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

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Abstract *(244 words)*

Recently adopted regulatory standards on infant and follow-on formula for the European Union stipulate that from 2021 onwards, all such products marketed in the European Union must contain 20-50 mg/100 kcal of omega-3 docosahexaenoic acid (DHA), which is equivalent to about 0.5-1 % of fatty acids and thus higher than typically found in human milk and current infant formula products, without the need to also include omega-6 arachidonic acid (ARA). This novel concept of infant formula composition has given rise to concern and controversy since there is no accountable evidence on the 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 ARA, 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 ARA. The DHA should equal at least the mean content in human milk globally (0.3 % of fatty acids) but preferably reach a level of 0.5 % of fatty acids. While optimal ARA intake levels remain to be defined, we strongly recommend that ARA should be provided along with DHA. At levels of DHA in infant formula up to about 0.64%, ARA contents should at least equal the DHA contents. Further well-designed clinical studies should evaluate the optimal intakes of DHA and ARA in infants at different ages based on relevant outcomes.

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Key Words: infant nutrition, breast milk substitutes, long-chain polyunsaturated fatty acids (LC-PUFA), European Commission Formula Delegated Act 2016/127, food safety

List of abbreviations:

ARA - arachidonic acid

CA - corrected age

DHA - docosahexaenoic acid

EFSA - European Food Safety Authority

FADS - fatty acid desaturase

LC-PUFA - long-chain polyunsaturated fatty acids

PC - phosphatidylcholine

PUFA **-** polyunsaturated fatty acid

RBC - red blood cell

RCT - randomized controlled trial

Introduction

Breastfeeding, which is universally recommended as the optimal choice of infant feeding, always supplies both the long-chain polyunsaturated fatty acids (LC-PUFA) docosahexaenoic acid (omega-3 [n-3] DHA, 22:6n-3) and arachidonic acid (omega-6 [n-6] ARA, 20:4n-6) (1-3). Many studies have evaluated outcomes in infants fed infant and follow-on formula containing the n-3 fatty acid DHA at levels from 0.1 to 0.5 % of total fatty acids together with the n-6 fatty acid ARA, usually with higher ARA levels than those of DHA. Many infant and follow-on formulas include DHA and ARA close to median worldwide levels of these fatty acids in human milk (~0.3 and 0.5% of total fatty acids, respectively) (1). Infant formulas with both DHA and ARA have been used worldwide for nearly 20 years 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 by February 2021 all infant and follow-on formula marketed in the European Union must contain DHA at higher levels than in currently marketed infant formulas (20-50 mg/100 kcal, approximately 0.5-1% of total fatty acids) without any requirement for also providing ARA (8). This choice was based on a preceding opinion paper by the European Food Safety Authority (EFSA) (9). EFSA stated in

this paper that formula with DHA but no ARA leads to reduced ARA concentrations in erythrocytes, but no direct functional consequences would have been observed, and it was therefore not considered necessity to add ARA to infant formula (9). The European legislation also stipulates that the content of the omega-3 fatty acid eicosapentaenoic acid (EPA, 20:5 n-3) shall not exceed that of DHA, based on the advice of EFS 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 ARA shall not exceed 1% of the total fat content, and the content of all n-6 long-chain polyunsaturated fatty acids together shall not exceed 2 % of total fat, which is not based on a recommendation of 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 ARA 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 ARA, 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 NDA panel of EFSA 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 organisation of parents, to review these questions at a workshop held on 24 to 25 May, 2019 at Berg near Munich, Germany. Here we report our key considerations and conclusions.

Previous guidance on DHA and ARA supply in infancy

Several bodies have provided recommendations on the desirable intakes of DHA and ARA 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 ARA, and for the content of DHA not to exceed the content of

144 ARA. For example, a joint report of the Food and Agriculture Organisation of the United Nations and the
145 World Health Organisation concluded there is convincing evidence to define adequate intakes for infants
146 from birth to age 6 months for ARA of 0.2-0.3 % of energy intake (E%, about 11-33 mg ARA/100 kcal), and for
147 DHA of 0.10-0.18 E% (about 11-20 mg DHA/100 kcal) (16). The Health Council of the Netherlands set an
148 adequate daily intake for ARA of 40 mg/kg bodyweight (bw) and for DHA of 20 mg/kg bw for infants aged 0
149 to 5 months (17). The French Food Safety Agency set an adequate intake for ARA of 0.5 % of total fatty acids
150 (about 24 mg ARA/100 kcal), and of DHA of 0.32 of total fatty acids (about 16 mg DHA/100 kcal) for infants
151 aged 0 to 6 months (18). In 2013, EFSA defined adequate daily intakes for infants aged 0-6 months as 100 mg
152 DHA and 140 mg ARA, while 100 mg DHA was recommended for the age range of 6-24 months and 250 mg
153 DHA + EPA at the age range of 24-36 months (9).

154 In 2009 EFSA concluded that a cause and effect relationship has been established between the intake of
155 infant and follow-on formula supplemented with DHA at levels around 0.3% of total fatty acids and
156 visual function at 12 months in term infants fed formula up to 12 months, including infants who were
157 initially breast fed and then fed formula after weaning up to age 12 months. EFSA recommended that a
158 health claim should be adopted with the wording “DHA contributes to the visual development of infants”
159 (19).

160 With respect to the composition of infant formula, the previous European legislation on infant and follow-on
161 formula stipulated the optional inclusion of DHA and ARA provided that the content of DHA does not exceed
162 that of ARA (11). A further requirement was that EPA content does not exceed DHA content, and total n-3
163 and n-6 LC-PUFA contents do not exceed 1% and 2% of total fat content, respectively (11). Similarly, the
164 global Standard of the Codex Alimentarius Commission of the Food and Agriculture Organisation of the
165 United Nations and the World Health Organisation on infant formula and formulas for special medical
166 puposes intended for infants stipulates the optional inclusion of DHA in infant formula, provided that ARA
167 reaches at least the same concentration as DHA, while EPA should not exceed the DHA content (20).

168 Similar conclusions were drawn by international expert groups who advised that infant formula for infants
169 born at term should provide 0.2-0.5 % of fatty acids as DHA along with at least the same contents of ARA

(21), or at least 0.3 % of fatty acids as DHA and ≥0.3 % ARA (22). An expert group advising the Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) concluded that optional addition of DHA should not exceed levels of 0.5% of total fat intake which has not been documented to be safe in clinical trials in healthy infants, and ARA contents should reach at least the DHA contents, 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 levels above 0.5% of total fat content, or of DHA without concomitant addition of ARA; such formula composition was therefore expressively discouraged (23).

In conclusion, these previous guidance documents support the provision of both DHA and ARA to infants, with intakes of ARA reaching at least those of DHA. Some of these reports also emphasized that metabolism and fatty acid needs during infant development are uniquely different from those in adults, and that knowledge of the metabolism and roles of these fatty acids 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 breast fed infants and meeting the adequate intake of 100 mg/day previously established by EFSA, but it considered the provision of ARA unnecessary even in the presence of DHA, even though only one year before EFSA had set the adequate daily ARA intake for infants in the first half year of life as 140 mg (9).

ARA supply during development

We reviewed the sources of ARA available to the developing fetus from placental uptake and transfer from the mother, and from postnatal infant consumption of human milk. DHA and ARA are preferentially supplied to the fetus compared to other fatty acids in the maternal circulation; however, ARA transfer, unlike DHA, apparently is not related to maternal ARA status and intake (24, 25). Similarly, human milk always supplies both ARA and DHA. In contrast to DHA, the content of ARA in human milk is much less variable and always

near 0.5 % of milk fatty acids, while it is typically higher than the milk DHA content (1-3, 26). We can only speculate about the physiological relevance of this rather stable ARA provision to the fetus and infant, along with a more variable DHA supply. It is noteworthy that significant amounts of ARA, along with some other n-6 LC-PUFA, 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 ARA, 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-PUFA accumulate rapidly in the last intrauterine trimester and exponentially during the first two years of postnatal life (27, 28). During this period of rapid early development, the ratio of ADA to ARA in brain continues to increase such that by two years of age, ADA constitutes nearly half of the n-6 LC-PUFA in brain, and n-6 LC-PUFA exceed n-3 LC-PUFA content by far (15).

Possible importance of ARA supply with infant formulas

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

220 Studies in preterm infants provide supportive evidence for a role of ARA in immune ontogeny. Martin et al
221 found a 40% increase in the risk of nosocomial sepsis for every one mol% decline in whole blood ARA in
222 preterm infants during the postnatal period (31). Preterm infants diagnosed with retinopathy of prematurity,
223 a disease characterized by dysregulated immune and inflammatory responses, showed lower serum ARA
224 levels compared to infants without this diagnosis (32). In a very large randomized trial in more than a
225 thousand preterm infants born before 29 weeks of gestation, enteral provision of a relatively high daily dose
226 of 60 mg DHA per kilogram bodyweight without ARA led to an increased occurrence of bronchopulmonary
227 dysplasia or death before 36 weeks of postmenstrual age (33).

228 Human milk fed term infants have approximately 75 mg ARA/L in plasma PC shortly after birth, an amount
229 that is similar in infants born preterm. In preterm infants fed formulas without ARA, the concentration in
230 plasma PC declines to approximately 40 mg/L and remains low from term corrected age (CA) until
231 approximately 6 months later, before gradually increasing over the next 6 months (34). If the formula
232 provides n-3 LCPUFA (0.2% DHA, 0.3% EPA) without ARA, the plasma PC ARA concentration declines further
233 to approximately 30 mg/L (34). In contrast, preterm infants fed formulas with 0.43% ARA and 0.1% DHA from
234 soon after birth until 12 months corrected age have a plasma PC ARA concentration like infants fed human
235 milk during the same months.

236 ARA availability has been associated with growth of cells *in vitro* and of human infants (35, 36). Birth weight
237 of preterm infants was significantly correlated with plasma ARA contents (36). In preterm infants, ARA
238 concentration in plasma PC was a significant predictor of normalized weight and length achievement during
239 the first year of life at all five ages assessed (2, 4, 6.5, 9 and 12 months CA); and higher PC ARA predicted
240 larger head circumference at 2 and 4 months CA (37). The two highest quartiles of plasma PC ARA were
241 associated with infant weight and length achievement near the 50th percentile for term infants, whereas
242 infants in the two lower quartiles achieved mean weight and length gains that were one standard deviation
243 lower (37). In another randomized controlled trial (RCT) in 194 premature infants given preterm formula
244 with no DHA or ARA, with 0.15% energy DHA, or with 0.14% DHA + 0.27% ARA, infants fed DHA+ARA formula
245 gained weight significantly faster than control infants (34.7 vs. 30.7 g/day) (38). A systematic review of 14

control trials showed no significant effect of LCPUFA 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 LCPUFAs without ARA on growth measures, but the sample size of the subgroup was limited (39). In contrast, the review of 32 randomized studies, 13 in preterm infants and 19 in term infants, showed that the supply of n-3 LC-PUFA without n-6 LC-PUFA can reduce growth achievement in preterm and term infants, but the reported effect sizes are often modest (40). While there is no conclusive evidence from RCTs in infants born in term comparing effects of formula feeding without and with ARA on infant growth, the available data suggest that dietary ARA 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 polyunsaturated fatty acid (PUFA) desaturation and the composition of human blood and tissues lipids (41). *FADS* polymorphisms show large effect sizes on plasma and tissue levels of ARA and other n-6 PUFA, whereas there are only small and in most studies non-significant effects on DHA and other n-3 PUFA (42). Infants with genetic *FADS* variants predicting a low activity of the delta-5 and delta-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, ARA synthesis is ineffectice, therefore they develop particularly low plasma ARA levels without a dietary supply of preformed ARA (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 ARA and DHA reduced asthma risk and imporved 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 ARA and other n-6 LC-PUFA and have only little effect on DHA and other n-3 LC-PUFA, it appears likely that the provision of preformed ARA with breastfeeding is important for asthma risk reduction and improved cognitive

development at least in infants with genetically low ARA synthesis. Due 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 in Asian and Latin American populations.

How much ARA do infants and young children receive from food?

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

Ratio of DHA to ARA in formula influences n-6 LC-PUFA in brain and appears to have functional consequences

Effects of adding DHA and ARA 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 ARA were evaluated in both baboons and human infants, including formulas without LC-PUFA, or with both ARA (~0.7% of total fatty acids or ~34 mg/100 kcal) and different DHA levels, providing DHA to ARA ratios of 0.5:1 and 1.5:1 (51, 52). Human infants also received a fourth formula with a DHA to ARA ratio of 1:1 (52). Brain n-3 and n-6 LCPUFA were measured in various organs and brain regions in baboon infants (51). In baboons, plasma and

297 RBC ARA increased in both the LCPUFA-containing formulas; however, the increase was smaller at a DHA to
298 ARA ratio of 1.5:1. A higher ratio of DHA to ARA (1.5:1) induced a decrease in brain contents of ARA as well
299 as of the other major LCPUFA in brain membrane lipids, n-6 ADA and n-6 docosapentaenoic acid (DPA,
300 22:5n-6).

301 Human infants fed the formula with a DHA to ARA ratio of 1.5:1, like baboon infants, also showed a decrease
302 in red blood cell ARA, with levels more similar to the group fed formula with no LC-PUFA (53). Cognitive tests
303 of these four groups of infants up to 9 years of age showed a similar pattern, with less favourable outcomes
304 in infants randomized to a formula with a high DHA to ARA ratio: the group fed the 1.5:1 ratio of DHA to ARA
305 generally performed less well than the other two supplemented groups (52). On sustained attention in the
306 first year of life, a test of rule learning requiring inhibition between 3 and 5 years, and on verbal IQ at 5 and 6
307 years of age, the children fed formulas with a DHA to ARA ratio of 0.5:1 and 1:1, but not the group fed a ratio
308 of 1.5:1, performed significantly better than the no LC-PUFA group. Brain evoked response potentials to a
309 test of inhibition (Go-No Go task) at 5.5 years and brain imaging studies at 9 years were consistent with
310 these results in showing lower white matter volume in the anterior cingulate cortex and parietal regions in
311 children previousl fed formula providing less ARA than DHA (54, 55).

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

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318 **Parents' expectations**

319 Representatives of the parent organization European Foundation for the Care of Newborn Infants (EFCNI)
320 emphasized that feeding their babies is one of the fundamental tasks for parents necessary to sustain life
321 and to support optimal growth and development. Every parent wants to keep their child safe and protect

them from harm. As formulas for infants are the only processed foodstuff which must meet *all* nutritional requirements of the infant until appropriate complimentary 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 is that the infant formula products on offer have been thoroughly tested in preclinical and clinical settings, that the decision to modify formula composition is risk free and strictly regulated by regulatory bodies. Whilst the above 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, whilst 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 pre-clinical 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 thiamine that both lead 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 relatively high DHA concentrations (20-50 mg/100kcal, equivalent to about 0.5-1 % of fatty acids) but no requirement to provide ARA. This novel infant formula composition has not been evaluated in infants

born at term, and there is 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 ARA, and from the composition of formula with added LC-PUFA as evaluated in many clinical trials and as used for about two 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 ARA may induce undesirable effects in infants, such as reduced ARA levels 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, 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 ARA 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 ARA. The DHA content in formulae for infants should equal at least the mean content in human milk globally (0.3 % of fatty acids) but preferably reach a level of 0.5 % of fatty acids, equivalent to the mean + 1 SD content in human milk globally (1), to cover higher needs of some subgroups of infants, for example due to variation in genes encoding enzymes mediating polyunsaturated fatty acid metabolism. While the minimal or optimal intake levels of ARA in infancy remain to be defined, and current evidence does not allow determining an optimal ratio of ARA to DHA in the infant diet, we strongly recommend that ARA should be provided along with DHA. At current formula DHA levels up to about 0.64% (53) we support the recommendation of the Codex Alimentarius that ARA 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 more than 1% DHA. Formulas that replicate these higher DHA levels and with ARA levels above 0.7% ARA have not been tested; these should be clinically evaluated prior to market introduction. Well-designed clinical studies should evaluate the optimal intakes of DHA and ARA 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 since common weaning foods during this period generally provide only small amounts of DHA and ARA. We recommend investment of public research funding to enable the execution of adequately designed and powered clinical studies.

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Contribution of authors

BK and SEC drafted the manuscript, all authors reviewed the manuscript, contributed to the revision and approved the final manuscript.

Declaration of interests

PCC has acted as an advisor or consultant to DSM, Danone/Nutricia, and Cargill. SEC has been a consultant for industry related to long chain polyunsaturated fatty acids. MTC received research funding from Wyeth and Mead Johnson Nutritionals. OH is member of Scientific Advisory Boards of Hero and Semper and has reveived honoraria from Arla Foods Ingredients. JC received research funding from Mead Johnson Nutrition and has consulted for Mead Johnson Nutrition, Wyeth/Nestle, Fonterra Brands, and Ingenuity Foods. BK tends to be biased towards breastfeeding as member of the German National Breastfeeding Committee and the national programme Becoming Breastfeeding Friendly, chair of the Nutrition Committee, German Paediatric Society and President Elect, the Int Soc Research in Human Milk & Lactation. LMU - Ludwig-Maximilians-Universität Munich and it's employee BK benefit from support for scientific and educational activities from the European Commission, European Research Council, German Ministry of Education and Research, US National Institutes of Health, Government of Norway, and different healthcare and nutrition companies, predominantly as part of publically funded research projects supported by the European Commission or German government. MD received research funding from Baxter, a consultancy fee from Nutricia and speaker fees from Baxter, Nestlé, Semper, Fresenius and Abbvie. CRM is member of Scientific Advisory Boards of Prolacta Biosciences Inc, Alcresta Therapeutics and Fresenius Kabi, and consultant of Mead Johnson Nutrition. CM received funding from Abbott Nutrition. JJS received support for research and consultancy from DSM. AL received payment or honorarium for lectures from Mead Johnson and Nestlé. PT received payment from Carrefour, Blédina, Mead Johnson, Nestlé, Novalac, Nutricia, PediAct and Sodilac. UR participated in the Nestlé Nutrition Workshop Series. CMS received traveling support from Unilever, DSM, and Sight and Life. JTB, KB, NFM, MD, TD, HD, IGC, JBvG, SM, VM and CT declare no conflict of interest in relation to the content of this manuscript.

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