Special Article

Should formula for infants provide arachidonic acid along with DHA? A position paper of the European Academy of Paediatrics and the Child Health Foundation

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ABSTRACT

Recently adopted regulatory standards on infant and follow-on formula for the European Union stipulate that from February 2020 onwards, all such products marketed in the European Union must contain 20–50 mg omega-3 DHA (22:6n–3) per 100 kcal, which is equivalent to about 0.5–1% of fatty acids (FAs) and thus higher than typically found in human milk and current infant formula products, without the need to also include ω-6 arachidonic acid (AA; 20:4n–6). This novel concept of infant formula composition has given rise to concern and controversy because there is no accountable evidence on its suitability and safety in healthy infants. Therefore, international experts in the field of infant nutrition were invited to review the state of scientific research on DHA and AA, and to discuss the questions arising from the new European regulatory standards. Based on the available information, we recommend that infant and follow-on formula should provide both DHA and AA. The DHA should equal at least the mean content in human milk globally (0.3% of FAs) but preferably reach 0.5% of FAs. Although optimal AA intake amounts remain to be defined, we strongly recommend that AA should be provided along with DHA. At amounts of DHA in infant formula up to ~0.64%, AA contents should at least equal the DHA contents. Further well-designed clinical studies should evaluate the optimal intakes of DHA and AA in infants at different ages based on relevant outcomes. *Am J Clin Nutr* 2019;00:1–7.

Keywords: infant nutrition, breast milk substitutes, long-chain PUFAs, European Commission Formula Delegated Act 2016/127, food safety

Introduction

Breastfeeding, which is universally recommended as the optimal choice of infant feeding, always supplies both the long-chain PUFAs (LC-PUFAs) DHA (22:6n–3) and arachidonic acid (AA, 20:4n–6) (1–3). Many studies have evaluated outcomes in infants fed infant and follow-on formula containing the n–3 fatty acid (FA) DHA at amounts from 0.1% to 0.5% of total FAs

together with the n–6 FA AA, usually with higher AA amounts than those of DHA. Many infant and follow-on formulas include DHA and AA at close to worldwide mean amounts of these FAs in human milk (~0.3% and 0.5% of total FAs, respectively) (1). Infant formulas with both DHA and AA have been used worldwide for nearly 20 y without any serious concern for their safety, and benefits, e.g., for visual, cognitive, and psychomotor development, have been reported in some but not in all studies (4–7). In 2016 the European Commission adopted legislation on infant and follow-on formula in the form of a Delegated Act, which stipulated that from February 2020 onwards, all infant and follow-on formula marketed in the European Union must contain DHA at higher amounts than in currently marketed infant formulas (20–50 mg/100 kcal, approximately 0.5–1% of total FAs) without any requirement for also providing AA (8). This choice was based on a preceding opinion paper by the European Food Safety Authority (EFSA) (9). The EFSA stated in this paper that formula with DHA but no AA leads to reduced AA concentrations in erythrocytes, but no direct functional consequences would have been observed, and it was therefore not considered a necessity to add AA to infant formula (9). The European legislation also stipulates that the content of the ω-3 FA EPA (20:5n–3) shall not exceed that of DHA, based on the advice of the EFSA which emphasized that EPA contents in human milk are low and do not exceed those of DHA (9). The European legislation also rules that the content of AA shall not exceed 1% of the total fat content, and the content of all n–6 LC-PUFAs together shall not exceed 2% of total fat, which is not based on a recommendation of the EFSA (10) but on the previous European Directive on infant and follow-on formula adopted in 2006 (11). Following the new regulation, the first commercial formula products with high contents of DHA and without AA have been recently introduced in Europe.

This novel concept of infant formula composition proposed by the recent European legislation, with relatively high mandatory contents of DHA but no need to provide AA, has raised considerable concern and controversy because there is no accountable documentation of the suitability and safety of this new approach (12–15).

Therefore, the charitable Child Health Foundation (Stiftung Kindergesundheit, www.kindergesundheit.de), in collaboration with the European Academy of Paediatrics (www.eapaediatrics.eu), invited experts in this area, including previous members of the EFSA panel on dietetic products, nutrition, and allergies and of the EFSA Working Group on Dietetic Products involved in the scientific report (10) on which the recent legislation has been based (8), along with representatives of an international organization of parents, to review these questions at a workshop held on 24–25 May, 2019 at Berg near Munich, Germany. Here we report our key considerations and conclusions.

Previous Guidance on DHA and AA Supply in Infancy

Several bodies have provided recommendations on the desirable intakes of DHA and AA in infancy and early childhood, based on reviews of the existing evidence. Consistent across these bodies was consensus in recommending the provision of both DHA and AA, and for the content of DHA not to exceed the content of AA. For example, a joint report of the FAO of the UN and the WHO concluded there is convincing evidence to define adequate intakes for infants from birth to age 6 mo for AA as 0.2–0.3% of energy intake (E%, ~11–33 mg AA/100 kcal), and for DHA as 0.10–0.18 E% (~11–20 mg DHA/100 kcal) (16). The Health Council of the Netherlands set an adequate daily intake for AA of 40 mg/kg bodyweight (bw) and for DHA of 20 mg/kg bw for infants aged 0–5 mo (17). The French Food Safety Agency set an adequate intake for AA of 0.5% of total FAs (~24 mg AA/100 kcal) and for DHA of 0.32% of total FAs (~16 mg DHA/100 kcal) for infants aged 0–6 mo (18). In 2013, the EFSA defined adequate daily intakes for infants aged 0–6 mo as 100 mg DHA and 140 mg AA, whereas 100 mg DHA was recommended for the age range of 6–24 mo and 250 mg DHA + EPA at the age range of 24–36 mo (9).

In 2009 the EFSA concluded that a cause and effect relation has been established between the intake of infant and follow-on

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Abbreviations used: AA, arachidonic acid;ADA, adrenic acid; bw, bodyweight; CA, corrected age; EFSA, European Food Safety Authority; E%, percentage of energy intake; FA, fatty acid; *FADS*, fatty acid desaturase; LC-PUFA, long-chain PUFA; PC, phosphatidylcholine; RCT, randomized controlled trial.

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formula supplemented with DHA at amounts ~0.3% of total FAs and visual function at 12 mo in term infants fed formula ≤12 mo, including infants who were initially breastfed and then fed formula after weaning up to age 12 mo. The EFSA recommended that a health claim should be adopted with the wording "DHA contributes to the visual development of infants" (19).

With respect to the composition of infant formula, the previous European legislation on infant and follow-on formula stipulated the optional inclusion of DHA and AA provided that the content of DHA does not exceed that of AA (11). A further requirement was that EPA content must not exceed DHA content, and total n–3 and n–6 LC-PUFA contents must not exceed 1% and 2% of total fat content, respectively (11). Similarly, the global Standard of the Codex Alimentarius Commission of the FAO of the UN and the WHO on infant formula and formulas for special medical purposes intended for infants stipulates the optional inclusion of DHA in infant formula, provided that AA reaches at least the same concentration as DHA, whereas EPA should not exceed the DHA content (20).

Similar conclusions were drawn by international expert groups who advised that infant formula for infants born at term should provide 0.2–0.5% of FAs as DHA along with at least the same content of AA (21), or at least 0.3% of FAs as DHA and ≥0.3% as AA (22). An expert group advising the Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Uses concluded that optional addition of DHA should not exceed 0.5% of total fat intake, which has not been documented to be safe in clinical trials in healthy infants, and AA content should reach at least the DHA content, whereas the EPA in infant formula should not exceed the DHA content (23). It also emphasized that there is not sufficient documentation of the benefits and safety of the addition of DHA to infant formula at amounts >0.5% of total fat content, or of DHA without concomitant addition of AA; such formula composition was therefore expressively discouraged (23).

In conclusion, these previous guidance documents support the provision of both DHA and AA to infants, with intakes of AA reaching at least those of DHA. Some of these reports also emphasized that metabolism and FA needs during infant development are uniquely different from those in adults, and that knowledge of the metabolism and roles of these FAs in adults should not be directly extrapolated to infants.

In contrast to these reports, an EFSA scientific opinion published in 2014 (10) concluded that DHA should be added to infant and follow-on formulae in amounts similar to those provided to breastfed infants and meeting the adequate intake of 100 mg/d previously established by EFSA, but it considered the provision of AA unnecessary even in the presence of DHA, even though only 1 y before EFSA had set the adequate daily AA intake for infants in the first half-year of life as 140 mg (9).

AA Supply during Development

We reviewed the sources of AA available to the developing fetus from placental uptake and transfer from the mother, and from postnatal infant consumption of human milk. DHA and AA are preferentially supplied to the fetus compared with other FAs in the maternal circulation; however, AA transfer, unlike DHA, apparently is not related to maternal AA status and intake (24, 25). Similarly, human milk always supplies both AA and DHA. In contrast to DHA, the content of AA in human milk is much less variable and always near 0.5% of milk FAs, and it is typically higher than the milk DHA content (1–3, 26). We can only speculate about the physiological relevance of this rather stable AA provision to the fetus and infant, along with a more variable DHA supply. It is noteworthy that significant amounts of AA, along with some other n–6 LC-PUFAs, accumulate in the membranes of organs and tissues, which may be supported by a stable human milk supply. Adrenic acid (ADA, 22:4n–6), an elongation product of AA, is a significant component in lipids of all membranes studied to date. In the membrane-rich brain tissue, both n–3 and to an even greater extent n–6 LC-PUFAs accumulate rapidly in the last intrauterine trimester and exponentially during the first 2 y of postnatal life (27, 28). During this period of rapid early development, the ratio of ADA to AA in brain continues to increase such that by 2 y of age, ADA constitutes nearly half of the n–6 LC-PUFAs in brain, and n–6 LC-PUFAs exceed n–3 LC-PUFA content by far (15).

Possible Importance of AA Supply with Infant Formulas

Several studies have evaluated n–6 LC-PUFA status in infants fed formulas with and without DHA and AA, comparing results with those of infants fed human milk. These data demonstrate that both term and preterm infants fed formula without AA have declining AA status, compared with human milk–fed infants. First reported in 1982, term infant formulas without LC-PUFAs resulted in approximately half the amount of AA in infant RBC phosphatidylcholine (PC) (29). A recent study in term infants compared formulas without and with AA (0 or 34 mg/100 kcal) and with DHA (17 mg/100 kcal) and also found less than half the amount of AA (weight percentage) in plasma of infants fed the formula without AA, compared with the formula with AA (30). The addition of both LC-PUFAs to infant formulas may thus be necessary to match circulating concentrations of DHA and AA of breastfed infants (14). In the cited recent study evaluating DHA-enriched infant formulas without or with AA, lymphocyte AA was also affected (30). In addition, infants receiving formula with AA showed significantly less expression of the activation markers CD54, CD80, and CD152 and a lower number of CD20+CD54+ B cells, indicating that preformed AA supply to infants may have an immunoregulatory role on B-cell activation.

Studies in preterm infants provide supportive evidence for a role of AA in immune ontogeny. Martin et al. (31) found a 40% increase in the risk of nosocomial sepsis for every 1 mol% decline in whole blood AA in preterm infants during the postnatal period. Preterm infants diagnosed with retinopathy of prematurity, a disease characterized by dysregulated immune and inflammatory responses, showed lower serum AA concentrations than did infants without this diagnosis (32). In a very large randomized trial in >1000 preterm infants born before 29 weeks of gestation, enteral provision of a relatively high daily dose of 60 mg DHA/kg bw without AA led to an increased occurrence of bronchopulmonary dysplasia or death before 36 wk of postmenstrual age (33).

Human milk–fed term infants have ∼75 mg AA/L in plasma PC shortly after birth, an amount that is similar in infants born preterm. In preterm infants fed formulas without AA, the concentration in plasma PC declines to ∼40 mg/L and remains low from term corrected age (CA) until ∼6 mo later, before gradually increasing over the next 6 mo (34). If the formula provides n–3 LC-PUFAs (0.2% DHA, 0.3% EPA) without AA, the plasma PC AA concentration declines further to ∼30 mg/L (34). In contrast, preterm infants fed formulas with 0.43% AA and 0.1% DHA from soon after birth until 12 mo CA have a plasma PC AA concentration similar to that of infants fed human milk during the same months.

AA availability has been associated with growth of cells in vitro and of human infants (35, 36). Birth weight of preterm infants was significantly correlated with plasma AA contents (36). In preterm infants, AA concentration in plasma PC was a significant predictor of normalized weight and length achievement during the first year of life at all 5 ages assessed (2, 4, 6.5, 9, and 12 mo CA); and higher PC AA predicted larger head circumference at 2 and 4 mo CA (37). The 2 highest quartiles of plasma PC AA were associated with infant weight and length achievement near the 50th percentile for term infants, whereas infants in the 2 lowest quartiles achieved mean weight and length gains that were 1 SD lower (37). In another randomized controlled trial (RCT) in 194 premature infants given preterm formula with no DHA or AA, at 0.15% of energy intake DHA, or with 0.14% DHA + 0.27% AA, infants fed DHA + AA formula gained weight significantly faster than control infants (34.7 compared with 30.7 g/d) (38). A systematic review of 14 control trials showed no significant effect of LC-PUFA supplementation on infant weight, length, or head circumference at any assessment age, and subgroup analyses found no significant effects of supplementation with only n–3 LC-PUFAs without AA on growth measures, but the sample size of the subgroup was limited (39). In contrast, a review of 32 randomized studies, 13 in preterm infants and 19 in term infants, showed that the supply of n–3 LC-PUFAs without n–6 LC-PUFAs can reduce growth achievement in preterm and term infants, but the reported effect sizes are often modest (40). Although there is no conclusive evidence from RCTs in infants born at term comparing effects of formula feeding without and with AA on infant growth, the available data suggest that dietary AA supply may be a relevant modulator of physiological growth in infancy.

Impact of Genetic Variability

Common variants in the fatty acid desaturase (*FADS*) gene cluster modify the activity of PUFA desaturation and the composition of human blood and tissue lipids (41). *FADS* polymorphisms show large effect sizes on plasma and tissue concentrations of AA and other n–6 PUFAs, whereas there are only small and, in most studies, nonsignificant effects on DHA and other n–3 PUFAs (42). Infants with genetic *FADS* variants predicting a low activity of the Δ-5 and Δ-6 desaturating enzymes comprise about one-quarter of the infant population in Europe, but about two-thirds to three-quarters of infants in Asia and Latin America (43–46). In these infants with genetically determined low desaturase activity, AA synthesis is ineffective, therefore they develop particularly low plasma AA concentrations without a dietary supply of preformed AA (47). Studies on variations in the *FADS* gene cluster provide impressive indications for marked gene–diet interactions in the modulation of complex phenotypes such as eczema, asthma, and cognition, with some studies indicating that breastfeeding providing both preformed AA and DHA reduced asthma risk and improved cognitive outcomes in those infants with a genetically determined low formation of LC-PUFA (42). Given that genetic *FADS* variants influence primarily the formation of AA and other n–6 LC-PUFAs and have only little effect on DHA and other n–3 LC-PUFAs, it appears likely that the provision of preformed AA with breastfeeding is important for asthma risk reduction and improved cognitive development, at least in infants with genetically low AA synthesis. Owing to the major differences in genotype distribution and PUFA metabolism, it seems inappropriate to extrapolate PUFA effects observed in infant populations with predominantly European or African genotypes to populations with genetically more frequent low desaturase activities, such as Asian and Latin American populations.

How Much AA Do Infants and Young Children Receive from Food?

A review of the worldwide dietary supply of DHA and AA shows wide variability of intakes, with particularly low dietary DHA and AA intakes found in some studies in lower-income countries (48, 49). The estimated daily dietary intake of AA from food in infants older than 6 mo and in young children evaluated in 76 countries of the developing world was 65 mg/d, with the major part provided by human milk. In this study, the lowest tertile for AA intake has a higher prevalence of childhood stunting and higher infant mortality (49). Infants in the US KUDOS cohort had median AA intakes from food of only 4 and 20 mg/d, respectively, at 9 (n = 190) and 12 (n = 201) mo of age (S. Carlson, Department of Dietetics and Nutrition, University of Kansas Medical Center, personal communication, 2019). Belgian preschool children had a mean AA intake of only 17 mg/d (50). It is evident that infants will not achieve the adequate dietary intake of 140 mg/d as set by the EFSA (9) unless they are fed human milk or an infant formula providing AA.

Ratio of DHA to AA in Formula Ifluences n–6 LC-PUFAs in Brain and Appears to Have Functional Consequences

Effects of adding DHA and AA to infant formula on neurodevelopmental outcomes have been described in some but not in other studies (4). Infant formulas with different amounts of DHA and AA were evaluated in both baboons and human infants, including formulas without LC-PUFAs, or with both AA (∼0.7% of total FAs or ∼34 mg/100 kcal) and different DHA amounts, providing DHA to AA ratios of 0.5:1 and 1.5:1 (51, 52). Human infants also received a fourth formula with a DHA to AA ratio of 1:1 (52). Brain n–3 and n–6 LC-PUFAs were measured in various organs and brain regions in baboon infants (51). In baboons, plasma and RBC AA increased for both the LC-PUFA-containing formulas; however, the increase was smaller at a DHA to AA ratio of 1.5:1. A higher ratio of DHA to AA (1.5:1) induced a decrease

in brain contents of AA as well as of the other major LC-PUFAs in brain membrane lipids: n–6 ADA and n–6 docosapentaenoic acid (22:5n–6).

Human infants fed the formula with a DHA to AA ratio of 1.5:1, like baboon infants, also showed a decrease in RBC AA, with concentrations more similar to the group fed formula with no LC-PUFAs (53). Cognitive tests of these 4 groups of infants ≤9 y of age showed a similar pattern, with less favorable outcomes in infants randomly assigned to a formula with a high DHA to AA ratio: the group fed the 1.5:1 ratio of DHA to AA generally performed less well than the other 2 supplemented groups (52). On sustained attention in the first year of life, a test of rule learning requiring inhibition between 3 and 5 y, and verbal IQ at 5 and 6 y of age, the children fed formulas with a DHA to AA ratio of 0.5:1 or 1:1, but not the group fed a ratio of 1.5:1, performed significantly better than the no LC-PUFAs group. Brain evoked response potentials to a test of inhibition (Go/No-Go task) at 5.5 y and brain imaging studies at 9 y were consistent with these results in showing lower white matter volume in the anterior cingulate cortex and parietal regions in children previously fed formula providing less AA than DHA (54, 55).

Although the study did not include a group that received DHA without AA, these results show that a formula providing nearly 1% DHA and close to 0.7% AA—and thus less AA than DHA—was generally attenuating tests of central nervous function as compared with formulas providing at least as much AA as DHA. These data reinforce the concern about the safety of feeding infants high amounts of DHA without providing adequate amounts of AA.

Parents' Expectations

Representatives of the parent organization European Foundation for the Care of Newborn Infants emphasized that feeding their infants is one of the fundamental tasks for parents necessary to sustain life and to support optimal growth and development. Every parent wants to keep their child safe and protect them from harm. Because formulas for infants are the only processed foodstuff which must meet *all* nutritional requirements of the infant until appropriate complementary feeding can be established, it is critical that there is full confidence by all concerned regarding the purity of the ingredients, the appropriate composition of the formulas, and the expected health outcomes. The assumption and expectation by families are that the infant formula products on offer have been thoroughly tested in preclinical and clinical settings, and that the decision to modify formula composition is risk free and strictly regulated by regulatory bodies. Although the aforementioned considerations do not take account of the barriers and difficulties faced by researchers in meeting the expectations of families, it is important that researchers, industry, learned societies, and regulatory bodies strive to meet the parental expectations regarding first infant formula to achieve optimal health and development outcomes, while maintaining the highest standard of safety.

Conclusions

The new European regulation on infant and follow-on formulae (8) stipulates that ingredients other than those covered by the regulation may only be added to infant or follow-on formulae if the suitability and safety of such additions have been demonstrated by appropriate studies, following the guidance of scientific experts (56–60). The authors fully agree with this principle; however, in addition they also strongly support that other major modifications of the composition of infant or follow-on formulae that have no documented history of safe use need to be scientifically evaluated in preclinical and generally also in clinical studies. The need for such evaluation is underlined by the tragic experience of induction of severe adverse health effects in infants fed formula with modified composition without the addition of any new ingredients, e.g., due to reduced contents of sodium chloride or of thiamin, which both led to serious adverse effects on health and brain development (61–63).

The European regulation on infant and follow-on formulae (8) proposes a novel composition with mandatory content of very high DHA concentrations (20–50 mg/100 kcal, equivalent to about 0.5–1% of FAs) but no requirement to provide AA. This novel infant formula composition has not been evaluated in infants born at term, and there are no accountable data to document the suitability and safety of this novel concept of infant formula composition in healthy infants. This proposed formula composition deviates markedly both from the usual composition of human milk, which has never been found to provide DHA without AA, and from the composition of formula with added LC-PUFAs as evaluated in many clinical trials and as used for ∼2 decades in Europe and in many other countries around the world. Moreover, studies reviewed above indicate that the provision of high DHA intakes without balanced amounts of AA may induce undesirable effects in infants, such as reduced AA concentrations in brain tissue, suboptimal neurodevelopment, and potentially also adverse effects on growth and immune development (64). Under conditions where scientific evidence cannot resolve uncertainty regarding possible risks for exposed populations, usually the precautionary principle is applied to prevent harm (65, 66). Therefore, we recommend that infants should not be fed formula with high DHA contents but without AA unless a thorough evaluation of this novel approach has been performed and evaluated by independent scientific experts.

Recommendations for the composition of infant and follow-on formula

Based on the available information, we recommend that all infant formula and follow-on formula should provide both DHA and AA. The DHA content in formulae for infants should equal at least the mean content in human milk globally (0.3% of FAs) but preferably reach 0.5% of FAs, equivalent to the mean + 1 SD content in human milk globally (1), to cover the higher needs of some subgroups of infants, for example due to variation in genes encoding enzymes mediating PUFA metabolism. Although the minimal or optimal intake amounts of AA in infancy remain to be defined, and current evidence does not allow determining an optimal ratio of AA to DHA in the infant diet, we strongly recommend that AA should be provided along with DHA. At current formula DHA amounts up to ∼0.64% (53) we support the recommendation of the Codex Alimentarius that AA contents in formulae for infants should be at least equal to the contents of DHA (20).

Breast-milk DHA in high fish-eating regions such as Japan may contain >1% DHA. Formulae that replicate these higher DHA amounts and with AA amounts >0.7% AA have not been tested; these should be clinically evaluated before market introduction. Well-designed clinical studies should evaluate the optimal intakes of DHA and AA in infants at different ages based on relevant outcomes, such as safety, growth, neurodevelopment, and immune development. The second half of the first year of life deserves specific attention because common weaning foods during this period generally provide only small amounts of DHA and AA. We recommend investment of public research funding to enable the execution of adequately designed and powered clinical studies.

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