Dear Sir:

Research into the role of individual long-chain polyunsaturated fatty acids (LCPUFAs) is providing exciting data on infant development. The recent meta-analysis, “Supplementation of infant formula with long-chain polyunsaturated fatty acids does not influence the growth of term infants” by Makrides et al (1) in the May issue of the Journal supports the safety of adding these LCPUFAs to infant formula. In their meta-analysis, Makrides et al showed that formula supplemented with docosahexaenoic acid (DHA) and arachidonic acid (AA) support growth equal to that from control infant formula without added LCPUFAs. We are concerned, however, that readers may draw an additional, unsupported conclusion that omission of AA from LCPUFA-supplemented infant formula is acceptable.

Confusion may result from the meta-analysis tool itself. This type of statistical analysis is currently used in some settings as a way to define “best practice” approaches for a desired clinical outcome or to conclude the “evidence-based” effectiveness of a drug or a treatment on a clinical outcome. The meta-analysis by Makrides et al simply defines the results of AA on growth at 4 and 12 mo. The review does not, in this case, imply that omitting AA from infant formula is either desirable or to be considered a best practice for supplementing infant formula.

In their article, Makrides et al state that “growth is the main criterion used to assess nutritional health and well-being of infants.” We agree that growth failure is a well-recognized result of poor nutrition, but, in fact, it is a late indicator of a nutrient deficiency. As in adults, nutrient status indicates a continuum of sufficiency, spanning from overt clinical deficiency (ie, growth) to overt clinical toxicity. Before a state of overt deficiency occurs, tissue and blood concentrations of a nutrient decrease and begin limiting the physiologic processes with which it is involved. In the case of AA and infant formula, growth failure would be an overt clinical sign of a gross deficiency.

In their meta-analysis, Makrides et al report that the trials they reviewed showed a mean reduction in plasma AA of ≈25% compared with the control treatment. This may represent an earlier, and perhaps more sensitive, indication of deficiency. More important, during this early stage of reduced AA concentrations, eicosanoid metabolism may be altered and the development and maturation of immune function may be limited or altered (2, 3).

Many studies have shown that the endogenous synthesis of AA in the neonate is insufficient and that blood and tissue concentrations decrease rapidly after birth unless either human milk (which always contains AA) or an AA-supplemented infant formula is provided. Plasma and red blood cell concentrations of AA are significantly lower in infants fed unsupplemented formula than in those who are breastfed (4, 5). Supplementation of formula with preformed AA is required to achieve plasma and red blood cell concentrations that are equivalent to those of the breastfed infant (6, 7).

Makrides et al credit the contributions of DHA in visual and mental performance. However, the effect of AA and DHA on neural development needs consideration. In one of the studies reviewed, formula supplemented with a combination of DHA and AA proved to be of benefit in mental development (8). In that study, DHA plus AA improved mental function compared with unsupplemented controls, whereas DHA alone did not perform better than did the unsupplemented controls. Most important, no research has been conducted that has shown long-term advantages of formula containing DHA without AA. The combination of DHA and AA, on the other hand, has shown benefits to visual function, cognitive development, and blood pressure well beyond the period of supplementation and into early childhood (9–11). Formulas supplemented with preformed DHA and AA are now widely available to provide these nutritional benefits to infants who cannot or will not be breastfed.

In summary, the analysis presented by Makrides et al shows that LCPUFA supplementation has no detrimental effect on growth. The importance of AA as a structural and metabolically active lipid, however, was not addressed. In addition, supplementation of infant formula with a combination of DHA and AA has long-term nutritional benefits compared with unsupplemented formula. Therefore, the addition of both DHA and AA to infant formulas is important for optimal health and development in formula-fed infants.

All authors are employees of Martek Biosciences, a nutritional products company that supplies long-chain polyunsaturated fatty acids from single-cell sources to companies for use in infant formulas.

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Contaminants in fish oil

Dear Sir:

The recent review in the Journal on long-chain polyunsaturated fatty acid (LCPUFA) supplements in milk substitutes for infants discusses the risks of possible adverse effects, including delayed growth and decreased serum arachidonic acid concentrations (1). The authors did not discuss the possible relevance of contaminants of LCPUFA supplements, possibly because most of the controlled trials reviewed did not provide data on the purity of the supplement. However, persistent lipophilic pollutants, such as polychlorinated biphenyls, may biomagnify in marine foods and occur as contaminants of LCPUFA products based on fish (2). Both delayed growth and decreased serum arachidonic acid concentrations have been reported as possible outcomes of developmental exposures to polychlorinated biphenyls (3, 4). These associations were robust to adjustment for possible effects of LCPUFAs, including eicosapentaenoic acid. If fish-oil contaminants are not taken into account, the true benefits of LCPUFA supplements may be underestimated. Future studies should therefore document the purity of the products used.

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REFERENCES

Reply to C Kuratko et al and to P Grandjean

Dear Sir:

The purpose of our systematic review was to evaluate the effect of supplementing infant formula with long-chain polyunsaturated fatty acids (LCPUFAs) on the growth of term infants (1). Growth was the primary focus because it is often used by health workers and public health authorities to assess the nutritional health and well-being in preverbal children. Our review included data from 14 randomized controlled trials of formula feeding with 1846 infants and showed no significant effect of LCPUFA supplementation on infant weight, length, or head circumference at any assessment age, regardless of the type (only n–3 LCPUFA or n–3 LCPUFA plus arachidonic acid (AA)) or the source (phospholipid or triacylglycerol) of supplementation (1). The original impetus to add AA to infant formulas was based on the results of early small-scale trials that used formulas containing only n–3 LCPUFAs, which suggested that preterm infants fed formulas supplemented with n–3 LCPUFAs alone had lower plasma AA concentrations and weighed less and were shorter than preterm infants fed standard unsupplemented formulas (2–4). Although term infants fed n–3 LCPUFAs alone also had a lower AA status, our data clearly show that their growth is not compromised (1).

Kuratko et al from Martek Biosciences, who market AA and docosahexaenoic acid (DHA) supplements for infant formula, do not dispute our findings, but they are concerned that readers may interpret these findings to indicate that AA supplementation of infant formulas is unnecessary and suggest that AA may be required for neurologic and immune development. This issue was not an objective of our review and, therefore, was not extensively discussed. However, few trials have been specifically designed to assess the health effects of AA supplementation. Only 3 trials involving term infants compared DHA plus AA supplementation with n–3 LCPUFA supplementation alone and a control (5–7). Two of the 3 trials involving >200 infants found no differences in either visual or neurologic outcomes through 2 y of age (5, 7). Only one study involving 68 infants reported a benefit of DHA plus AA supplementation at a single assessment age (6). We are aware of no published trials that assessed the addition of only AA to infant formula. Definitive statements regarding the specific health effects of AA can only be made after a sufficient body of evidence is aggregated from appropriately designed randomized controlled trials with sufficient power to detect effects if they are there.

The issue of environmental contaminants in LCPUFA supplements for infant formulas and their influence on growth was not specifically addressed in our review. No published data regarding concentrations of lipophilic pollutants or heavy metals in infant formulas are available. However, our discussions with the infant formula manufacturers that provided data for our systematic review indicated that, although highly purified oils are used in the manufacture of infant