



Scientific Advisory Committee on Nutrition

**Folate Subgroup  
Meeting held on Friday 10th September 2004  
at the FSA, Aviation House, Conference Room 2.**

**Attendees**

**Chair:** Professor Sheila Bingham  
**Members:** Professor Alan Jackson  
Dr Anthony Williams  
Mrs Christine Gratus  
Dr Anita Thomas (apologies)

**Secretariat:** Dr Alison Tedstone (FSA)  
Dr Peter Sanderson (FSA)  
Ms Lynn Burns (FSA)  
Dr Sheela Reddy (DH)

**Chairs' introduction and welcome**

1. The Chair defined the purpose and background to the meeting. At their horizon-scanning meeting SACN had requested an update on folate and disease prevention. The purpose of the meeting was to: consider the evidence that has arisen since the COMA report, Folic Acid and the Prevention of Disease (Department of Health, 2000); advise on any gaps in the evidence base, with particular reference to the issue of folic acid masking vitamin B<sub>12</sub>-deficiency; and consider when and how to review the previous COMA risk assessment.

**Discussion paper: folate and disease prevention - an update.**

2. The Subgroup discussed the paper. It was noted that in those countries where mandatory fortification had been introduced – Canada, Chile and US – a reduction in neural tube defect (NTD)-affected births had been reported.
3. The Subgroup noted that the rates of NTD-affected births for Scotland, Northern Ireland, Wales and England varied considerably, with populations in Scotland and Northern Ireland having higher rates than in England.
4. The masking of vitamin B<sub>12</sub>-deficiency by folic acid was discussed. Vitamin B<sub>12</sub>-deficiency causes anaemia and neuropathy. The anaemia may be resolved by giving folic acid, but the neuropathy is not.

5. The Subgroup noted that with regard to the masking of vitamin B<sub>12</sub>-deficiency by folic acid, doses of folic acid of less than 1mg/d were safe. The references for this are cited in the EVM report, and this should be included in the paper.

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6. Since the COMA report there has been significant debate surrounding the vitamin B<sub>12</sub> status of the elderly. In those countries that have introduced mandatory fortification, however, there appears to be no monitoring, pre- and post-fortification, of changes in neuropathy due to vitamin B<sub>12</sub>-deficiency; the focus of any monitoring has been on changes in the rates of NTD-affected births. Some studies have monitored changes in vitamin B<sub>12</sub> plasma concentrations and anaemia in the elderly pre- and post-fortification; these observed an increase in folate plasma concentrations, but no difference in vitamin B<sub>12</sub> plasma concentrations or the incidence of anaemia.
7. The proposed effect of periconceptual folic acid supplementation on the risk of increased multiple birth was discussed. It was noted that Chile and US have not reported a difference in multiple birth rate since fortification.
8. The relationship between folate and non-communicable chronic diseases was discussed. It was noted that in the COMA report the available evidence was considered insufficient to draw any conclusions of the relationship between folate and cardiovascular disease. Since then, however, more evidence has become available. The Subgroup discussed the three meta-analyses of total plasma homocysteine (tHcy) and cardiovascular disease. It was noted that the Wald et al., meta-analysis also included the methylenetetrahydrofolate reductase (MTHFR) polymorphism evidence. It was noted that the relationship observed between the common MTHFR polymorphism and cardiovascular disease (CVD) risk was less clear for colo-rectal cancer risk.
9. The Subgroup discussed the relationship between folate and cognitive function. It was noted that although there is some evidence linking folate and other B vitamins with cognitive function and Alzheimer's disease, a Cochrane review of four randomized trials concluded there was no evidence of an effect of folic acid supplementation on cognitive decline. It was also noted that these trials were generally small studies.
10. The Subgroup requested that the prospective nested case-control studies be included with the prospective studies in tabular format.

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11. The issue of whether to consider the dietary reference values for folate was raised. It was noted that in the USA the dietary reference value for folate was increased to reflect doses that reduce NTD-affected births, and these levels were unattainable without fortification. The Subgroup discussed what the outcome of significance for the dietary reference values (DRV) should be.
12. The issue of overage with regard to folic acid fortification in the USA was discussed. It was noted that it has been estimated that the USA population is receiving more folic acid than was intended based upon the modelling studies used to define the level of fortification. The Subgroup requested this be included in the report.

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13. Possible adverse effects of the periconceptual supplementation of women with folic acid were discussed. It was noted that a small literature, of largely animal work, had suggested possible adverse effects.

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14. The evidence investigating the relationship between dietary folate and CVD risk was discussed. While some prospective studies suggest a small benefit of dietary folates on CVD risk, the results from two randomized controlled trials (RCT) have suggested no effect; also, RCTs investigating the effect of folic acid supplementation on restenosis after stent surgery had shown both positive and negative effects. Concerns had been expressed whether the trials investigating the effect of folic acid supplementation on CVD had sufficient power to detect an effect. It was noted that a large RCT, SEARCH, would report in the next couple of years. Questions were also raised about the duration of the earlier studies and the use of large doses of B vitamins – as this would make extrapolation difficult. It was also noted that no long-term studies of sufficient duration in the general population for folic acid and CVD were planned.
15. The question of whether tHcy is marking the process related to the development of CVD or whether it is involved directly as a causative factor as part of a critical metabolic chain leading to CVD was discussed. It was noted that it is important to understand whether tHcy plays a specific role in the development of CVD. The association of MTHFR genotype with CVD, especially in subjects with low folate status, lends support to the possibility of folate playing a direct role in CVD.
16. The Subgroup considered that currently evidence was not sufficient to prove causality or to justify intervention with folic acid. This will have to await the outcome of the further intervention trials.
17. It was noted that the evidence base examining the relationship between folate and cancer was less than that for CVD. Some studies suggest a different relationship between natural folates and folic acid in the development of cancer, and the subgroup requested the papers which provide evidence for this difference.

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18. The issue of confounders was discussed in relation to prospective epidemiological studies, e.g. the extent to which consumption of folates might be marking the intake of fruit and vegetables and therefore the need to adjust for fruit and vegetable intake. It was noted that the USA studies controlled for a wide range of variables including fibre. It was noted that there are important non-plant dietary sources of folates, such as liver.
19. The Subgroup wished to review the available evidence examining the relationship of dietary folic acid/folate and the incidence of certain cancers. It was noted that no intervention studies had as yet been conducted in this area. Possible limitations in the use of the recurrence of polyps as a surrogate end-point for colo-rectal cancer were noted, as only a small proportion of polyps go on to become malignant.
20. The Subgroup discussed the relationship between dietary folate and cognitive function. The evidence base was considered insufficient to draw firm conclusions

from at this stage. It was noted that diet and cognitive function would be examined in the EPIC cohort. It was noted that more intervention studies are needed that examine the effect of folate on cognitive decline.

21. The Subgroup discussed nutrient deficiencies in the elderly. It was noted that in the NDNS survey of people aged over 65 years about 20% of subjects over 80 years had inadequate folate intakes; equally, deficiencies in iron, thiamin, riboflavin, vitamin B<sub>12</sub> and vitamin C were common, and this tends to be more common in institutionalized subjects rather than free-living subjects. Other deficiencies apart from vitamin B<sub>12</sub>-deficiency are also common in the elderly; thus, to investigate the effect of correcting vitamin B<sub>12</sub> or folate deficiencies in intervention studies in the elderly, recognition of co-existing micronutrient deficiencies may also be important.
22. The Subgroup noted reported concerns about the possible masking of vitamin B<sub>12</sub>-deficiency in the elderly, but there was a lack of available data in the literature. It was noted that it would be useful for an assessment of the elderly population to be conducted in countries where mandatory fortification has been introduced.
23. The Subgroup noted that folic acid fortification would reduce NTD-affected births, which would benefit a small population group. While there were theoretical benefits for risk of CVD, cancer and cognitive decline there is insufficient data. It was pointed out that, based on previous COMA modelling data, folic acid fortification could potentially put 0.6% of people over 50 years (those who consume 1mg/d folic acid or more) at risk of vitamin B<sub>12</sub>-deficiency masking at the recommended level of fortification.
24. Folic acid fortification would also benefit the elderly population, as folate-deficiency is common in this group. It was noted that this needed further consideration together with other micronutrient deficiencies in the elderly.

**Action Secretariat** to provide a paragraph on the derivation of the DRV for folic acid in UK and other countries. DH to provide minutes from meeting where these were discussed and details of Disability Adjusted Life Years in relation to folic acid fortification.

25. The Subgroup noted that new evidence had arisen since the COMA risk assessment of the prevalence of vitamin B<sub>12</sub>-deficiency in the elderly in the UK. These studies provide evidence of biochemically-defined vitamin B<sub>12</sub>-deficiency; however, there is an absence of data in relating this to clinical manifestations. The studies do raise the possibility that vitamin B<sub>12</sub>-deficiency in the elderly may be more prevalent than previously considered.
26. It was agreed that the Secretariat would update the paper and circulate it to the members prior to the next meeting.