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

Koletzko, B., Bergmann, K., Brenna, T., Calder, P., Campoy, C., Clandinin, T., Colombo, J., Daly, M., Decsi, T., Demmelmair, H., Domellof, M., FildlerMis, N., Gonzalez-Casanova, I., van Goudoever, J. B., Hadjipanayis, A., Hernell, O., Lapillonne, A., Mader, S., Martin, C., ... Carlson, S. (2020). Should formula for infants provide arachidonic acid along with DHA? A position paper of the European Academy of Paediatrics and the Child Health Foundation. *American Journal of Clinical Nutrition*, *111*(1), 10-16. https://doi.org/10.1093/ajcn/nqz252

Published in:
American Journal of Clinical Nutrition

Publication Status:
Published (in print/issue): 01/01/2020

DOI:
10.1093/ajcn/nqz252

Document Version
Author Accepted version

Choices for adding long-chain polyunsaturated fatty acids to infant formula.

A position paper of the European Academy of Pediatrics and the Child Health Foundation

Berthold Koletzko, Karin Bergmann, J. Thomas Brenna, Philip C. Calder, Cristina Campoy, M. Tom Clandinin, John Colombo, Mandy Daly, Tamás Descsi, Hans Demmelmair, Magnus Domellöf, Nataša Fidler Mis, Ines Gonzalez-Casanova, Johannes B van Goudoever, Adamos Hadjipanayis, Olle Hernell, Alexandre Lapillonne, Silke Mader, Camilia R. Martin, Valerie Matthäus, Usha Ramakrishan, Sean JJ Strain, Conny Tanjung, Patrick Tounian, Susan E. Carlson, on behalf of the European Academy of Pediatrics and the Child Health Foundation

Affiliations:

Berthold Koletzko, LMU - Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Univ. of Munich Medical Center, Lindwurmstr. 4, 80337 Munich, Germany, and Stiftung Kindergesundheit (Child Health Foundation), Lindwurmstr. 4, 80337 Munich, Germany, berthold.koletzko@med.uni.muenchen.de

Karin Bergmann, Stiftung Kindergesundheit (Child Health Foundation), c/o Dr. von Hauner Children's Hospital, Univ. of Munich Medical Center, Lindwurmstr. 4, 80337 Munich, Germany, bergmann@kindergesundheit.de

J. Thomas Brenna**,** Dell Pediatric Research Institute, Depts of Pediatrics, of Chemistry, and of Nutrition, University of Texas at Austin, 1400 Barbara Jordan Blvd, Austin, TX; Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA, tbrenna@utexas.edu

Philip C. Calder, Human Development and Health, Faculty of Medicine, University of Southampton, Southampton SO16 6YD, United Kingdom, and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton SO16 6YD, United Kingdom, P.C.Calder@soton.ac.uk

Cristina Campoy, Dept. Paediatrics,University of Granada, Granada, Spain, ccampoy@ugr.es

M. Tom Clandinin, Dept. Agriculture, Food and Nutritional Science and Dept. Medicine, University of Alberta Edmonton, Alberta, Canada, tclandin@professorpufa.com

John Colombo, Dept. Psychology and Schiefelbusch Institute for Life Span Studies, Univ. of Kansas, Lawrence, KS 66045 USA, colombo@ku.edu

Mandy Daly, Irish Neonatal Health Alliance**,** 26 Oak Glen View , Southern Cross, Bray, CO. Wicklow, Ireland, mandy.daly@yahoo.co.uk

Tamás Decsi, Department of Paediatrics, University of Pécs, Pécs, Hungary, decsi.tamas@pte.hu

Hans Demmelmair, LMU - Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Univ. of Munich Medical Center, Lindwurmstr. 4, 80337 Munich, Germany, Hans.Demmelmair@med.uni-muenchen.de

Magnus Domellöf, Dept of Clinical Sciences, Pediatrics, Umeå University, Sweden, magnus.domellof@umu.se

Nataša Fidler Mis, Dept. Gastroenterology, Hepatology and Nutrition, University Children's Hospital, University Medical Centre Ljubljana, Slovenia, natasa.fidler@kclj.si

Ines Gonzalez-Casanova, Hubert Department of Global Health, Emory University, Atlanta, GA, USA, igonza2@emory.edu

Johannes B. van Goudoever, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Emma Children's Hospital, Amsterdam, The Netherlands, h.vangoudoever@amsterdamumc.nl

Adamos Hadjipanayis, Paediatric Department, Larnaca General Hospital, Larnaca, Cyprus and School of Medicine, European University Cyprus, Nicosia, Cyprus, adamos@paidiatros.com

Olle Hernell, Dept of Clinical Sciences, Pediatrics, Umeå University, Sweden, olle.hernell@umu.se

Alexandre Lapillonne, M.D., Ph.D., Paris Descartes University, APHP Necker-Enfants Malades hospital, Paris, France and CNRC, Baylor College of Medicine, Houston, Texas, alexandre.lapillonne@aphp.fr

Silke Mader, European Foundation for the Care of Newborn Infants, Munich, Germany, Silke.Mader@efcni.org

Camilia R. Martin, MD Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, MA USA, cmartin1@bidmc.harvard.edu

Valerie Matthäus, European Foundation for the Care of Newborn Infants, Munich, Germany, Valerie.Matthaeus@efcni.org

Usha Ramakrishnan, Hubert Dept of Global Health, Emory University, Atlanta, GA, USA, uramakr@emory.edu

Sean JJ Strain, Northern Ireland Center for Food and Health, Ulster University, Northern Ireland, 'jj.strain@ulster.ac.uk

Conny Tanjung, Pantai Indah Kapuk Hospital, Jakarta, Indonesia, mfconnytanjung@yahoo.com

Patrick Tounian, Pediatric nutrition and gastroenterology department, Trousseau hospital, APHP, Sorbonne University, Paris, France, p.tounian@aphp.fr

Susan E. Carlson, University of Kansas Medical Center, Dept. of Dietetics and Nutrition, MS 4013, Kansas City, KS, USA, scarlson@kumc.edu

Correspondence

Berthold Koletzko, Dr. med. Dr.med.habil. (MD PhD) Dres. h.c. Professor of Paediatrics, LMU - Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Univ. of Munich Medical Center, Lindwurmstr. 4, 80337 Munich, Germany, and Stiftung Kindergesundheit, Lindwurmstr. 4, 80337 Munich, Germany, office.koletzko@med.lmu.de, ph: +49 89 4400 52826

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 current formulas DHA levels and up to about 0.64%, ARA contents in formulae for infants 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 clinical outcomes.

.

Key Words: infant nutrition, breast milk substitutes, long-chain polyunsaturated fatty acids (LC-PUFA), 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 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 widely used worldwide for nearly 20 years without any serious concern for their safety, and benefits have been reported in some but not in all studies (4-6). 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 (7). 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 a preceding opinion paper of the European Food Safety Authority (EFSA) which emphasized that EPA contents in human milk are low and do not exceed those of DHA (8). 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 (9) but on the previous European Directive on infant and follow-on formula adopted in 2006 (10). 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 (11-14).

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 (9) on which the recent legislation has been based (7), 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 ARA. For example, a joint report of the Food and Agriculture Organisation of the United Nations and the World Health Organisation concluded there is convincing evidence to define adequate intakes for ARA of 0.2-0.3 % of energy intake (E%, about 11-33 mg ARA/100 kcal), and for DHA of 0.10-0.18 E% (about 11-20 mg DHA/100 kcal) (15). The Health Council of the Netherlands set an adequate daily intake for ARA of 40 mg/kg bodyweight (bw) and for DHA of 20 mg/kg bw for infants aged 0 to 5 months (16). The French Food Safety Agency set an adequate intake for ARA of 0.5 % of total fatty acids (about 24 mg ARA/100 kcal), and of DHA of 0.32 of total fatty acids (about 16 mg DHA/100 kcal) for infants aged 0 to 6 months (17). In 2013, EFSA defined adequate daily intakes for infants aged 0-6 months as 100 mg DHA and 140 mg ARA, while 100 mg DHA was recommended for the age range of 6-24 months and 250 mg DHA + EPA at the age range of 24-36 months (8).

In 2009 EFSA concluded that a cause and effect relationship has been established between the intake of infant and follow-on formula supplemented with DHA at levels around 0.3% of total fatty acids and visual function at 12 months in in term infants fed formula up to 12 months, including breastfed infants

139 fed formula after weaning up to 12 months, and it recommended that a health claim should be adopted with
140 the wording “DHA contributes to the visual development of infants” (18).

141 With respect to the composition of infant formula, the previous European legislation on infant and follow-on
142 formula stipulated the optional inclusion of DHA and ARA provided that the content of DHA does not exceed
143 that of ARA (10). A further requirement was that EPA content does not exceed DHA content, and total n-3
144 and n-6 LC-PUFA contents do not exceed 1% and 2% of total fat content, respectively (10). Similarly, the
145 global Standard of the Codex Alimentarius Commission of the Food and Agriculture Organisation of the
146 United Nations and the World Health Organisation on infant formula and formulas for special medical
147 puposes intended for infants stipulates the optional inclusion of DHA in infant formula, provided that ARA
148 reaches at least the same concentration as DHA, while EPA should not exceed the DHA content (19).

149 Similar conclusions were drawn by international expert groups who advised that infant formula for infants
150 born at term should provide 0.2-0.5 % of fatty acids as DHA along with at least the same contents of ARA
151 (20), or at least 0.3 % of fatty acids as DHA along with ARA (21). An expert group advising the Codex
152 Alimentarius Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) concluded that optional
153 addition of DHA should not exceed levels of 0.5% of total fat intake which has not been documented to be
154 safe in clinical trials in healthy infants, and ARA contents should reach at least the DHA contents, whereas
155 the EPA in infant formula should not exceed the DHA content (22). It also emphasized that there is no
156 sufficient documentation of the benefits and safety of the addition of DHA to infant formula at levels above
157 0.5% of total fat content, or of DHA without concomitant addition of ARA; such formula composition was
158 therefore expressively discouraged (22).

159 In conclusion, these previous guidance documents support the provision of both DHA and ARA to infants,
160 with intakes of ARA reaching at least those of DHA. Some of these reports also emphasized that metabolism
161 and fatty acid needs during infant development are uniquely different from adult principles, and that
162 knowledge of the metabolism and roles of these fatty acids in adults should not be directly extrapolated to
163 infants.

In contrast to these reports, an EFSA scientific opinion published in 2014 (9) 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 (8).

ARA supply during development

We reviewed the sources of ARA available to the developing fetus and infant from placental uptake and transfer from the mother, and from postnatal 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 (23, 24). 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, and typically higher than DHA (1-3, 25). 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. Adrenic acid (ADA, 22:4n-6), an elongation product of ARA, is a significant component in all membranes studied to date. For example, in brain both n-3 and n-6 LC-PUFA (to an even greater extent) accumulate rapidly in the last intrauterine trimester and exponentially during the first two years of postnatal life (26, 27). 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 (14).

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) (28). Surprisingly, a 3-fold increase in linoleic acid (18:2n-6) in one of the two infant formulas resulted in the lowest ARA percentage in RBC PC (28). 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 found less than half the amount of ARA (weight%) in plasma of infants fed the formula without ARA, compared to the formula with ARA (29). Lymphocyte ARA was also affected, and the authors proposed that ARA supply may have an immunoregulatory role on B-cell activation. The role of ARA in immune ontogeny is supported by the finding that for every one mol% decline in whole blood ARA in the postnatal period of preterm infants, there is a 40% increase in the risk of nosocomial sepsis (30). Furthermore, preterm infants diagnosed with retinopathy of prematurity, a disease characterized by dysregulated immune and inflammatory responses, demonstrated lower serum ARA levels compared to infants without this diagnosis (31).

Human milk fed term infants have approximately 75 mg ARA/L in plasma PC shortly after birth, an amount that is similar in infants born preterm. In preterm infants fed formulas without ARA, the concentration in plasma PC declines to approximately 40 mg/L and remains low from term corrected age until approximately 6 months later, before gradually increasing over the next 6 months (32). If the formula provides n-3 LCPUFA (0.2% DHA, 0.3% EPA) without ARA, the plasma PC ARA concentration declines further to approximately 30 mg/L (32). In contrast, preterm infants fed formulas with 0.43% ARA and 0.1% DHA from soon after birth until 12 months corrected age (CA) have a plasma PC ARA concentration like infants fed human milk during the same months. These data indicate that the the addition of both LC-PUFAs to infants formulas is necessary to match circulating levels of DHA and ARA of breastfed infants (13).

ARA availability has been associated with growth of cells *in vitro* and of human infants *in vivo* (33, 34). Birth weight of preterm infants was significantly correlated with plasma ARA contents (34). In preterm infants, ARA concentration in plasma PC was a significant predictor of normalized weight and length achievement during the first year of life at all five ages assessed (2, 4, 6.5, 9 and 12 months CA); and higher PC ARA

predicted larger head circumference at 2 and 4 months CA (35). The two highest quartiles of plasma PC ARA were associated with infant weight and length achievement near the 50th percentile for term infants, whereas infants in the two lower quartiles achieved mean weight and length gains that were one standard deviation lower (35). In another randomized controlled trial (RCT) in 194 premature infants given preterm formula with no DHA or ARA, with 0.15% energy DHA, or with 0.14% DHA + 0.27% ARA, infants fed DHA+ARA formula gained weight significantly faster than control infants (34.7 vs. 30.7 g/day) (36). The review of review of 32 randomized studies, 13 in preterm infants and 19 in term infants, indicate that the suppl,y of n-3 LC-PUFA without n-6 LC-PUFA can reduce growth achievement in preterm and term infants, although the reported effect sizes are often modest (37).

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 (38). *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 (39). 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 (40). 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 (41). Genetic *FADS* variants are also associated with important health related outcomes such as plasma lipid concentrations, eczema, and cognitive function (39). 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 (39). 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 (42, 43). 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 (43). 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 (44). It is evident that infants will not achieve the adequate dietary intake of 140 mg/day as set by EFSA (8) 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 (45, 46). Human infants also received a fourth formula with a DHA to ARA ratio of 1:1 (46). Brain n-3 and n-6 LCPUFA were measured in various organs and brain regions in baboon infants (45). In baboons, plasma and RBC ARA increased in both the LCPUFA-containing formulas; however, the increase was smaller at a DHA to ARA ratio of 1.5:1. The highest ratio of DHA to ARA (1.5:1) induced a decrease in brain contents of ARA as well as in n-6 ADA and n-6 docosapentaenoic acid (DPA, 22:5n-6), with DPAn-6 showing the greatest decrease.

Human infants fed the formula with a DHA to ARA ratio of 1.5:1, like baboon infants, also showed a decrease in red blood cell ARA, with levels more similar to the group fed formula with no LC-PUFA (47). Cognitive tests of these four groups of infants up to 9 years of age showed a similar pattern, with less favourable outcomes 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 generally performed less well than the other two supplemented groups (46). On sustained attention in the first year of life, a test of rule learning requiring inhibition between 3 and 5 years, and on verbal IQ at 5 and 6 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 of 1.5:1, performed significantly better than the no LCPUFA group. Brain evoked response potentials to a test of inhibition (Go-No Go task) at 5.5 years and brain imaging studies at 9 years were consistent with these results (48, 49).

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

Parents' expectations

Representatives of the parent organization European Foundation for the Care of Newborn Infants (EFCNI) emphasized that feeding their babies is one of the fundamental tasks for all parents; it is necessary to sustain life and it is necessary to support optimal growth and development. Too often parents are judged by the success or otherwise of their ability to feed their child and the process of feeding. The decisions surrounding the task can be a source of enormous stress for mothers and fathers alike.

Todays parents are better educated, better informed and have a greater understanding of the importance of the first 1000 days of an infant's life for long-term outcomes. While the decision to breastfeed or not may depend on circumstances or choice, the expectations regarding the choice of an infant formula are the same. 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. Families are often confused about the differences between the various infant formulas available on the market. The assumption and expectation by families is that the infant formula products on offer have been thoroughly tested in preclinical and clinical settings. They expect that the decision to modify formula composition is risk free and strictly regulated by regulatory bodies, that the manufacturing process is strictly controled and that the industry has learned from the mistakes of the past.

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 (7) 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 (50-54). 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 (55-57).

The European regulation on infant and follow-on formulae (7) 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 (58). Under conditions where scientific evidence cannot resolve uncertainty regarding possible risks for exposed populations, the precautionary principle is applied to prevent harm (59, 60). 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. This level of 0.5 % DHA is also equivalent to intakes reported to provide functional benefit in several clinical studies (61). 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 formulas DHA levels up to about 0.64% (47) 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 (19).

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 clinical 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.

Acknowledgements

The expert workshop that discussed the topic and developed the conclusions presented here was hosted and supported by the charitable Child Health Foundation (Stiftung Kindergesundheit, www.kindergesundheit.de) seated at Dr. von Hauner Children's Hospital, Ludwig-Maximilians-Universität,

Munich, Germany. The Foundation has received donations from Arla Foods, Dair Goat Co-operative, Danone S.A., Hipp, Koninklijke DSM N.V., Ordesa, and Reckitt Benkiser; none of these had any influencece on the programme and content of the workshop and of this manuscript. No industry observers attended the workshop.

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. 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.

References:

1. Brenna JT, Varamini B, Jensen RG, Diersen-Schade DA, Boettcher JA, Arterburn LM. Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. The American journal of clinical nutrition. 2007;85(6):1457-64.
2. Grote V, Verduci E, Scaglioni S, Vecchi F, Contarini G, Giovannini M, et al. Breast milk composition and infant nutrient intakes during the first 12 months of life. Eur J Clin Nutr. 2016;70(2):250-6.
3. Koletzko B. Human milk lipids. Annals of nutrition & metabolism. 2016;69(Suppl 2):28-40.
4. Jasani B, Simmer K, Patole SK, Rao SC. Long chain polyunsaturated fatty acid supplementation in infants born at term. Cochrane Database Syst Rev. 2017;3:CD000376.
5. Qawasmi A, Landeros-Weisenberger A, Bloch MH. Meta-analysis of LCPUFA supplementation of infant formula and visual acuity. Pediatrics. 2013;131(1):e262-72.
6. Qawasmi A, Landeros-Weisenberger A, Leckman JF, Bloch MH. Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. Pediatrics. 2012;129(6):1141-9.
7. European-Commission. Commission Delegated Regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding. Official Journal of the European Union. 2016:L 25/1.
8. EFSA-Panel-on-Dietetic-Products. Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. EFSA Journal 2013;11(10):3408.
9. EFSA-Panel-on-Dietetic-Products. Scientific Opinion on the essential composition of infant and follow-on formulae. EFSA Journal. 2014;12:106.
10. European-Commission. COMMISSION DIRECTIVE 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC. Official Journal of the European Union. 2006(L 401/1).
11. Koletzko B, Carlson SE, van Goudoever JB. Should infant formula provide both omega-3 DHA and omega-6 arachidonic acid? Annals of nutrition & metabolism. 2015;66:137-8.
12. Crawford MA, Wang Y, Forsyth S, Brenna JT. The European Food Safety Authority recommendation for polyunsaturated fatty acid composition of infant formula overrules breast milk, puts infants at risk, and should be revised. Prostaglandins Leukot Essent Fatty Acids. 2015;102-103:1-3.
13. Lien EL, Richard C, Hoffman DR. DHA and ARA addition to infant formula: Current status and future research directions. Prostaglandins Leukot Essent Fatty Acids. 2018;128:26-40.
14. Brenna JT. Arachidonic acid needed in infant formula when docosahexaenoic acid is present. Nutr Rev. 2016;74(5):329-36.
15. Food-and-Agriculture-Organization-of-the-United-Nations. Fats and fatty acids in human nutrition. Report of a Joint FAO/WHO Expert Consultation. Rome: FAO; 2010.
16. Health-Council-of-the-Netherlands(Gezondheidsraad). Dietary Reference Intakes: energy, proteins, fats and digestible carbohydrates. Publication no. 2001/19R. The Hague: Health Council of the Netherlands; 2001.
17. Agence-Nationale-de-Sécurité-Sanitaire-Alimentation -E, -Travail. Actualisation des apports nutritionnels conseillés pour les acides gras. Maisons-Alfort Cedex: ANSES; 2011.
18. European-Food-Safety-Authority. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies. DHA and ARA and visual development. Scientific substantiation of a health claim related to docosahexaenoic acid (DHA) and arachidonic acid (ARA) and visual development pursuant to Article14 of Regulation (EC) No 1924/20061S (Question No EFSA-Q-2008-211) . Adopted on 22 January 2009. The EFSA Journal. 2009;941:1-14.

19. Codex-Alimentarius-Commission. Standard for infant formula and formulas for special medical purposes intended for infants. Codex Stan 72 – 1981 Rome: Codex-Alimentarius-Commission; 2007. p. 1-21.
20. Koletzko B, Lien E, Agostoni C, Bohles H, Campoy C, Cetin I, et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med. 2008;36(1):5-14.
21. Koletzko B, Boey CCM, Campoy C, Carlson SE, Chang N, Guillermo-Tuazon MA, et al. Current information and Asian perspectives on long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy. Systematic review and practice recommendations from an Early Nutrition Academy workshop. Annals of nutrition & metabolism. 2014;65(1):i49-80.
22. Koletzko B, Baker S, Cleghorn G, Neto UF, Gopalan S, Hernell O, et al. Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group. J Pediatr Gastroenterol Nutr. 2005;41(5):584-99.
23. Larque E, Pagan A, Prieto MT, Blanco JE, Gil-Sanchez A, Zornoza-Moreno M, et al. Placental fatty acid transfer: a key factor in fetal growth. Annals of nutrition & metabolism. 2014;64(3-4):247-53.
24. Larque E, Ruiz-Palacios M, Koletzko B. Placental regulation of fetal nutrient supply. Curr Opin Clin Nutr Metab Care. 2013;16(3):292-7.
25. Fu Y, Liu X, Zhou B, Jiang AC, Chai L. An updated review of worldwide levels of docosahexaenoic and arachidonic acid in human breast milk by region. Public Health Nutr. **2016**;19:2675–87.
26. Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. The American journal of clinical nutrition. 1994;60(2):189-94.
27. Martinez M. Tissue levels of polyunsaturated fatty acids during early human development. J Pediatr. 1992;120(4 Pt 2):S129-38.
28. Putnam JC, Carlson SE, DeVoe PW, Barness LA. The effect of variations in dietary fatty acids on the fatty acid composition of erythrocyte phosphatidylcholine and phosphatidylethanolamine in human infants. The American journal of clinical nutrition. 1982;36(1):106-14.
29. Miklavcic JJ, Larsen BM, Mazurak VC, Scalabrin DM, MacDonald IM, Shoemaker GK, et al. Reduction of Arachidonate Is Associated With Increase in B-Cell Activation Marker in Infants: A Randomized Trial. J Pediatr Gastroenterol Nutr. 2017;64(3):446-53.
30. Martin CR, Dasilva DA, Cluette-Brown JE, Dimonda C, Hamill A, Bhutta AQ, et al. Decreased postnatal docosahexaenoic and arachidonic acid blood levels in premature infants are associated with neonatal morbidities. J Pediatr. 2011;159(5):743-9 e1-2.
31. Lofqvist CA, Najm S, Hellgren G, Engstrom E, Savman K, Nilsson AK, et al. Association of Retinopathy of Prematurity With Low Levels of Arachidonic Acid: A Secondary Analysis of a Randomized Clinical Trial. JAMA Ophthalmol. 2018;136(3):271-7.
32. Carlson SE. Arachidonic acid status of human infants: influence of gestational age at birth and diets with very long chain n-3 and n-6 fatty acids. J Nutr. 1996;126(4 Suppl):1092S-8S.
33. Sellmayer A, Koletzko B. Long-chain polyunsaturated fatty acids and eicosanoids in infants--physiological and pathophysiological aspects and open questions. Lipids. 1999;34(2):199-205.
34. Koletzko B, Braun M. Arachidonic acid and early human growth: is there a relation? Annals of nutrition & metabolism. 1991;35(3):128-31.
35. Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Tolley EA. Arachidonic acid status correlates with first year growth in preterm infants. Proc Natl Acad Sci U S A. 1993;90(3):1073-7.
36. Innis SM, Adamkin DH, Hall RT, Kalhan SC, Lair C, Lim M, et al. Docosahexaenoic acid and arachidonic acid enhance growth with no adverse effects in preterm infants fed formula. J Pediatr. 2002;140(5):547-54.
37. Lapillonne A, Carlson SE. Polyunsaturated fatty acids and infant growth. Lipids. 2001;36(9):901-11.
38. Glaser C, Lattka E, Rzehak P, Steer C, Koletzko B. Genetic variation in polyunsaturated fatty acid metabolism and its potential relevance for human development and health. Matern Child Nutr. 2011;7 Suppl 2:27-40.
39. Koletzko B, Reischl E, Tanjung C, Gonzalez-Casanova I, Ramakrishnan U, Meldrum SJ, et al. FADS1 and FADS2 polymorphisms modulate fatty acid metabolism and dietary impact on health. Ann Rev Nutr. 2019:in press.
40. Tanjung C, Rzehak P, Sudoyo H, Mansyur M, Munasir Z, Immanuel S, et al. The effect of fatty acid desaturase gene polymorphisms on long chain polyunsaturated fatty acid composition in Indonesian infants. The American journal of clinical nutrition. 2018;108:1135-44. .
41. Salas Lorenzo I, Chisaguano Tonato AM, de la Garza Puentes A, Nieto A, Herrmann F, Dieguez E, et al. The Effect of an Infant Formula Supplemented with AA and DHA on Fatty Acid Levels of Infants with Different FADS Genotypes: The COGNIS Study. Nutrients. 2019;11(3):(pii:E602.
42. Forsyth S, Gautier S, Salem N, Jr. Estimated Dietary Intakes of Arachidonic Acid and Docosahexaenoic Acid in Infants and Young Children Living in Developing Countries. Annals of nutrition & metabolism. 2016;69(1):64-74.

43. Forsyth S, Gautier S, Salem N, Jr. Dietary Intakes of Arachidonic Acid and Docosahexaenoic Acid in Early Life - With a Special Focus on Complementary Feeding in Developing Countries. Annals of nutrition & metabolism. 2017;70(3):217-27.
44. Sioen I, Huybrechts I, Verbeke W, Camp JV, De Henauw S. n-6 and n-3 PUFA intakes of pre-school children in Flanders, Belgium. Br J Nutr. 2007;98(4):819-25.
45. Hsieh AT, Anthony JC, Diersen-Schade DA, Rumsey SC, Lawrence P, Li C, et al. The influence of moderate and high dietary long chain polyunsaturated fatty acids (LCPUFA) on baboon neonate tissue fatty acids. Pediatr Res. 2007;61(5 Pt 1):537-45.
46. Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, Kerling EH, Thodosoff JM, et al. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. The American journal of clinical nutrition. 2013;98(2):403-12.
47. Colombo J, Jill Shaddy D, Kerling EH, Gustafson KM, Carlson SE. Docosahexaenoic acid (DHA) and arachidonic acid (ARA) balance in developmental outcomes. Prostaglandins Leukot Essent Fatty Acids. 2017;121:52-6.
48. Liao K, McCandliss BD, Carlson SE, Colombo J, Shaddy DJ, Kerling EH, et al. Event-related potential differences in children supplemented with long-chain polyunsaturated fatty acids during infancy. Dev Sci. 2017;20(5).
49. Lepping RJ, Honea RA, Martin LE, Liao K, Choi IY, Lee P, et al. Long-chain polyunsaturated fatty acid supplementation in the first year of life affects brain function, structure, and metabolism at age nine years. Dev Psychobiol. 2019;61(1):5-16.
50. Scientific-Committee-on Food -E-C, -prepared-by, Koletzko B, Saris WH, Flynn A, Palou A, Wal JM, et al. Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae. Brussels: European Commission; 2003.
51. ESPGHAN-Committee-on-Nutrition, Aggett PJ, Agostini C, Goulet O, Hernell O, Koletzko B, et al. The nutritional and safety assessment of breast milk substitutes and other dietary products for infants: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2001;32(3):256-8.
52. Aggett P, Agostoni C, Axelsson I, Goulet O, Hernell O, Koletzko B, et al. Core data for nutrition trials in infants: a discussion document--a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2003;36(3):338-42.
53. Koletzko B, Ashwell M, Beck B, Bronner A, Mathioudakis B. Characterisation of infant food modifications in the European Union. Annals of nutrition & metabolism. 2002;46(6):231-42.
54. Committee-on-Medical-Aspects-of-Food-and-Nutrition-Policy. Guidelines on the nutritional assessment of infant formulas. Report of the Working Group on the Nutritional Assessment of Infant Formulas of the Committee on Medical Aspects of Food and Nutrition Policy. Rep Health Soc Subj (Lond). 1996;$/:1-41.
55. Malloy MH. The follow-up of infants exposed to chloride-deficient formulas. Adv Pediatr. 1993;40:141-58.
56. Kaleita TA, Kinsbourne M, Menkes JH. A neurobehavioral syndrome after failure to thrive on chloride-deficient formula. Dev Med Child Neurol. 1991;33(7):626-35.
57. Mimouni-Bloch A, Goldberg-Stern H, Strausberg R, Brezner A, Heyman E, Inbar D, et al. Thiamine deficiency in infancy: long-term follow-up. Pediatr Neurol. 2014;51(3):311-6.
58. Calder PC. Functional Roles of Fatty Acids and Their Effects on Human Health. JPEN J Parenter Enteral Nutr. 2015;39(1 Suppl):18S-32S.
59. Bschir K. Risk, Uncertainty and Precaution in Science: The Threshold of the Toxicological Concern Approach in Food Toxicology. Sci Eng Ethics. 2017;23(2):489-508.
60. Blouin M, Coulombe M, Rhainds M. Specimen plastic containers used to store expressed breast milk in neonatal care units: a case of precautionary principle. Can J Public Health. 2014;105(3):e218-20.
61. European-Food-Safety-Authority-(EFSA). Scientific Opinion on the safety and suitability for use by infants of follow-on formulae with a protein content of at least 1.6 g/100 kcal. EFSA Journal. 2017.