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Comment on the Vitamin E Content in Infant Formulas, Follow-On Formulas, and Formulas for Low Birth Weight Infants

The addition of long-chain polyunsaturated fatty acids to infant formulas has raised concerns about a possible increased risk of oxidative damage both to formula components and to the infants fed these products. Vitamin E, the principal lipid-soluble biologic antioxidant, is composed of a mixture of several derivatives of tocol and tocotrienol (1,2). Sufficient availability of vitamin E is of major importance for the response to oxidative stress that may damage lipids and lipoproteins, proteins and enzymes, and DNA, as well as membrane systems and their functions(3). Such oxidative stress and damage appear to be important in the pathophysiology of many disorders, including retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary disease, haemolytic anemia, chronic liver disease, malnutrition, and infection. A key factor in the development of such diseases is the relative balance of the oxidative stress and intrinsic antioxidant defense mechanisms. Thus, low birth weight infants, in whom the latter mechanisms might be inadequate, are at particular risk.

The Committee has previously commented on the content of vitamin E in infant formulas, follow-on formulas, and formulas for low birth weight infants(4). Both the Committee (4) and a European Union directive (5) have advised that infant formulas and follow-on formulas should contain a minimum content of vitamin E calculated on the basis of their linoleic or total polyunsaturated fatty acid (PUFA) content. This is irrespective of the PUFA composition of formulas, and concern has arisen about the safety and adequacy of such a generalised recommendation in view of the variable content of PUFA in infant formulas and the recent introduction of added long-chain polyunsaturated fatty acids (LCP), which may be more susceptible to oxidation and consequently may lead to an increased use and degradation of vitamin E under certain conditions(6,7). For example, several studies have produced results showing that fish oils containing highly unsaturated □-3 LCP reduce vitamin E plasma concentrations(8-10).

Results of studies in vitro have shown that as the number of double bonds in a fatty acid molecule increase from 1 to 6, the relative maximum rate of auto-oxidation of individual, pure fatty acid methyl esters at 37 °C increase in the ratios 0.025:1:2:4:6:8 (11). Witting and Horwitt (12) fed tocopherol-deficient rats with mixtures of unsaturated fatty acids and used creatinuria as evidence of muscle membrane lipid peroxidation. Based on this approach, they calculated that the relative rates of peroxidation of mono-, di-, tri-, tetra-, penta-, and hexaenoic fatty acids would respectively correspond to vitamin E requirements of 0.3, 2, 3, 4, 5,
and 6 mg □-tocopherol equivalents per gram PUFA. There are no comparable systematic studies in humans, but it appears reasonable to calculate the relative vitamin E requirement on the same basis of relative sensitivity to peroxidation of the known dietary PUFA content and composition.

Thus, on the basis of a vitamin E content of 0.5 mg/g linoleic acid, as recommended by the European Union (5) the advisable vitamin E content of formulas for infants can be determined taking into account the number of unsaturated bonds provided by the PUFA content. On this basis, 140.2 mg of □-tocopherol equivalents would be needed to protect 1 mol of linoleic acid, which in turn represents 70.1 mg of vitamin E per unsaturated bond in 1 mol PUFA. This value can be used to calculate vitamin E content relative to the contents of other fatty acids- for example, as follows:

- 0.5 mg vitamin E/g linoleic acid
- 0.75 mg vitamin E/g □-linolenic acid
- 1 mg vitamin E/g arachidonic acid
- 1.25 mg vitamin E/g eicosapentaenoic acid
- 1.5 mg vitamin E/g docosahexaenoic acid

However, the information outlined before may be too limited to justify such a complicated approach. As implied above, there is no conclusive evidence to suggest that there is a strictly linear relationship between the number of double bonds of ingested PUFA and the requirement of antioxidants. In fact, lipid peroxidation was reported to increase exponentially, rather than in a linear fashion, with rising PUFA contents of cell membranes(13). However, at high tocopherol tissue contents, the increase of requirements with higher PUFA intakes may be relatively lower because a higher proportion of oxidised tocopherol may be regenerated (14). Furthermore, it is generally assumed that there is a basal vitamin E requirement irrespective of PUFA intake(3,15,16).

At this time, precise conclusions on the infantile tocopherol requirement under different circumstances cannot be drawn, partly because assessment of tissue antioxidant status in vivo is difficult, and plasma □-tocopherol levels are not closely related to indicators of lipid peroxidation(2,10,17). This variability may arise partly from the nature of the fatty acids in the diet, the effects of other pro-oxidants (e.g., iron and copper) and antioxidants (e.g., tocopherols, ascorbic acid, retinol, and □-carotene) and further influencing factors, such as the total amount of PUFA and lipid in the diet, which influence the bioavailability of vitamin E (8,18). Under certain physiological circumstances, such as in very low birth weight infants exposed to major oxidative stress, or chronic cholestasis, vitamin E requirements may exceed the supply from human milk or infant formula.

In conclusion and in consideration of these uncertainties, the Committee maintains its previously issued recommendations of vitamin E contents in formulas □0.9 mg/g PUFA, but no less than 0.6 mg/100 kcal)(4). These minimum levels should suffice to cover the theoretically higher tocopherol requirements in formulas with added LCP not exceeding the maximum LCP levels recommended in Europe(4,19).

REFERENCES


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