kinetics both during long-term intake of supplements of folate, folic acid, or both and after cessation of such supplementation, which would, by necessity, involve dynamics between RBC kinetics and whole-body folate kinetics.

Quinlivan further comments that a steady state of RBC folate may have been reached between weeks 16 and 24. In our intervention study, blood drawings were performed every 4 wk, and RBC folate significantly increased between week 16 and week 20 and between week 20 and week 24 (4). This continuous increase was observed in all 3 supplementation groups that received either 400 μg folic acid/d, 416 μg [6S]-5-methyltetrahydrofolate/d, or 208 μg [6S]-5-methyltetrahydrofolate/d (4). To our knowledge, no intervention study has yet been conducted to measure the long-term effect of supplementation with folate, folic acid, or both on saturation kinetics of RBC folate. To date, the longest intervention trials lasted 24 wk, and neither of those trials (4, 5) could determine a plateau in RBC folate concentration. Meanwhile, Quinlivan states that it will take ≥21 wk for RBC folate to reach steady state. He explains that “plateau RBC folate enrichment may be further delayed by the amount of time it takes for the RBC progenitor cells, presumably in the bone marrow, to reach maximum enrichment.” This statement supports our hypothesis that RBC folate concentrations plateau later than after 24 wk of supplementation.

In conclusion, we wish to emphasize that our model is in fact a testable hypothesis that suggests a possible description for the behavior of RBC folate during and after long-term supplementation with folate, folic acid, or both. The appearance of RBC folate in the model is partly confirmed by 2 independent studies, and the kinetic model for RBC folate elimination is currently being tested in a long-term intervention trial.

Neither of the authors had a personal or financial conflict of interest.

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REFERENCES

Ensuring the quality of vitamin A capsules used in supplementation programs

Dear Sir:

We are writing to comment on a letter by Newton et al (1) that was published recently in the Journal. The authors raised important questions about the issue of the quality of vitamin A capsules used in the trial they discuss in the letter; however, their findings cannot be generalized to vitamin A supplementation programs.

Together, the United Nations Children’s Fund (UNICEF) and Micronutrient Initiative (MI) provide >95% of the global supply of vitamin A capsules. Therefore, they can confirm that >95% of the 100 000–IU and 200 000–IU vitamin A capsules manufactured, procured, and delivered through child survival programs and other public health programs to children <5 y old in >100 countries undergo rigorous quality-assurance procedures.

The soft-gel vitamin A capsules supplied by UNICEF and MI are in the World Health Organization, UNICEF, and International Vitamin A Consultative Group (WHO/UNICEF/IVACG)-recommended dosages of 100 000 and 200 000 IU. They also are manufactured according to strict specifications set by the WHO, UNICEF, and MI and are very closely monitored for quality assurance at the point of production and onward for distribution to countries.

Because the effect on child survival of vitamin A supplementation programs relies heavily on the quality of the supplementation itself, the specifications and procedures are taken very seriously. Before a vitamin A capsule supplier is selected, it must show that its product, in its defined packaging, has undergone a rigorous stability testing in the laboratory, in accordance with guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Through this process, we are assured of their stability and performance throughout their shelf life in field conditions, which can include high temperatures and humidity. All capsule manufacturers are also required, through regular authorized Good Manufacturing Practice (GMP) inspections by UNICEF, to ensure that the product is manufactured in accordance with WHO GMP guidelines. Moreover, random sampling and testing of the capsules by UNICEF’s Supply Division on receipt from the suppliers validates the accompanying certificates of analysis, and past sampling and testing of capsules showed satisfactory and reassuring performance. In the unlikely event that problems arise in the field, UNICEF and MI have stringent processes in place to follow through on the batches in question and to investigate breaks in the supply chain process all the way back to the manufacturer.

However, despite the assurances of performance in the laboratory, we agree that it is very important to periodically assess on a larger scale the retinol stability of vitamin A capsules that have been exposed to real field conditions. For this reason, MI in collaboration with UNICEF is in the process of systematically collecting samples of capsules that have been in the field since 2004 from 20 countries for independent laboratory analysis. Newton et al also raised the very important point that all stakeholders involved in vitamin A supplementation programs, from manufacturer through purchaser to end user, should remain vigilant against any practices that will compromise product quality.
We therefore believe that the quality assurance systems currently in place will continue to reinforce the current high level of confidence in vitamin A supplementation programs and will allow us to focus on increasing the coverage of these life-saving supplements so that more children around the world have a chance to reach—and exceed—their fifth birthday.

Neither of the authors had a personal or financial conflict of interest.

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Pentadecanoic acid (15:0), milk, and ischemic heart disease

Dear Sir:

Several studies have shown that 15:0 is an acceptable marker for the dietary intake of dairy fat (1, 2), and Qi Sun et al (3) have now reported on 15:0 and ischemic heart disease (IHD). Estimations of this fatty acid were made in samples of plasma that had been collected at baseline from 166 women in the Nurses’ Health Study cohort who later experienced a nonfatal myocardial infarct or died from IHD and from 327 control women who had been free of IHD at the time of the cases’ diagnosis. The adjusted risk for IHD in the third of the women with the highest plasma 15:0 concentrations, relative to that in the third of the women with the lowest levels, was 2.36 (95% CI: 1.16, 3.89).

This result imply a very high vascular risk from dairy consumption, but it is inconsistent with the results for 15:0 made in another cohort. Thomas et al (4) conducted fatty acid analyses of adipose tissue taken from the anterior abdominal wall of 59 men within the Caerphilly cohort (5), who had experienced a silent infarct (echocardiographic evidence of infarction with no relevant symptoms) and from 61 matched control men who had had neither symptoms nor echocardiographic evidence suggestive of infarction. The mean weight of 15:0 as a proportion of total fatty acids in the control samples was 0.49%, and the mean (±SE) difference in 15:0 between cases and controls was −0.01 ± 0.02%.

Wolk et al (2) comment that, in relation to coronary artery disease, “we do not really know whether the biomarker (15:0) or intake estimates are superior... both are informative.” Furthermore, in their article on 15:0, Smedman et al (1) comment on the fact that relations between the intake of fat from milk products and a number of vascular risk factors are all in a favorable direction. These comments indicate that it would be unwise to base conclusions about milk and dairy products and vascular disease on plasma or adipose tissue concentrations of 15:0 alone.

In fact, the coronary heart disease risk of milk consumption within the Nurses’ Health Study cohort had already been reported on, using estimates based on food-frequency questionnaires (6). The risk in the fifth of women with the highest consumption of milk, relative to the risk in the fifth with the lowest milk consumption, was 1.67 (95% CI: 1.14, 1.90) for whole milk and 0.78 (95% CI: 0.63, 0.96) for skim milk. Twenty percent of the women in this cohort had been consuming whole milk (3), and an estimate of the relative risk from milk consumption within the total cohort can be assumed to have been about 1.06 (95% CI: 0.90, 1.25). This is markedly different from the estimate by Qi Sun et al (3) based on 15:0 concentrations in selected women within the same cohort.

Estimates of vascular risk associated with milk and or dairy consumption, using a variety of dietary enquiry methods, including 7-d weighed food intake records, have been made in a number of prospective studies (7, 8). These estimates were based on milk intake, dairy food intake, and dairy calcium intake as surrogates for milk consumption. The subjects totaled almost 400 000, and the number of incident vascular events was >8000. The risk estimates reported are all statistically homogeneous, and, for the most part, the studies had been conducted before fat-reduced milks became popular. A meta-analysis of the results gives an overall estimate of vascular risk in the subjects with the highest milk or dairy intake (usually one fifth) of 0.87 (95% CI: 0.74, 1.03) for IHD and 0.83 (95% CI: 0.77, 0.90) for stroke, relative to the risk in the fifth of subjects with the lowest intakes.

On the basis of all of this evidence, it seems inappropriate to accept an estimate of IHD risk based on plasma concentrations of 15:0 to be relevant to the health consequences of milk and dairy food consumption.

All authors stated that they had nothing to declare. All are, and have been, independent research workers, and no funding for the work described in this letter was received.

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