

**From the Chair,  
Dame Deirdre Hutton CBE**

Tel: 020 7276 8010 Fax: 020 7276 8627  
Email: private.office@foodstandards.gsi.gov.uk

Sir Liam Donaldson  
Chief Medical Officer  
Department of Health  
Richmond House  
79 Whitehall  
London SW1A 2NS

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**Mandatory fortification of flour or bread with folic acid**

Further to my letter in October 2007, and following your request for a further expert view of the evidence on folic acid and colorectal cancer (CRC) risk, I am writing to inform you of the outcome of deliberations on this issue. In addition, discussions with industry to limit exposure to intakes of folic acid above safe upper levels are ongoing, and I will be in contact with you separately about this.

The Agency drew together an Expert Group comprising members of the Scientific Advisory Committee on Nutrition (SACN) working group on folate, members of the Committee on Carcinogenicity (CoC) and the two cancer experts that you suggested (details of the membership of the Group can be found at Annex 1). The Group met on 21<sup>st</sup> January 2008; the outcome of their discussion was subsequently considered by SACN on the 7<sup>th</sup> February.

The purpose of the Expert Group meeting was to consider the papers by Cole et al (2007)<sup>1</sup> and Mason et al (2007)<sup>2</sup> and to consider if SACN's recommendation for the introduction of mandatory fortification with controls on voluntary fortification and guidance on supplement use, should be revised in the light of findings from the two studies. Members were provided with additional published studies and opinion pieces published in the scientific literature since SACN reported on *Folate and Disease Prevention* in 2006. Full details of the papers provided are available at [www.sacn.gov.uk](http://www.sacn.gov.uk).

Overall the Group agreed that 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. However, the increased risk appears to be associated

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

<sup>2</sup> 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



with doses in excess of the upper safe level of 1mg/day of folic acid, which is a much higher intake than the estimated increase in population average intakes of folic acid if mandatory fortification is introduced in the UK (80-100µg/day).

The trend data in Mason et al (2007) showing increases in CRC incidence in the USA and Canada at around the same time as the introduction of voluntary fortification in these countries might be explained either by increased screening or by increased intakes of folic acid as a result of fortification.

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

Following the meeting, new information on the timing of on-going trials was received. A significant amount of randomised trials evidence is due to become available early in 2009<sup>3</sup>.

The outcome of the Expert Group meeting and the new information on the future evidence were discussed by SACN at their meeting on the 7 February 2008. SACN agreed to defer agreeing its final advice on folic acid and cancer risk until these data could be considered. It is anticipated that this advice will be provided in mid 2009.

I hope you find the above information useful. The Chair of SACN, Professor Alan Jackson, would be happy to meet with you to discuss the reasons for SACN's decision. In addition, Dr Alison Tedstone, the lead policy official on this issue, or I, would be more than happy to further brief you, if required.

I am copying this letter for information to Dr Michael McBride, Dr Harry Burns and Dr Tony Jewell.

Yours sincerely  
Deirdre

**DAME DEIRDRE HUTTON**

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<sup>3</sup> There are a number of large ongoing trials investigating the effect of folic acid on cardiovascular disease (CVD) risk. A collation of cancer data from these trials will be available towards the end of 2008; this may provide further insights on the association between folic acid and cancer risk. Findings from a trial in the USA, looking at the effect of 1mg/day of folic acid on preventing recurrence of colorectal adenomas, is also due to be submitted for publication in 2008.

**Membership of the expert group**

Chair

Professor Alan Jackson (SACN chair)

SACN members

Professor Sheila Bingham (SACN member)

Professor Tim Key (SACN member)

Dr Paul Haggerty (co-author of the Mason et al paper)

Committee on Carcinogenicity

Professor David Phillips (COC chair)

Professor Alan Boobis (COC member) – **Written comments only**

External experts

Professor Peter Boyle (Director of International Agency for Research on Cancer) – **Sent apologies**

Professor Elio Riboli (Imperial College London)

Further detail on the folic acid and cancer studies

Cole et al (2007)

The study was a double-blind randomised controlled trial that investigated the potential of folic acid supplementation (1mg/day) to prevent new colorectal adenomas. Participants in the trial had been recruited between 1994 to 1998, which was when mandatory fortification was introduced in the USA.

The study did not find any evidence that folic acid supplementation prevents the development of new colorectal adenomas. There was no significant difference in the incidence of at least 1 colorectal adenoma, advanced lesions, or multiple adenomas between the placebo group and the folic acid group in the first (after 3 years) or second (further 3-5 years) follow-up intervals.

In the second interval there was a significantly greater incidence of advanced lesions in the folic acid group compared to the placebo group, however after adjustment<sup>4</sup> the difference was no longer significant. There were also significantly more people in the folic acid group with 3 or more adenomas in the second interval. The difference remained highly significant after adjustment<sup>3</sup>.

Overall the findings of the study were considered to be robust. 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 (80-100µg/day).

Mason et al (2007)

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 non-significant increases in CRC incidence. Mason et al (2007) hypothesise that folic acid fortification may have been responsible for this increase.

In the paper the data were analysed as a deviation from trend, rather than as changes in absolute terms. As there was a significant deviation from the pre-fortification trend, the paper raises the concerns that the deviation in trend around this period could not simply be attributed to chance. Possible explanations for any step change were considered. The two explanations that appear most likely are improved screening for CRC and/or folic acid fortification.

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<sup>4</sup> 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]); additional analysis carried out by authors of the Cole study.