levels than those from women without accessibility. The ARA content remains higher than the DHA content in most countries, including France. From an evolutionary point of view, it is hypothesized that the simultaneous evolution of mammals and new plants with seeds rich in linoleic acid, the latter being introduced into the diet, may not be simply a coincidence considering the pleiotropic functions of ARA [29].

4.2. ARA synthesis may not be sufficient in regard to its wide-ranging biological functions

Both preterm and term infants are capable of synthesizing DHA and ARA. The conversion rates are influenced by genetics, gender, and the amount of precursor fatty acids available in the diet. However, as demonstrated by studies using stable isotopes, the whole-body endogenous synthesis rates remain insufficient to maintain stable plasma and red blood cell LCPUFA content, reliable indicators of LCPUFA status [15]. Due to the stronger affinity of desaturase 6 for n-6 precursors, the competition between n-6 and n-3 substrates for desaturases, and additional elongation and desaturation steps, the rate of conversion of ALA to DHA is of the order of 1% in infants [30]. As a result DHA is now considered a conditionally essential fatty acid for infants [6]. Likewise, the rate of conversion of labeled LA to ARA, even if higher than the one of DHA, remains insufficient to sustain adequate whole-body ARA levels [15]. ARA synthesis decreases in preterm and term infants as early as in the first 6 months of life [31]. As a result, feeding infants with formulae without preformed ARA results in a dramatic decrease of up to 40% of ARA in erythrocytes shortly after birth, especially in preterm infants who do not receive the third trimester maternal supply of ARA and DHA [15]. Manipulation of LA:ALA ratios never managed to reach the blood LCPUFA levels of breastfed infants. Circulating levels of DHA and ARA in breastfed infants can only be matched with the addition of both LCPUFAs to formulae [16]. Given ARA is more widely distributed in the body and serves many more functions (inflammation, immune response, cardiovascular functions, etc.) than DHA, the biosynthetic production of

ARA is not sufficient and thus the ARA status of non-CNS (central nervous system) tissues, mainly heart, muscle, vascular endothelium, T-lymphocytes, adrenal, kidneys, and liver, remains highly dependent on diet [16]. Additionally, achieving a healthy LCPUFA status in early life is important not only to support normal growth and development in infants but also to support health throughout life. Indeed, dietary supplementation of LCPUFAs in early life proved to have beneficial long-lasting effects and to prevent the occurrence of diseases, such as allergy, hypertension and cardiovascular disease, as well as neurodegeneration, later in life [1].

4.3. Variants in genes coding for desaturases and elongases alter LCPUFA status

Variants have been identified in desaturase and elongase genes. Fatty acid desaturase (FADS) 1 and 2 genes are grouped in a cluster and encode the rate-limiting enzymes of the LCPUFA synthesis pathway Δ5 and Δ6 desaturases, respectively (Fig. 1). Elongases are encoded by ELOVL2, ELOVL5 [32]. Gene variants in the FADS gene cluster affect 30% of the general population and have been the most widely studied [33]. In general, precursor fatty acids, such as LA and ALA, are elevated in biological tissues in adults, children, and human milk with minor alleles, while end products, ARA and EPA are reduced, up to 30% for ARA, indicating an impaired enzyme activity. DHA status is less affected by FADS variants, which underlies the fact that DHA is predominantly derived from dietary sources and not from endogenous synthesis [33]. FADS variants can influence infant LCPUFA status as early as during fetal life. Indeed, both maternal and child genotypes have been associated with cord plasma levels of n-6 LCPUFA precursors and ARA [34]. FADS genotypes have been shown to modulate the effect of nutrition on cognition and immune development. In a large cohort of children aged 8 who had been either breastfed or formula-fed, the intellectual quotient (IQ) of breast-fed children was higher than in formula-fed regardless of the genotype, but the most interesting result was that the beneficial effect of breastfeeding was much more pronounced in homozygous carriers of the minor allele associated with a low ability to synthesis LCPUFAs. Homozygous carriers of the minor allele performed worse than other children on a formula devoid of LCPUFAs [35]. With regard to immune development, the association between exclusive breastfeeding and asthma prevalence later in life proved to be modified by FADS genotypes. Indeed, exclusive breastfeeding for at least 3–4 months after birth had a protective effect against asthma occurrence until up to 10 years of age in individuals carrying the minor allele when compared with those who were fed a formula devoid of LCPUFAs [36]. Recently, Salas-Lorenzo et al. showed that a membrane LCPUFA level similar to the one in breastfed infants could be obtained with ARA- and DHA-supplemented formula only in major allele carriers, unlike in minor allele carriers [37]. It is noteworthy that the supplementation levels, i.e., 23 and 16.2 mg/100 kcal for ARA and DHA, respectively, may not have been sufficient to compensate for the lower desaturase activity in minor allele carriers. As suggested by Miklavcic et al., increasing the formula supplementation to ARA 34 mg/100 kcal and DHA 17 mg/100 kcal prevents the reduction in ARA due to minor alleles [38].

Further studies are still needed to clarify the biological mechanisms that underlie these FADS–nutrition interactions, all the more since taken as a whole the studies performed in the field have not led to consistent results. Nonetheless, variants in the desaturase gene introduce a new variable to be considered in the evaluation of the effects of LCPUFA supplementation on growth, development, and health of infants and young children. It is noteworthy that in vitro studies highlighted that myristic acid, a saturated fatty acid representing 9–15% of the total fatty acid content in milk, activates Δ6 desaturase [39]. In infant formulae, the fatty acid composition varies according to lipid sources [40]. In this consideration, and taking into account the vulnerable infants who carry the FADS gene associated with a low desaturase activity, developing infant formulae in which the fat blend originates from dairy fat instead of plant oils, as is usually the case, appears more relevant.

4.4. ARA/DHA ratio in infant formulae

Studies involving LCPUFA supplementation, especially the most recent ones, support a well-balanced supply of DHA and ARA from infant formulae to ensure an optimal neurologic and immune development.

To date, studies undertaken to evaluate the beneficial effects of LCPUFAs on term infant development were performed with DHA alone or with DHA and ARA. They concentrated on growth, brain development, and immune development.

With regard to growth, as previously mentioned, LCPUFA supplementation, whether with DHA only or with DHA and ARA, does not affect physical growth, neither positively nor negatively, throughout the first 2 years of life [19].

On the contrary, despite mixed results, many studies documented the importance of LCPUFA supplementation on visual and cognitive development as long as adequate levels and ratios of both LCPUFAs are provided. In regard to visual development, trials performed with formulae containing a level of DHA close to the mean one in BM, i.e., 0.32% of total fatty acids, proved to be more likely to yield an improvement in visual maturation. The latter was observed when DHA was provided alone, but the addition of ARA did not impair the beneficial effect [26,41]. Recently, the DIAMOND study, based on an RCT design, was conducted to evaluate the long-term dose–response effects of LCPUFA-supplemented formula feeding during infancy. The term infants were fed experimental formulae with three levels of DHA (0.32, 0.64, 0.96% total fatty acids) and one level of ARA (0.64% total fatty acids), to cover a range of DHA:ARA ratios found in BM worldwide. The results showed that when the sole source of nutrition for at least the first 4 months of life was the supplemented formula, infants had a better visual acuity development at 12 months of age than their counterparts from the unsupplemented control group. The beneficial effect was obtained with 0.32% DHA, but higher amounts of DHA supplementation were not associated with additional improvement of visual acuity [42]. An at least 1-year-long supplementation with DHA and ARA (ratio 1:2) results in a maturation level of vision near that of breastfed infants [43]. The global measures of cognition and general intelligence performed in children having received LCPUFAs in infancy have provided mixed results with regard to the impact of an early supplementation in life on later neurodevelopment due to the great diversity of outcome measurement tools. However, only supplementation with both DHA and ARA yields functional benefits, when observed, and the DHA:ARA ratio exerts an effect per se. Verbal IQ was reported to be lower in the study that showed a beneficial effect of the sole supplementation of DHA on visual acuity [26]. In the DIAMOND study, LCPUFA supplementation for the first 4 months of age affected some, but not all measures of cognitive functions in the long term. Positive effects of DHA and ARA supplementation were observed on several tasks related to sustained attention, filter information, rule-learning, and inhibition tasks at 3 and 5 years of age or verbal and composite IQ at 5 and 6 years of age [44,45]. It is noteworthy that in all but one task, the group fed 0.96% DHA/0.64% ARA performed less well than the 0.32% and 0.64% DHA groups but

better than the unsupplemented control group, underlying the impact of the DHA:ARA ratio [44]. Not all cognitive domains tested showed behavioral effects of DHA and ARA supplementation. At the age of 2, children in the control group had better receptive vocabulary than those in the supplementation group. The supplementation did not influence performance on standardized tests of language at 18 months, school readiness at 2.5 or 3.5 years of age, tests of spatial memory, or advanced problem-solving until 6 years of age [44]. However, from a purely conceptual point of view, it was not unexpected that a specific class of dietary nutrients like LCPUFAs may influence some, but not all, aspects of cognitive development that rely on many other influences. The better performance of LCPUFA-supplemented children on executive tasks was reflected in brain electrophysiology and multimodal brain imaging, which suggest that LCPUFAs would exert a programming effect during a critical period of human development and this effect would last until at least 8 years after supplementation ends [45,46]. The previous results go against the most recent Cochrane study, which concluded that routine supplementation of full-term infant formula with LCPUFAs cannot be recommended at this time since the majority of the studies did not show any clinically relevant effect [19]. However, the studies included were heterogenous with regard to design, methodology, and outcomes measured and did not adjust for the major impact of genetic variation, as many parameters that preclude the obtention of conclusive results from meta-analyses [47]. The supplementation duration is also a critical parameter to take into account when evaluating beneficial effects of DHA and ARA on cognitive maturation [48]. The latest report by FAO-WHO about fats and fatty acids in human nutrition concluded: "There can be little doubt about the essentiality of DHA and ARA for the brain" [5]. This report, based on a rigorous prior review of a great number of background papers, represents, as a result, an unrivalled reference document when it comes to defining lipid intakes appropriate for an optimal neurologic development.

4.5. ARA/DHA ratio and immune functions

As previously mentioned, there is also growing evidence from preclinical and clinical studies that ARA bolsters infant health through its effects on the immune system and the modulation of the inflammatory response. Feeding non-breastfed infants and young children with formulae enriched in both LCPUFAs, with ratios found in BM, alters the markers of immune functions in a direction that is closer to those of exclusively breastfed children [16,49]. Conversely, feeding infants with diets providing very high doses of n-3 LCPUFA, without adding ARA, lowers the n-6/n-3 LCPUFA ratio of the diet and leads to anti-inflammatory and immunosuppressive effects primarily by reducing the cell content of ARA [49]. This unbalanced diet is undesirable in the early postnatal period when the immune system is rapidly developing and acquiring many essential functions [49]. Intervention studies evaluating the impact of infant formulae enriched in ARA and DHA (0.34–0.72% ARA and 0.2–0.96% DHA) on health outcomes consistently reported a lower incidence of infections or allergic diseases early in life [50]. Likewise, infant formulae enriched in ARA and DHA allow for a better Th1/Th2 (lymphocytes T helpers) response after T cell stimulation, which is known to support the establishment of oral tolerance [50].

5. What is expected next?

The aforementioned studies did not cover the status of most organ systems that are influenced by ARA and its derivatives. As a consequence, only further trials accounting for these numerous functions and involving formulae with different kinds of supplementation—DHA and ARA, or either DHA alone, or ARA alone, and at doses and ratios whose the safety has been evaluated beforehand—would help dissociate the effects of ARA from those of DHA and lead to an evidenced-based conclusion that ARA addition is essential for infant and young child early optimal development that also conditions the long-term health status.

The optimal ARA:DHA ratio in infant formulae still remains to be determined. As previously mentioned, the FAO-WHO and EFSA study groups have set adequate LCPUFA intakes to meet infant and young child nutritional needs [5,6]. Both recommendations are intended for children until at least 6 months of age. No quantitative advice with regard to adequate ARA supply has been made beyond 6 months since there is considerable variation in ARA supply after the introduction of complementary feeding. Nonetheless, estimates of ARA and DHA dietary intakes from complementary foods tend to be low and depend on the economic status of the country and/or the family, with infants being most commonly weaned on food of plant origin in low-income countries [1]. For all these reasons, continuing to feed infants with formulae providing both DHA and ARA beyond 6 months of age appears more safe and suitable for an optimal growth and development.

6. Conclusion

In the last 25 years, a great deal of work addressing the role played by LCPUFAs in infant and young child health and development has been performed. Despite discrepancies in study results, there is enough conclusive evidence that only a balanced dietary supply of ARA and DHA can ensure infant and young child LCPUFA status, growth, and brain and immune development similar to those in breastfed infants. However, ARA serves a wider range of biological functions that are still to be explored. Scientific research has made it possible to improve infant formulae by developing them closer to the composition of BM. Regulations require the safety and suitability of new formulae to be convincingly demonstrated through dedicated studies before they can be placed on the market. Formulae containing DHA only, specifically at the high doses advised by the recent EFSA panel and European regulation, have not been subjected to a preclinical evaluation of nutritional adequacy and safety yet. As a result, pending the confirmation/denial that such formulae based on a composition that departs from the one of human milk is safe and suitable for infants and young children, the precautionary principle endorses the addition of ARA to infant formulae.

Declaration of interest

P. Tounian: Carrefour, Danone, Mead Johnson, Nestlé, Novalac, Nutricia, PédiAct, SILL, Sodilac.

M. Bellaiche: Danone, DSM, Mead Johnson, Nestlé, Novalac, Nutricia, PédiAct, Sodilac.

P. Legrand declares that he has no competing interest.

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