



ADDITIONAL MEETING TO DISCUSS FOLIC ACID & CRC RISK

21st January 2008, Congress Centre, Great Russell Street, London

Final Minutes

Chair	Professor Alan Jackson
Members	Professor Sheila Bingham Dr Paul Haggarty Professor Tim Key Professor David Phillips (CoC) Professor Elio Riboli (external expert)
Government Observers	Mrs Rosemary Hignett (FSA) Dr Elaine Stone (FSA) Mr Chris Bryant (FSA) Ms Rachel Stratton (FSA) Dr Vivien Lund (FSA) Mr Ian Stone (DH) Mrs Frances Hill (FSA)
Secretariat	Dr Alison Tedstone (FSA) Dr Sheela Reddy (DH) Ms Mamta Singh (FSA) Ms Lynda Harrop (FSA) Ms Rachel Coomber (DH)

Agenda item 1 – Chair's welcome and introduction

1. The Chair welcomed members to the special meeting that had been convened specifically to further consider the issue of folic acid and colorectal cancer (CRC) risk.
2. Apologies had been received from Professor Peter Boyle (external expert) and Professor Alan Boobis (Committee on Carcinogenicity). Written comments had been received from Professor Boobis.

3. The Chair gave a brief background of the purpose of the meeting. In June 2007, the Food Standards Agency (FSA) had recommended fortification of a food (bread or flour) with folic acid to UK Health Ministers in order to reduce the number of pregnancies affected by neural tube defects (NTDs). The recommendation, which was based on advice from SACN, was with the proviso that there are controls on voluntary fortification and clear guidance on the appropriate use of supplements containing folic acid. In October 2007 the Agency had received a letter from the Chief Medical Officer (CMO) of England, on behalf of UK CMOs, requesting SACN to consider in further detail two papers by Cole et al (2007)¹ and Mason et al (2007)², suggesting that folic acid may increase the risk of colorectal cancer, which had not been published at the time of the SACN report. The CMO had suggested co-opting members with particular expertise in cancer epidemiology. It had therefore been agreed that SACN, together with members of the Committee on Carcinogenicity (CoC) and external experts on cancer epidemiology would re-examine the published studies as requested and report back to the CMOs in the near future.
4. The Chair clarified that the working group comprised members of the SACN folate subgroup, two external cancer experts (Professor Elio Riboli and Professor Peter Boyle), and two members of CoC (Professor David Phillips, the Chair of CoC and Professor Alan Boobis).
5. The Chair reminded Members of the purpose of the meeting which was to consider the papers by Cole et al (2007) and Mason et al (2007) and then to decide whether SACN's recommendation for the introduction of mandatory fortification with controls on voluntary fortification and guidance on supplement use should be revised.

¹ Cole BF *et al.* Folic acid for the prevention of colorectal adenomas. *JAMA*. 2007; 297:2351-2359.

² Mason JB *et al.* A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. *Cancer Epidemiol Biomarkers Prev.* 2007; **16**:1325-29.

Agenda Item 2 – Discussion of papers by Cole et al (2007) and Mason et al (2007)

6. The Chair informed members that as well as the papers by Cole et al (2007) and Mason et al (2007), they had been provided with several other papers for information, including additional trend data on CRC incidence which had previously been seen by SACN but not by the CoC or the external experts. A briefing on folic acid and CRC risk had also been prepared by the Secretariat which included a summary and critique of the Cole study (2007) and further analyses provided by John Baron (principle investigator in the study).
7. It was noted that SACN and CoC had previously considered unpublished data of both studies and that CoC had also considered the published Cole (2007) study.

Paper by Cole et al (2007)

8. The Chair summarised the study, which was a double-blind randomised controlled trial to investigate the potential of folic acid supplementation (1mg/day) for the prevention of new colorectal adenomas (which can develop into colorectal cancer). The Chair noted that the subjects had been recruited between 1994 and 1998, which was when mandatory fortification was introduced in the USA.
9. The Secretariat summarised the findings of the study and made some additional observations. The main points are listed below:
 - Results from the study show that folic acid supplementation does not prevent the development of new colorectal adenomas;
 - There was no significant difference in the incidence of at least 1 colorectal adenoma (the primary outcome) between the placebo group and the folic acid group in the first or second follow-up interval (unadjusted RR, 1.04; CI, 0.90-1.20; p=0.58). Supplements of folic acid did not therefore confer protection against the development of colorectal adenomas;
 - There were some important differences in certain baseline characteristics between the folic acid and placebo groups; the most important difference was that the folic acid group had more people who had had an adenoma

≥1cm in diameter removed during the previous 16 months. More people in the folic acid group may therefore have been at greater risk of colorectal adenoma occurrence. The Secretariat had therefore asked for further adjustments by the authors³.

- There was no difference in advanced lesions and multiple adenomas (secondary outcomes) between the two groups in the first interval. In the second interval there was a greater incidence of advanced lesions in the folic acid group compared to the placebo group (unadjusted RR, 1.67; CI, 1.00-2.80; p=0.05), however after adjustment³ the difference was no longer significant (RR, 1.57; CI, 0.92-2.67; p value not provided).
- There was no difference in the incidence of 3 or more adenomas between the two groups in the first interval; however, in the second interval there were significantly more people in the folic acid group with 3 or more adenomas. The difference remained highly significant after adjustment³ (RR, 2.20; CI, 1.15-4.21; p value not provided).
- Since folic acid fortification was mandatory by the time of the second phase the folic acid group would have had higher folic acid intakes than the 1mg/day provided in the trial and much higher intakes than the estimated increase in population average intakes of folic acid if mandatory fortification is introduced in the UK.

10. Members were invited to make any general comments on the study. These are summarised below:

- CoC had considered the Cole (2007) paper after it had been published and concluded that that “*on balance*” SACN’s recommendation for mandatory fortification with controls on voluntary fortification and guidance on supplement use was appropriate;
- CoC had also noted that although prostate cancer was not the focus of the study, there was a statistically significant higher incidence of prostate cancer in the folic acid group;
- The findings of the study were considered to be robust;

³ age, sex, study centre, length of follow-up, lifetime number of adenomas at baseline, aspirin treatment assignment, smoking status [never, former, current], large [≥1 cm] baseline adenoma [yes/no], baseline advanced adenoma [yes/no])

- The outcomes should not be referred to as “primary” and “secondary” as the secondary outcomes (advanced lesions and multiple adenomas) were also important indicators of increased CRC risk.
12. Members were informed that preliminary findings on B vitamin intake and CRC risk from the ongoing EPIC study indicate that for subjects with plasma folate concentration in the highest quintile of plasma folate there was no evidence of increased risk of CRC. It was noted however that the EPIC study had investigated CRC incidence rather than colorectal adenoma incidence in a population not exposed to high levels of folic acid. The EPIC study had also examined the influence of two polymorphisms for the MTHFR gene (MTHFR C677T and MTHFR A1298C). The preliminary results showed that adjusting for genotype did not make any difference in terms of folate and CRC. However, plasma folate concentration would have been largely derived from food folate, not folic acid in this study.
 13. It was noted that in the study by Logan et al (2007), another RCT which had investigated the potential of folic acid supplementation for the prevention of colorectal adenomas, subjects in the folic acid group had been supplemented with 0.5mg/day of folic acid. Although the relative risk of adenoma incidence was 1.07 (CI, 0.85-1.34; p=0.58) the folic acid group compared to the placebo group, this was not significant. It was also noted that the study may have been underpowered and that the numbers for an RR of this magnitude to be statistically significant would not be achievable and that smoking status of participants had not been provided.
 14. It was noted that the paper by Hubner et al (2007) which examined the combined effect of polymorphisms in genes coding for thymidylate synthase (an enzyme involved in folate metabolism) and folate intake on colorectal adenoma risk, found a protective effect of one of these polymorphisms on colorectal adenoma risk.
 15. It was noted that there were a number of ongoing trials investigating the effect of folic acid on CVD. A pooled analysis of the CRC risk from these and past trials may provide further insights on the association between folic acid and CRC risk.

16. It was reported that findings from a similar trial in the USA, looking at the effect of 1mg/day of folic acid on preventing recurrence of colorectal adenomas, were due to be submitted for publication in 2008; however data analysis was not sufficiently advanced to share the results at this stage and it was very unlikely that the investigators would make their results available before the study was published.

Action: Secretariat to check CVD/folic acid trials

17. The Chair noted that in order to clarify the relationship between folic acid and CRC risk, forthcoming studies would need to: look more closely at the dose of folic acid associated with any effect; take careful account of the mix of nutrients as in the NORVIT trial an increased CVD risk (primary outcome) was reported, however folic acid was combined in the supplement with other nutrients; and take account of the size of the study and the size needed to observe a clear effect.

Paper by Mason et al (2007)

18. Members were informed that as the Secretariat had been in correspondence with Joel Mason, the primary author, during the development of the paper, SACN were aware of the substance of the paper before its publication.

19. Time trends for CRC incidence in the USA and Canada have shown that fortification of foods with folic acid occurred around the same time as increases in CRC incidence. The paper by Mason et al (2007) hypothesises that folic acid fortification may have been responsible for this increase.

20. Members were invited to comment on whether they considered that the increase in CRC incidence was caused by folic acid fortification as suggested by Mason et al (2007) or whether it could be explained by another factor such as increased screening for CRC risk.

21. It was noted that the SACN report and the briefing paper provided by the secretariat stated that mandatory fortification occurred around the same time as

non-significant increases in CRC incidence, whereas the paper by Mason et al stated that the increase in incidence was statistically significant. Members were informed that this depended on how the data were considered. The SACN report and the briefing by the secretariat refers to the overall trend in CRC incidence while the paper by Mason et al refer to a significant *deviation* from the pre-1996/1997 linear decline in CRC incidence.

22. In the discussion that followed, the following points were noted:

- As screening for large bowel cancer is being introduced in the UK it may be possible to find out in the near future if a similar increase in incidence is observed in the UK as a result of increased screening.
- Of the two cancers for which screening has been introduced widely, different effects have been observed on incidence. With *breast cancer*, the screening detects the actual cancer which results in an increase in the incidence however the incidence does not return to the previous level; overall, an increase in incidence but a decrease in mortality is observed. With *cervical cancer*, the screening for dysplasia and subsequent treatment are so effective that incidence is substantially reduced and overall there is a reduction in incidence and mortality. With *CRC*, there is no large scale screening programme in place and therefore the expected time trends in incidence as a result of an increase in screening are less clear. In the short-term, an immediate increase would be expected because the cancer is detected at an earlier stage. A decrease would also be expected, as the benefits of removing polyps may not be observed for an extended period of time, say 5-10 years after the introduction of the screening programme.

23. It was also noted that:

- In 1995 the US Preventive Services Task Force reversed earlier position statements and endorsed screening with fecal occult blood testing (FOBT) and sigmoidoscopy for people at average risk of CRC and that this step change in policy might have led to the observed increase in CRC incidence. However, the Mason data had indicated that the major change in colonoscopy rates occurred after the rise in colorectal cancer incidence.

Although there was not a similar step change in policy in Canada which could explain the increase there, it was noted that national data on CRC screening rates were not available from Canada.

- If the increase in CRC incidence was due to increased screening then CRC incidence might be expected to return towards the previous rate. However if screening rates increased gradually over a number of years this delay could offset the return to previous incidence rates.
- The increase in incidence occurred at different times for men and women in the US and Canada and the changes in blood levels of folate were not clearly consistent with the trend data; e.g. the CRC incidence started to decline after 1997 for men and after 1998 for women, which was before the decrease in population blood concentrations.
- Although a causal effect of fortification would be consistent with the similarities and differences between the USA and Canada in CRC changes (very similar level of fortification and CRC change, although about a year later in Canada), the response would have to be almost immediate; as current knowledge does not adequately explain a causal link between folic acid and CRC on this timescale, the nature of the possible response is hypothetical.
- If there was a threshold effect of folic acid on CRC risk (e.g. at intake levels above 1 mg/day) then the recommendation to limit voluntary fortification, combined with advice on supplement use, should minimise any risk to the UK population. If the dose/response is linear, the possibility of an increased risk can not be excluded. However there is currently insufficient data to assess the intake levels that might be associated with risk.
- Members agreed that there was no certain explanation for the increase in CRC incidence observed in the USA and Canada at around the same time as the introduction of folic acid fortification but either increase rates of colonoscopy or higher intakes of folic acid at the time of fortification of flour may have been responsible.

Agenda item 3 – Review of SACN recommendations for mandatory fortification

26. Members were asked in turn to comment on whether they considered that the papers by Cole et al (2007) and Mason et al (2007) provided additional evidence that folic acid increased CRC risk and whether they provided sufficient basis to revise SACN's recommendation for the introduction of mandatory fortification with controls on voluntary fortification and guidance on supplement use.

27. The main points of the discussion were:

- The trial by Cole et al (2007) raises concerns as it suggests that folic acid may increase the risk of developing multiple and advanced adenomas and consequently increase the CRC risk;
- The increased risk appears to be associated with doses in excess of 1mg/day of folic acid;
- The trend data might be explained either by increased screening or by increased intakes of folic acid as a result of mandatory flour fortification. It was noted that if introduction of fortification coincided with NHS colorectal cancer screening it would introduce the same interpretation difficulties as seen in US and Canada;
- Mandatory fortification with restrictions on voluntary fortification would have the advantage of increasing the intake of those with low folic acid intakes without increasing intakes of those who currently have high intakes;
- A meta analysis of cancer/precursor lesion incidence from existing folic acid and CVD intervention trials might provide more information on the relationship between folic acid and cancer risk;
- It is important to clearly distinguish in briefing documents and discussions between folic acid and dietary natural folate obtained from food when considering the evidence with cancer risk.

28. On balance, the Group agreed with SACN's recommendation that mandatory fortification should only be introduced with controls on voluntary fortification and guidance on supplement use. However, it was agreed that the recommendation to

restrict voluntary fortification should be strengthened, by legislation if necessary, if mandatory fortification is introduced.

29. The Secretariat informed Members that negotiations between Agency officials and the food industry regarding controls on voluntary fortification had been taking place since the Board meeting in June 2007. In addition, the European Commission had been notified about the possibility of legislation if the necessary reductions in fortification are not agreed on a voluntary basis.
30. It was agreed to prepare a narrative statement summarising the discussions and conclusions of the meeting for the Chair of the FSA. The statement would need to be agreed by the full SACN Committee at its next meeting on 7th February 2008.

Action: Secretariat