NASPGHAN
714 N Bethlehem Pike
Suite 300
Ambler, PA 19002
215-641-9800
naspghan@naspghan.org

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Roger D. Klein, M.D., J.D., FCAP
Director
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Director Klein,

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) is pleased to have the opportunity to respond to the draft comparative effectiveness review: *Dietary Total Fat Intake and Dietary Polyunsaturated Fatty Acid (PUFA) Intake and Child Growth and Development Outcomes: A Systematic Review*.

NASPGHAN represents more than 3,000 pediatric gastroenterologists and pediatric registered dietitian nutritionists in the United States, Canada, and Mexico and is the only professional organization singularly dedicated to advocating for children with gastrointestinal, liver and nutrition-related diseases and disorders.

NASPGHAN and its members are dedicated to assuring that each child receives the best possible nutrition to optimize healthy development. NASPGHAN is pleased to have recently submitted a response to the Food and Drug Administration's (FDA) request for information (RFI) as it initiates review of infant formula nutrient requirements. The FDA's RFI, as well as this comparative effectiveness review, reflects an evolution in recent years in the understanding of the role of early nutrition to assure optimal growth, neurodevelopment, maturation of the immune system, programming of the metabolic system and of the complex interplay of nutrition with the developing microbiome. As such, NASPGHAN applauds the objective of this comparative effectiveness review with the goal of aligning dietary recommendations with the most current and comprehensive evidence.

NASPGHAN offers the following feedback on draft comparative effectiveness review:

General Comments

The title of the report, and many of the subtitles, use the language "dietary intake" or "dietary total fat intake," which may not accurately capture what the report discusses and lead to public confusion about the nature of the evidence for its findings. The report refers to both "dietary" and "supplementation." Supplementation was more predominant in the studies reviewed and discussed throughout the report. The report title and subtitles should be revised to reflect the "supplementation" component. For example, the title of the report could be modified to: "Total Fat Intake and Polyunsaturated Fatty Acid Intake Through Diet and Supplementation on Child Growth and Development Outcomes: A Systematic Review."

Introduction

Section 1.1.1. on Page 4, Table 1 includes "Common n-3 and n-6 polyunsaturated fatty acids and their sources." It is well established that plant-based oceanic materials (e.g., algae, seaweed) also have significant amounts of omega 3 fatty acids. These plant-based sources of fatty acids should be recognized and included. Cultural, allergy, and economic barriers exist, making algal DHA is a viable alternative that should be appropriately recognized.

Methods Summary

Limitations of the evidence review included the potential exclusion of relevant studies, as elaborated on below.[1] With strict selection criteria, there are significant gaps in being able to answer key questions adequately. The draft evidence review appropriately identifies key areas for future research, including more research on PUFA intake among adolescents, studies with longer exposure durations, more longitudinal studies, and greater focus on diet interventions rather than supplement interventions.

Discussion

As noted in Section 4.1, "Key Findings and Strength of Evidence," limitations of the review include significant variability in study methodologies and the lack of focused findings on important subgroups (e.g., preterm infants, individuals with chronic disease, overweight/obesity).

Specific to Key Question 4: Exposure (PUFA) Throughout Childhood, difficulties in completing a comprehensive and scientifically supported review are discussed in Decsi T et al.[2] To quote from their manuscript:

> "Opinions expressed in Cochrane reviews are usually attributed decisive importance, so there appears to be some controversy between the Cochrane opinion and the existing European recommendation of mandatory supplementation of infant formula with DHA. This controversy may be at least partially explained by the extreme complexity of the question to be addressed in RCTs. Genetic factors including the gender of the infant, environmental factors including maternal diet during pregnancy, different dosages and forms of DHA supplementation, as well as widely different methods to assess various outcome parameters may all contribute to mudding the water of research on the developmental effects of supplementing infant formula with LCPUFA."

The authors further conclude:

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[1] Deoni S et al, Early nutrition influences developmental myelination and cognition in infants and young children. Neuroimage 2018;178:649

[2] Decsi T, Marosvolgyi T, Szabo E. Docosahexaenoic Acid in Formulas for Term Infants: The Way from Pioneer Idea to Mandatory Dietary Recommendation. Life(Basel). 2023 Jun 05;13(6):05. doi: 10.3390/life13061326. PMID: 37374109.

> "In summary, the long list of potentially significant confounding variables in RCTs on DHA supplementation in infancy (Table 2) makes it understandable that no high-grade evidence was presented up to now and makes it somewhat unlikely that such evidence will be revealed in the immediate future."

The authors proceed to discuss the rationale for inclusion of docosahexaneoic acid (DHA) and (and likely arachidonic acid (ARA)) in infant formula, which balances the somewhat conflicting evidence, potential for meaningful benefit in some subpopulations and lack of any evidence of harm.

Studies have shown improved cognitive outcomes, improved visual development and reductions in allergy risk with addition of DHA and ARA to infant formula but others show no benefit. As this draft effectiveness review concludes, as well as a previous Cochrane review,[3] there is no well-established benefit but also no evidence of harm associated with addition of DHA to infant formula. The high variability in study designs and endpoints contribute to difficulties in excluding potential benefit from the addition of DHA to infant formula. Likely more important is the recognition that a subpopulation of individuals with certain fatty acid desaturase (FADS) genotypes have a more limited ability to synthesize DHA.[4] These genotypes are more common among various ethnic groups including Latinos and Asians[5] who were not included in many of the outcome studies.

DHA is well-established to not be harmful, DHA is present in human breast milk, and dietary supplementation potentially benefits visual and cognitive development. In sum, DHA fulfills criteria for mandatory supplementation as recommended by EFSA (similar to iron inclusion in infant formula to prevent iron deficiency in a subset of infants despite concerns about safety). However, EFSA neglected to require simultaneous supplementation with ARA. Most international regulations require that ARA be added in at least a 1:1 ratio when DHA is added as an optional ingredient. There is a lack of evidence that the addition of DHA without ARA is safe and suitable to support growth and development in infants.[6,7]

This evidence review concurs with other reviews regarding the inadequacy to draw definitive conclusions from the available data. A basic principle of "mass supplementation" across a population requires that there be a vulnerable subpopulation that will benefit from supplementation; that defining this subpopulation is not practical; and that supplementation with the nutrient is not associated with risk in the overall population. If the high-quality studies that include dose response evidence of developmental benefit for some infants are credible, then these criteria seem to be satisfied. As detailed in the Decsi manuscript the subpopulations include those with certain FADS genotypes, female sex, and those with maternal diets low in DHA. The AHRQ review also did not include the recent observations of both development outcomes and central nervous system myelination among infants fed formula differing in DHA levels, Deoni S, et al.[8] Although that study is retrospective, the findings provide a further validation of meaningful differences with supplementation.

In summary, we suggest the draft evidence review may have excluded important expert reviews that could help guide clinical and consumer decision-making, and that the discussion should specifically address dose response based on current evidence.

NASPGHAN's response to the FDA's request for information concerning infant formula nutrient requirements included a recommendation that the FDA convene a group of experts to consider whether DHA and ARA addition to infant formula would benefit a substantial portion of U.S. infants receiving infant formula, and, if so,

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[3] Jasani, B.; Simmer, K.; Patole, S.K.; Rao, S.C. Long chain polyunsaturated fatty acid supplementation in infants born at term. Cochrane Database Syst. Rev. 2017, 2017, CD000376

[4] Mathias RA et al, Genetic Variants in the FADS Gene: Implications for Dietary Recommendations for Fatty Acid Intake. Curr Nutr Rep. 2014.

[5] Harris DM et al, Evolution of Hominin Polyunsaturated Fatty Acid Metabolism: From Africa to the New World, Genome Biol. Evol. 11(5):1417–1430.

[6] Koletzko B et al, Should formula for infants provide arachidonic acid along with DHA? A position paper of the European Academy of Paediatrics and the Child Health Foundation, Am J Clin Nutr2020

[7] Tounian P et al, ARA or no ARA in infant formulae, that is the question. Archives de Pediatrie 2021

[8] Deoni S et al, Early nutrition influences developmental myelination and cognition in infants and young children. Neuroimage 2018;178:649

consider requiring mandatory inclusion of both DHA and ARA in infant formula to align with European DHA recommendations but to additionally require that ARA is added with at least the same concentrations as the added DHA. NASPGHAN also suggested review of newer data derived from brain MRI studies showing improved patterns of de novo myelination and cognitive outcomes in breast-fed versus formula-fed infants.

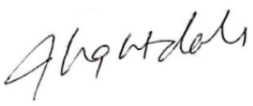
Of note, the European Food Safety Authority (EFSA) now requires the addition of 20 to 50 mg/100 kcal (0.5-1.0% of fatty acids) to infant formula based upon the concentrations found in human breast milk and upon studies in infants where benefits of DHA addition were demonstrated. EFSA does not require addition of ARA but most European formulas contain ARA. Other international regulatory agencies have continued to allow DHA and ARA as optional ingredients but have not required inclusion in infant formula.

Conclusion

We hope AHRQ will look to NASPGHAN as a resource as it completes its review. For additional information or to be connected with NASPGHAN members who can serve as topic experts to AHRQ, please contact Camille Bonta, NASPGHAN policy advisor, at cbonta@summithealthconsulting.com or (202) 320-3658.

Sincerely,

Vicky Lee Ng, MD, FRCPC
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition



Jenifer R. Lightdale, MD, MPH
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

Jeannie S. Huang, MD, MPH
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition