Folic acid nutrition: what about the little children?

Dear Sir:

Two articles (1, 2) in the January issue of the Journal thoroughly document the sources of folic acid used by the US adult population, but, as pointed out in Rosenberg’s editorial (3), these studies raise other questions. More than 12 y after the introduction of mandatory fortification, it was disappointing to read that, even with the inclusion of intake from ready-to-eat (RTE) cereals and dietary supplements, ~1 in 6 women of childbearing age are still not meeting the estimated average requirement for folate (1). Before we assume that this can simply be corrected by increasing the amount of folic acid added to flour, we have to note another finding (1): ~5% of US women and men aged ≥50 y had total folic acid intakes above the Upper Limit (UL) of 1 mg. Although Yang et al (2) seek to reassure us that it is only those who take supplements who exceed the UL, it is important to note that they only report on adults older than 19 y. Studies that have looked at all ages found that the group with by far the highest serum folate concentrations in the United States in 1999–2000 was children between the ages of 3 and 11 y (4, 5). The concentrations in children are ≥70% higher than those in adults younger than 60 y. Children aged 3–5 y had a geometric mean serum folate concentration of 45.5 nmol/L; in those aged 6–11 y the concentration was 43.8. The next highest concentration (39.4 nmol/L) was found in those aged ≥60 y, whereas in adults aged 20–39 y this concentration was only 26.2 nmol/L (4). It is noteworthy that in those aged ≥60 y, the new study (2) shows that 58% of those eating RTE cereals and taking supplements had serum folate concentrations >45 nmol/L, equivalent to an intake of >800 μg/d according to the formula of Quinlivan and Gregory (6). After mandatory fortification, young children (age 4–11 y) also showed high folate concentrations: in the National Health and Nutrition Examination Survey (NHANES) 1999–2000, 42% had serum folate concentrations >45 nmol/L, although this proportion declined to 19% in the survey carried out in 2003–2004 (5). The Quinlivan formula was obtained for adults so it cannot easily be applied here, but it is likely that many children are today consuming more than the Institute of Medicine’s UL for children of 300–400 μg/d. These recent articles (1, 2) do not examine the sources of folic acid in children, and so we have no idea whether these high concentrations are related to flour fortification (ie, through amount of flour products consumed by the child), to the child’s choice of RTE cereal, or to the use of supplements. Multivitamin supplement use is surprisingly common and is reported in 43% of children aged 2–4 y (7). Another study has shown that noninfant cereals and supplements are the 2 most important sources of folate in children aged between 1 and 2 y, making up 34% of the total folate intake (8).

Why should we be concerned about the prevalence of very high folate concentrations in young children? From birth to adolescence, there is a 4-fold increase in the volume of the human brain. This reflects anatomic changes that underlie the development of higher brain functions, such as the remodeling of synaptic connections and the deposition of myelin (9). These processes are susceptible to environmental factors, and folate may well be one of these factors. Adequate folate status is clearly required for the development of the neural tube and for later brain development (10), but we simply do not know whether or not high concentrations of folate, and possibly exposure to unmetabolized folic acid, might influence brain development adversely, perhaps through epigenetic mechanisms (11).

For these and other reasons, we need to know where the folate comes from that gives young children such high concentrations after mandatory fortification. If fortification of flour has raised the baseline amount of intake such that children might be harmed, then we may need to reconsider voluntary fortification of RTE cereals and/or the use of folic acid–containing supplements in children.

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REFERENCES
Critique on equations of net endogenous acid production (NEAP) and indirect proof of constant organic acid excretion

Dear Sir:

In their recent article, Ströhle et al (1) address acid-base balance of diets in the light of historical hunter-gatherer lifestyles using formulas as developed by Kleinman and Lehmann (2) and as used by Sebastian et al (3), which have been under recent criticism, especially in regard to the organic acid component (4). Without referring to this criticism, the authors have made an effort to justify the formulas exactly on points criticized, but not in clear elucidation of the shortcomings of the formulas but a continued justification.

The authors state that the organic component is predictable from the unmeasured anion content (mEq/d) of the diet. In other words, diet is the determinant in estimating “organic acid production” (2, 3), a historical term also under indirect criticism (4), with which the authors make an apparently minor semantic correction and replace it with “organic acid excretion,” with the explanation that organic anions are metabolized to bicarbonate when not excreted. That is to say that the formula, even if developed for endogenous “organic acid production” (2), disregards the partial coefficient of endogenous organic acid production in capturing only the dietary partial coefficient of organic acid excretion and hence overestimates the alkalinity of a net alkaline diet (4). That is, the formula works but only when the diet is net acid producing and estimates not “organic acid production” but “organic acid excretion” on net acid–producing diets (4) in an adult age group (ie, inadequate for children and adolescents) (5) and within a broad definition of health (4).

Independent studies have reliably shown that there is organic acid excretion even on net alkaline diets (6, 7). This has been explained by a ketoadic production–excretion on net alkaline diets, although not on net acid diets (7, 8), which would allow constant organic acid production corrected for body size (4, 5, 9), regardless of whether the diet is net alkaline or acidic (4, 6–8). Instead of accepting the limitation of this formula (4), the authors provide a convoluted correction by defining 4 whole-body fat percentages—3%, 10%, 15%, and 20%—in reference to net acid excretion (NAE) as indexed by net endogenous acid production (NEAP). In effect, the authors state that as fat increases, the coefficient of plant to animal food decreases; in other words, NEAP decreases. Indeed, the authors undertake a covert correction for the unaccounted endogenous ketoacid production (4) without ever stating it. A retraction from an earlier original research finding (3), which reported that most hunter-gatherer diets were net alkali producing, to presently report in this study the very opposite, ie, that most hunter-gatherer diets would have been net acid producing, not once attending to the basic flaw in the formulas (4) that led to 2 completely different study results, is a bit mistaken. Furthermore, the use of artificial terminology such as plant-to-animal food ratio, at least in terms of core acid-base dynamics, is also misleading: it would be enough to call it food. Finally, the observation of a relatively constant intercept value for the authors’ published equations 3, 4, 5, and 6 hints at a constant organic acid excretion corrected for body surface area (4–6, 9). I thank the authors for providing the proof for which I have been working.

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Reply to AD Smith

Dear Sir:

We thank Smith for his letter. We appreciate his thoughtful review of and response to our article related to folic acid intake in adults and his identification of the gaps in our knowledge regarding the need for similar information about children (1). We agree that we need to know more about how the different sources of folic acid among children are associated with usual daily intake of folic acid and folate status after fortification. We have been working to answer these important questions and have just completed analyses in children. In addition, we are using newly available data and techniques on the basis of the amounts of folic acid added to enriched cereal grain products, supplements, and ready-to-eat cereals. We anticipate that future publication of these analyses will address many of the key questions raised by Smith.

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