



**Paper for information: Briefing for review of SACN  
recommendations for mandatory fortification**

**Agenda item: 3**

Please see attached paper for discussion

## FOLIC ACID AND CANCER RISK

1. Human prospective studies suggest high intakes of folate have a protective effect on colorectal (CRC) cancer risk.
2. Animal models suggest a dual role of folic acid in cancer development: high intakes may suppress development of early lesions in normal tissue but may increase progression of established neoplasms.
3. A study from USA (Cole et al, 2007<sup>1</sup>) suggests a role of folic acid in progression of colorectal adenomas in people with a previous history of the condition.
4. Time trend data from USA & Canada for CRC incidence show a non-significant increase around the same time as the introduction of folic acid fortification.

### **Scientific Advisory Committee on Nutrition (SACN) Report: *Folate and Disease Prevention* (2006)<sup>2</sup>**

5. In their report on *Folate and Disease Prevention* (2006), SACN considered a broad range of evidence (animal studies, epidemiological studies, time trend data from the USA & Canada for CRC incidence) for the relationship between folic acid and cancer risk. Results from the study by Cole et al (2007) were not available at the time of SACN's risk assessment, however preliminary results of this study (Cole et al, 2005<sup>3</sup>) were considered. SACN also requested an expert view from the Committee on Carcinogenicity (see paragraphs 18-19).
6. SACN concluded that the relationship between folic acid and increased or reduced cancer risk was unclear. As there were insufficient data for a full assessment of folic acid intake levels in relation to cancer risk, SACN recommended that, as a precaution, there should not be a substantial increase in average population intakes of folic acid or in the numbers consuming intakes above the Guidance Level/Upper level (GL/UL<sup>4</sup>).
7. SACN recommended that mandatory fortification should only be introduced in the UK if it is accompanied by:

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

<sup>2</sup> Scientific Advisory Committee on Nutrition. *Folate and Disease Prevention*. TSO, London 2006.

<sup>3</sup> Cole BF, Baron JA, Sandler RS et al. A randomized trial of folic acid to prevent colorectal adenomas [abstract]. *Proc Am Assoc Cancer Res*. 2005; 46:4399.

<sup>4</sup> The UL represents the highest level of daily nutrient that is likely to pose no risk to health. UL for adults (≥18y): 1mg/d; UL for children (Europe): 300µg/d for 4-6y; 400µg/d for 7-10y; 600µg/d for 11-14y; 800µg/d for 15-17y.

The GL is an approximate indication of intakes that would not be expected to cause adverse effects and this is set at 1mg/d in the UK.

- Action to reduce folic acid intakes from voluntarily fortified foods to ensure that the numbers of people with intakes above the GL/UL per day do not exceed current levels and there is no substantial increase in mean intakes or in the folate status of the UK population;
  - measures for careful monitoring of emerging evidence on the effects of long-term exposure to folic acid intakes above the GL/UL per day and postulated adverse effects, including neurological damage, CVD, and cancer;
  - a review of the evidence on benefits and postulated adverse effects after a period of five years.
8. SACN also recommended that if mandatory fortification is introduced, clear guidance should be provided on the use of folic acid containing supplements by the general population.
9. A summary of the SACN report is attached as *Annex 1*

**Study by Cole et al (2007): Folic acid for the prevention of colorectal adenomas**

10. The aim of this study was to investigate the potential of folic acid supplementation for the prevention of new colorectal adenomas (which can develop into colorectal cancer) in persons with a recent history of colorectal adenomas. The study was a double-blind randomised trial in which participants received 1mg/day of folic acid (with or without aspirin) or placebo (with or without aspirin). Adenoma occurrence was determined by 2 colonoscopic examinations (the first at 3 years and the second at 3 or 5 years later).
11. The unadjusted analyses presented in the paper show that in the first follow-up interval, there was no difference in the incidence of at least 1 colorectal adenoma between the folic acid (44%) and placebo (42%) groups or in the incidence of at least 1 advanced lesion (11% in the folic acid group and 9% in the placebo group). In the second follow-up interval, no difference was found in the incidence of colorectal adenomas in the folic acid group (42%) and the placebo group (37%), however, the incidence of at least 1 advanced lesion was significantly greater in the folic acid group (12%) than in the placebo group (7%). There was also an increased risk of having 3 or more adenomas in the folic acid group compared to the placebo group. The risk of colorectal cancer was not increased in the folic acid group compared to the placebo group.
12. Results from this study show that folic acid supplementation at 1 mg/day for up to 6 years does not reduce colorectal adenoma risk. The authors conclude that the evidence for an increased risk of adenomas with folic acid is equivocal and requires further research.

13. See *Annex 2* for a more detailed analysis of the paper by Cole et al (2007). This includes the results of adjusted analyses which were obtained from the authors.

**Paper by Mason et al (2007): A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: A hypothesis**

14. Time trends for CRC incidence in the USA and Canada show that mandatory fortification of foods with folic acid occurred at around the same time as non-significant increases in CRC incidence. Mason et al hypothesise that the introduction of folic acid fortification may have been responsible for the observed increase in CRC incidence.
15. Trends in colorectal cancer (CRC) incidence following fortification in the USA and Canada, were examined in considerable detail by SACN. The paper by Mason et al was prompted by the SACN secretariat contacting the Centers for Disease Control & Prevention (CDC) in the USA to ask if they had considered whether the observed increase might be linked to folic acid fortification. Mason contacted the SACN secretariat after the trend data were brought to his attention by a CDC colleague. SACN was therefore aware of the substance of this paper prior to its publication and prior to the publication of the SACN report.
16. If the increased rate was caused by folic acid fortification, the effect of folic acid on cancer progression would have to have been immediate. Longer periods of exposure are generally expected before an increase in cancer or precancerous lesions can be detected. When examined in more detail, the trend data show that the increases in CRC incidence occurred at different times for men and women in both countries. In the USA, the timing of the increase in CRC incidence also varied for different age groups. The timing of changes in average blood folate concentration of the USA population was also not clearly consistent with changes in CRC incidence. The increases in CRC incidence rates cannot be readily explained by changes in screening practices for CRC detection. Time trends in national cancer incidence rates can be affected by various factors; fluctuations in rates over a few years are often observed but can rarely be attributed with confidence to any single factor.
17. A more detailed discussion of the trend data, taken from the SACN report, is attached as *Annex 3*.

**Committee on Carcinogenicity (CoC)**

18. The CoC examined the evidence on the relationship between folic acid and cancer risk in July 2006. The Committee recommended a precautionary approach to fortification and agreed that SACN's recommendation, that mandatory fortification should only be introduced if there are controls on voluntary fortification and advice on supplement use, was consistent with this approach.
19. The full paper by Cole et al (2007) was discussed by the CoC in July 2007. The Committee concluded that, *'on balance, it was content with the proposals regarding mandatory fortification recommended by the FSA Board which includes monitoring of the folic acid intakes and status of the UK population and postulated risks, including cancer incidence, and a review of the data on the benefits and possible risks 5 years after introduction of mandatory fortification'*<sup>5</sup>.

### **The potential impact of mandatory fortification of flour with folic acid**

20. SACN investigated the potential effect of fortifying flour with different doses of folic acid (100-450 µg/100g) on the total folate intake (including current levels in fortified foods, supplement use, processing losses, overage) of different population age groups by modelling intake data from the National Diet and Nutrition Survey series.
21. Currently, the main dietary sources of folic acid are supplements and foods which are fortified on a voluntary basis (including a number of breakfast cereals and some brands of low-fat spreads). SACN estimated that folic acid intake from voluntarily fortified foods and supplements is currently placing about 127,000 people in the UK at risk of consuming intakes above the UL/day for folic acid. As levels of folic acid in voluntarily fortified foods is uncontrolled, the number of people with intakes above this level could be higher if folic acid levels in these foods are increased in the future.
22. Although voluntary fortification of foods may contribute to reducing NTD risk, these foods are more expensive and are not consumed by all sections of the population. Results from the modelling exercise showed that without intakes of folic acid from voluntary sources, mandatory fortification of flour with folic acid would lead to redistribution of folic acid intakes within the population and would be the most effective way to reach those sections of the population with the lowest folate intakes who are at greatest risk of NTD-affected pregnancies: younger women from the most socioeconomically deprived areas who do not follow advice regarding

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<sup>5</sup> Draft minutes of meeting of 12 July 2007.

preconceptional supplementation with folic acid or routinely consume supplements or foods with the highest levels of voluntary fortification.

23. Without the contribution of folic acid from voluntary fortification of foods, mandatory fortification would also reduce risks of intakes exceeding the UL/day relative to the current practice of voluntary fortification. This is because voluntary fortification of foods with folic acid and inappropriate supplement use are harder to quantify and control and, unlike flour, their consumption is very variable.

24. See *Annex 4* for a summary of SACN's modelling exercise.

### **FSA Board recommendation**

25. Following receipt of SACN's advice the Agency consulted widely on the options for improving the folate intake of women of reproductive age. It considered the potential benefits in terms of reducing the number of pregnancies affected by NTDs and the proportion of the population with lower than recommended intakes of folate. Particular consideration was given to the potential risks, including cancer, to those with high intakes of folic acid.

26. In May 2007, the Board agreed to recommend mandatory fortification alongside controls on voluntary fortification and guidance on the use of supplements. This combined approach of mandatory fortification with limits on voluntary fortification would significantly reduce the number of NTD-affected pregnancies without increasing the number of people with intakes of folic acid above recommended upper levels compared to the current situation. Uncertainties in relation to cancer risk were key to the recommendation for controls on voluntary fortification of foods with folic acid which means that the proportion of people with intakes above the UL/day would be unlikely to increase.

27. In June 2007, the Board agreed that this combined approach should be designed to deliver the following outcome:

- reduce the incidence of NTDs by 11-18% (i.e. 77-162 NTD pregnancies/year);
- ensure that the number of people exceeding the GL/UL for folic acid does not increase above current levels;
- reduce the number of people not achieving the reference nutrient intake from the current level of about 23% to 5%.

28. SACN estimated that the above outcomes could be achieved by increasing folic acid intakes by about 80 µg/day.

**Question to be considered by the folic acid/cancer expert group**

***29. The purpose of the meeting is to consider whether SACN's recommendation for the introduction of mandatory fortification with controls on voluntary fortification and guidance on supplement use should be revised following publication of the papers by Cole et al (2007) and Mason et al (2007).***

**Annex 1****Scientific Advisory Committee on Nutrition: *Folate and Disease Prevention*****SUMMARY****Background**

1. In 2004, the Scientific Advisory Committee on Nutrition (SACN) was asked by UK Health Ministers to consider the wider impact of folic acid fortification, particularly in relation to the elderly.
2. The main issues considered were: UK dietary intakes of folate and other B vitamins; trends in rates of NTD-affected pregnancies in the UK and in countries with fortification policies; possible effects of fortification on people aged 65 years and over with vitamin B<sub>12</sub> deficiency; the relationship between folate and cardiovascular disease, cancer, cognitive function, depression, and bone health. The report also explored the potential impact of mandatory fortification of flour with folic.

**Recommended upper intake level for folic acid in the USA, Europe, and the UK**

3. In the USA and Europe, the tolerable upper intake level (UL<sup>1</sup>) of 1 milligram/day for adults has been set for folic acid. In the UK, the evidence for adverse effects of folic acid was considered insufficient to confidently establish a safe upper level<sup>2</sup> (SUL). Instead, a Guidance Level (GL) of 1 milligram/day was recommended for adults. The GL is less robust than an SUL as it is based on limited data and represents an approximate indication of intakes that would not be expected to cause adverse effects. The UL/GL for folic acid was based on concerns relating to vitamin B12 deficiency.
4. There are no data to suggest that high intakes of folic acid have any adverse effects on children. The critical endpoints relating to vitamin B12 deficiency which were used to set the UL/GL for adults, have not been reported for children. ULs set for children in the USA and Europe were therefore extrapolated from the UL for adults on the basis of body weight. In the UK, GLs were not recommended for children.

**Dietary intakes and status of folate, vitamins B<sub>2</sub>, B<sub>6</sub>, and B<sub>12</sub> in the UK**

5. Data from the National Diet and Nutrition Survey (NDNS) series was used to assess the intakes and status of the UK population. Although average daily folate intakes were above the recommended nutrient intake (RNI<sup>3</sup>) in all age groups, there was some evidence of marginal folate status in young women and people aged 65 years and over. Lower intakes of vitamin B<sub>2</sub> and marginal vitamin B<sub>2</sub> status were widespread in all age groups, particularly in women, girls, and boys. Most age and sex groups had adequate vitamin B<sub>6</sub> intakes but a relatively high proportion of females aged 15-24 years, and over 65 years, had intakes below the lower reference nutrient intake (LRNI<sup>4</sup>). Marginal vitamin B<sub>6</sub> status was found in 10% of the UK population. Although there was no evidence of inadequate vitamin B<sub>12</sub> intakes, serum concentrations indicated poor vitamin B<sub>12</sub> status in older adults.

**Folate and NTD**

<sup>1</sup> The UL represents the highest level of a daily nutrient that is likely to pose no risk of adverse health effects

<sup>2</sup> The SUL represents the amount of nutrient that can be consumed daily over a lifetime without significant risk to health.

<sup>3</sup> The RNI represents the amount of a nutrient that is considered sufficient to meet the requirements of 97.5% of the population.

<sup>4</sup> The LRNI is the amount of a nutrient that is considered sufficient to meet the requirements on 2.5% of the population.

6. Although supplementation with folic acid is advised prior to conception until the 12<sup>th</sup> week of pregnancy approximately half of all pregnancies are unplanned, which limits the value of recommendations. European Union countries with policies recommending women to consume folic acid supplements to reduce NTDs have observed no effect on NTD reduction.
7. Available data on the number of NTD-affected pregnancies are insecure due to under-reporting. Taking account of under-reporting in England and Wales, but not in Scotland and Northern Ireland, there were approximately 700-900 NTD-affected pregnancies in the UK in 2003.

#### **Folic acid fortification strategies and incidence of NTD in other countries**

8. Countries that have introduced mandatory fortification (USA, Canada, Chile) have reported significant reductions in NTD-affected pregnancies of 27% to over 50%. As a result of *overage*, the impact of fortification on folate status has been greater than predicted.

#### **Possible adverse effects of mandatory fortification of flour with folic acid**

##### Risks to older people with vitamin B<sub>12</sub> deficiency

9. There are concerns that mandatory fortification of flour with folic acid might have adverse effects on neurological function in people aged 65 years and over with vitamin B<sub>12</sub> deficiency. Clinical signs of vitamin B<sub>12</sub> deficiency are anaemia and/or neurological impairment. Folic acid can alleviate the anaemia and therefore delay diagnosis of vitamin B<sub>12</sub> deficiency, which can lead to the irreversible and serious condition of sub acute combined degeneration of the spinal cord.
10. The assessment of vitamin B<sub>12</sub> deficiency is complicated by the limitations of current diagnostic techniques. Low serum concentrations of vitamin B<sub>12</sub> are not always predictive of a clinical response to vitamin B<sub>12</sub> therapy. The prevalence of low vitamin B<sub>12</sub> status in the UK has been estimated to be 5% in people aged 65-74 years and 10% in people aged 75 years and over.
11. Evidence suggests that masking of vitamin B<sub>12</sub> deficiency is not associated with doses of folic acid up to 1 milligram / day. There are no reports from countries that have introduced mandatory fortification indicating deleterious effects on older people with low vitamin B<sub>12</sub> status.

##### Epilepsy

12. It has been suggested that folic acid modifies the pharmacokinetics of phenytoin, an anti-epileptic drug, and may lower serum phenytoin concentrations leading to poorer seizure control. Evidence from Canada has shown that mandatory fortification, estimated to provide an average of 200 micrograms / day did not lower serum phenytoin concentrations in epileptic patients.

##### Multiple births

13. There is no substantive evidence to suggest that folic acid fortification is associated with multiple births resulting from natural conception. However, high intakes of folic acid may increase the likelihood of twin births in women undergoing multiple embryo transplant fertility treatment.

##### Embryo selection

14. It has been proposed that the use of folic acid in pregnancy could increase survival of embryos with genotypes associated with deleterious effects. There is no substantive evidence from countries where supplementation is advised or mandatory fortification has been introduced to support this.

#### Anti-folate chemotherapy

15. There are concerns that folic acid may reduce the efficacy of anti-folate drugs used in chemotherapy regimens and treatment of autoimmune diseases. There are insufficient human data on the effect of folic acid on antifolate medication or the doses at which folic acid might affect their action to conclude that mandatory folic acid fortification would modify their efficacy.

#### Unmetabolised folic acid in the systemic circulation

16. The appearance of unmetabolised folic acid in the systemic circulation has raised concerns regarding the long-term effects of high intakes of folic acid. Overall, there are insufficient data in humans to assess the long-term effects of exposure to unmetabolised folic acid in the systemic circulation.

### **Folate, B vitamins, and chronic disease**

#### Folate and cardiovascular disease

17. Observational studies have suggested a protective effect of increasing folate intake, but not circulating folate concentrations, on CVD risk. No randomised controlled trials (RCTs) have demonstrated a beneficial or harmful effect of folic acid supplements on CVD risk. One RCT found an increased CVD risk with supplementation of folic acid in combination with vitamins B<sub>12</sub> and B<sub>6</sub>.

#### Folate and cancer

18. Some animal studies suggest that folic acid may inhibit tumour development in normal tissues but promote the progression of established neoplasms. The doses of folic acid used in these studies were considerably higher than the amounts that would be consumed by humans as a result of fortification.
19. Although evidence from prospective studies in humans suggests a trend towards a protective effect of folate intake on colon cancer risk, some studies did not adjust for all confounding factors. No RCTs designed to investigate the relationship between folic acid and cancer incidence have yet reported.
20. Time trends for colorectal cancer (CRC) incidence in the USA and Canada show that mandatory fortification of foods with folic acid occurred at around the same time as non-significant increases in CRC incidence. If this was caused by folic acid fortification, the effect of folic acid on cancer progression would have to have been immediate, which may not be plausible. The increase in rates occurred at different times for men and women and in different age groups. The timing of changes in average blood folate concentrations of the USA population was also not clearly consistent with changes in CRC incidence.
21. The evidence for an association between folic acid and increased or reduced cancer risk in humans is equivocal.

#### Folate and cognitive function

22. Overall, the evidence for either beneficial or deleterious effects of folic acid or vitamin B<sub>12</sub> therapy on cognitive function in older people is presently inconclusive.

### Folate and bone health

23. There is insufficient evidence to suggest beneficial effects of folic acid on bone health and no evidence to suggest any deleterious effects.

### **The potential impact of mandatory fortification of flour with folic acid**

24. The potential effect of fortifying flour with different doses of folic acid (100-450 micrograms / 100 grams) on total folate intake (including current levels in fortified foods, supplement use, processing losses, overage) of different population age groups was investigated by modelling intake data from the NDNS series. The aim of the modelling exercise was to explore the effect of mandatory fortification on: risk of NTD-affected pregnancies; the number of people with folic acid intakes above the UL/day<sup>5</sup>; and the number of people aged 65 years and over with low vitamin B<sub>12</sub> status, exceeding folic acid intakes of 1 milligram / day.
25. Results from the modelling exercise showed that at current levels of folic acid intake (including intake from voluntarily fortified foods and supplements) mandatory fortification of flour with folic acid would progressively reduce NTD risk. However it would increase the proportion of people with folic acid intakes above the UL/day and the number of people aged 65 years and over with low vitamin B<sub>12</sub> status consuming more than 1 milligram / day of folic acid.
26. If no foods were voluntarily fortified, the option that would provide the optimum balance between benefits and possible risks is mandatory fortification at a level of 300 micrograms of folic acid / 100 grams flour (excluding wholemeal flour). At this level it is estimated that, compared to current levels: 77-162 NTD-affected pregnancies per year could be prevented (11-18% risk reduction); the proportion of the population with intakes below the RNI would be reduced from 23% to 5%; the number of people with folic acid intakes above the UL / day would be reduced by 12,000; there would be no change in the number of adults aged 65 years and over, with low vitamin B<sub>12</sub> status, exceeding intakes of 1 milligram/day.
27. Without folic acid intake from voluntary sources, mandatory fortification would confer a more even distribution of folic acid intakes across the population compared to current voluntary fortification and supplement use. This means that women at greatest risk of NTD-affected pregnancies, i.e. those with the lowest folate intakes, would be reached through mandatory fortification.

### **Conclusions**

28. The current recommendation is that women planning a pregnancy should supplement their diet with 400 micrograms / day of folic acid (5 milligrams / day for women with a previous pregnancy affected by NTD) prior to conception until the twelfth week of pregnancy. About half of all pregnancies are unplanned which limits the value of recommendations. Policies in the EU, recommending folic acid supplementation to reduce NTD-affected pregnancies have been ineffective.

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<sup>5</sup> As GLs were not set for children in the UK (see paragraph 4) ULs were used for the purpose of the modelling exercise.

29. Introduction of mandatory fortification of flour with folic acid at current levels of folic acid intake (including intake from voluntary fortification and supplements) would reduce the risk of NTD-affected pregnancies in the UK. However, it would also increase the proportion of people in the population at risk of exceeding folic acid intakes above the UL/day and the number of people aged 65 years and over with low vitamin B12 status at risk of consuming more than 1 milligram / day of folic acid.
30. There are approximately 127,000 people in the UK who are currently consuming intakes of folic acid above the UL/day from voluntarily fortified foods and supplements. As there are presently no controls on the levels of folic acid which can be added to foods, the number of people with intakes above the UL/day could be higher if levels in these foods are increased in the future.
31. Without the contribution of folic acid from voluntarily fortified foods, mandatory fortification would reduce risks of intakes exceeding the UL/day for folic acid relative to the current practice of voluntary fortification. This is because voluntary fortification of foods with folic acid and inappropriate supplement use are harder to quantify and control and, unlike flour, their consumption is very variable.
32. Replacement of voluntary folic acid fortification of certain foods with mandatory fortification of flour would result in a redistribution of folic acid intakes within the population and would be the most effective way to reach those sections of the population with the lowest folate intakes, i.e., younger women from the most socio-economically deprived areas.
33. Without the contribution of folic acid intakes from voluntarily fortified foods, the optimal level for mandatory fortification of flour with folic acid would be 300 micrograms/100 grams flour. This level would be effective in reducing NTD risk without increasing the number of people with intakes of folic acid above the UL per day or the number of adults aged 65 years and over, with low vitamin B<sub>12</sub> status and folic acid intakes above 1 milligram/day. Exempting wholemeal flour from fortification would have little effect on NTD risk but would further reduce numbers with intakes of folic acid above the UL/day.
34. There is currently insufficient evidence from RCTs examining chronic disease risk (cardiovascular disease, certain cancers, bone disease and age-related cognitive decline) to either support or advise against mandatory fortification of flour with folic acid on these grounds.
35. There is currently insufficient evidence for an adequate risk assessment of folic acid and cancer risk or the intake levels which might be associated with risk. A substantial increase in current average population intakes of folic acid and the numbers consuming more than the GL/UL per day for folic acid should therefore be avoided.

### **Recommendations**

36. As previously recommended by COMA (DH, 2000), all women who could become pregnant should take 400 micrograms/day folic acid as a medicinal or food supplement prior to conception and until the twelfth week of pregnancy. Women with a history of a previous NTD-affected pregnancy are advised to take 5 milligrams/day of folic acid prior to conception and until the twelfth week of pregnancy. This recommendation is applicable even if mandatory fortification of flour with folic acid is introduced.

37. Individual long-term intakes of folic acid from fortified foods and supplements above the GL/UL per day for folic acid should be avoided. The risk currently posed by voluntary fortification of food with folic acid and supplement use in contributing to intakes above the GL/UL per day for folic acid needs to be addressed.
38. Mandatory fortification of flour with folic acid would improve the folate status of women most at risk of NTD-affected pregnancies. However, if mandatory fortification is combined with the current practice of voluntary fortification of foods with folic acid and inappropriate supplement use, the numbers of people consuming levels of folic acid above the GL/UL per day would be substantially increased.
39. Mandatory fortification should only be introduced in the UK if it is accompanied by:
  - Action to reduce folic acid intakes from voluntarily fortified foods to ensure that the numbers of people with intakes above the GL/UL per day do not exceed current levels and there is no substantial increase in mean intakes or in the folate status of the UK population;
  - Measures for careful monitoring of emerging evidence on the effects of long-term exposure to folic acid intakes above the GL/UL per day and postulated adverse effects, including neurological damage, CVD, and cancer.
40. The establishment of a new baseline for folic acid intakes and blood folate concentrations will be required prior to fortification to ensure that mandatory fortification does not lead to substantial increases in folic acid intake/status and so trends can be monitored in future surveillance programmes. The adoption of a common standard analytical method to measure folate status at baseline and all future surveillance studies will also be required as well as the establishment of suitable reference ranges to predict folate adequacy and deficiency.
41. If mandatory fortification is introduced, careful consideration should be given to the issue of overage and the evidence on benefits and postulated adverse effects should be reviewed after a period of five years.
42. Clear guidance is needed on the use of folic acid containing supplements by the general population.
43. More reliable diagnostic indices to identify vitamin B<sub>12</sub> deficiency should be developed. The development of a clinical strategy to manage issues related to vitamin B<sub>12</sub> is necessary irrespective of a decision on future mandatory fortification of flour with folic acid.
44. The prevalence of poor vitamin B<sub>2</sub> status in the UK needs to be addressed.

**ANNEX 2**

**Cole BF, Baron JA, Sandler RS et al. Folic acid for the prevention of colorectal adenomas. *JAMA*. 2007; 297:2351-2359.**

1. The aim of this study was to investigate the potential of folic acid supplementation for the prevention of new colorectal adenomas (which can develop into colorectal cancer) in persons with a recent history of colorectal adenomas.
2. The study was a double-blind randomised trial. Participants received 1mg/day of folic acid (with [81 or 325 mg/d] or without aspirin) or placebo (with [81 or 325 mg/d] or without aspirin) for a 3 year period. Aspirin treatment was then discontinued and participants were invited to continue their treatment with either folic acid (1mg/d) or placebo for a further 3-5 years. Adenoma occurrence was determined by 2 colonoscopic examinations (the first at 3 years and the second 3 or 5 years later).
  - **1021** randomised (505 received either placebo, 81mg/d aspirin, or 325mg/d aspirin; 516 received either 1mg/d folic acid, 1mg/d folic acid + 81mg/d aspirin, or 325 mg/d aspirin);
  - **987** (97%) underwent a colonoscopy during the first interval;
  - **926** (91%) agreed to participate in 2<sup>nd</sup> follow-up interval;
  - **729** (71%) agreed to continue with folic acid/placebo treatment;
  - **607** (60%) actually had a second colonoscopic examination after further 3-5 years;
  - **501** (49%) actually continued with treatment (254 received placebo; 247 received folic acid).
3. The primary outcome measure was the occurrence of at least 1 colorectal adenoma. Secondary outcome measures were advanced lesions, adenoma multiplicity, and adverse events.
4. Allocation to the folic acid group resulted in a pronounced increase in plasma folate and a modest decrease in total plasma homocysteine. At the 3 year examination, mean plasma folate increased from 10.4 µg/L at baseline to 13.2 µg/L in the placebo group and from 10.5 µg/L to 32.8 µg/L in the folic acid group. The plasma folate status at the end of the second follow-up interval is not provided.

**RESULTS**

Table 1 provides unadjusted analyses of adenoma occurrence in the trial population (equivalent to table 3 in the Cole paper). Analyses adjusted for *age, sex, study centre, length of follow-up, lifetime number of adenomas at baseline, aspirin treatment assignment* were obtained from the authors. On request, the authors also provided analyses that were further adjusted to include the covariates that differed most between the folic acid and placebo groups: *smoking status, advanced lesions, adenoma ≥ 1cm in diameter removed before recruitment*.

Table 4 shows the unadjusted and adjusted risk ratios for folic acid by randomised aspirin treatment in the first interval and the unadjusted risk ratios in the second follow-up interval (adjusted RRs were not available).

**Primary outcome results**

Occurrence of at least 1 colorectal adenoma

***First follow-up interval***

5. There was no difference in the incidence of at least 1 colorectal adenoma between the placebo group (42.4%) and the folic acid (44.1%) groups (unadjusted RR, 1.04; CI, 0.90-1.20; p=0.58).

### ***Second follow-up interval***

6. For the whole group (n=607) there was no difference in the incidence of colorectal adenomas in the placebo group (37.2%) and the folic acid group (41.9%) (unadjusted RR, 1.13; CI, 0.93-1.37; p=0.23). Results of the subgroup who continued to take pills (n=501) were similar: the incidence of adenomas was 36.2% in the placebo group and 42.9% in the folic acid group (unadjusted RR, 1.18; CI, 0.95-1.47; p=0.13).

### **Secondary outcome results**

#### ***First follow-up interval:***

#### **Advanced lesions**

7. Advanced lesions occurred in 8.6% of participants in placebo group and 11.4% of participants in the folic acid group (unadjusted RR, 1.32; CI, 0.90-1.92; p=0.15).

#### **Multiple adenomas**

8. Three or more adenomas occurred in 7.8% of placebo group and 9.4% in the folic acid group (unadjusted RR, 1.2; CI, 0.80-1.81; p=0.38).

### ***Second follow-up interval***

#### **Advanced lesions**

9. In the group who had a second examination (n=607) the incidence of at least 1 advanced lesion was 6.9% in the placebo group and 11.6% in the folic acid group (unadjusted RR, 1.67; CI, 1.00-2.80; p=0.05); after adjustment<sup>6</sup> the RR was 1.57 (CI, 0.92-2.67; p value not provided).
10. When analysis was restricted to participants who continued with treatment (n=501) advanced lesions occurred in 7.1% of placebo group and 11.7% in the folic acid group (unadjusted RR, 1.66; CI, 0.95-2.90; p=0.08); after adjustment the RR was 1.57 (CI, 0.88-2.81; p value not provided).

#### **Multiple adenomas**

11. For the group who completed second examination (n=607) there was no significant difference between placebo (32.9%) and folic acid (32%) groups in the occurrence of 1-2 adenomas (unadjusted RR, 0.97; CI, 0.77-1.22/adjusted RR, 0.99; CI, 0.78-1.30). However, 3 or more adenomas occurred in 4.3% of the placebo group and 9.9% of the folic acid group (unadjusted RR, 2.32; CI, 1.23-4.35; p=0.007/adjusted RR, 2.20; CI, 1.15-4.21; p value not provided).
12. When analysis was restricted to participants who continued with treatment (n=501) there was no significant difference between groups in the occurrence of 1-2 adenomas (unadjusted RR, 1.00; CI, 0.78-1.30/adjusted RR, 1.03; CI, 0.79-1.34). However 3 or more adenomas occurred in 4.3% of the placebo group and 10.9% of the folic acid group (unadjusted RR, 2.52; CI, 1.28-4.98; p=0.008/adjusted RR, 2.40; CI, 1.20-4.80; p value not provided).

#### **Adverse events (n=1021)**

13. The risk of colorectal cancer was not increased in the folic acid group compared to the placebo group.

<sup>6</sup> age, sex, study centre, length of follow-up, lifetime number of adenomas at baseline, aspirin treatment assignment, smoking status [never, former, current], large [ $\geq 1$  cm] baseline adenoma [yes/no], baseline advanced adenoma [yes/no])

14. A higher rate of prostate cancer was observed among the participants in the folic acid group, however the authors suggest this may be a spurious association given the number of adverse events evaluated.
15. No significant association was found between allocation to folic acid and risks of myocardial infarction, coronary revascularisation, stroke, or death (although risk of death in the placebo group was nearly double that of the folic acid group [ $p=0.09$ ]).

### Comment

16. This was a large well-designed double-blind randomised controlled trial. However, the following points should be noted:
  - Although they did not reach statistical significance, there were some important differences in certain baseline characteristics between the folic acid group and the aspirin placebo group: the folic acid group had a greater number of cigarette smokers and more individuals with an advanced lesion at examinations qualifying for study entry. The most important difference which reached near significance (0.06) was that there were more people in the folic acid group who had had an adenoma  $\geq 1$ cm in diameter removed during the previous 16 months. It is therefore possible that more people in the folic acid group were at greater risk of colorectal adenoma occurrence than in the placebo group and it is also possible that they were more likely to have had smaller lesions that were not detected at the entry examination.
  - In the notes under Table 1 of the paper by Cole et al (2007), which lists the baseline characteristics of the study participants, it states that family history of colorectal cancer was missing for 202 (20%) of the participants. The high level of missing data regarding family history was due to subjects who responded "don't know" to the question. Missing family history did not differ by treatment group ( $p=0.98$ ).
  - Only unadjusted analyses of adenoma risk are presented (in Table 3 of paper) and the paper states that there was little difference in the results when adjustments were made for *age, sex, clinical centre, length of follow-up, number of lifetime adenomas at baseline, and randomised aspirin treatment*. However, in the second interval, the RR for advanced lesions is 1.67 (CI, 1.00-2.80;  $p=0.05$ ) in the unadjusted analysis and 1.68 (CI, 0.95-2.78;  $p$  value not provided) after adjustment for the above factors. After further adjustment to include the covariates which differ the most between folic and placebo groups (*smoking status, advanced lesions, adenoma  $\geq 1$ cm in diameter removed before recruitment*), the RR for advanced lesions was 1.57 (CI, 0.92-2.67;  $p$  value not provided) for the group that had a second colonoscopic examination ( $n=607$ ) and also 1.57 (CI, 0.88-2.81;  $p$  value not provided) for the group who continued treatment ( $n=501$ ).
  - After adjustment for all the factors listed above, the risk of 3 or more adenomas in the second interval remained significantly greater in the folic acid group compared to the placebo group: RR, 2.20 (CI, 1.15-4.21;  $p$  value not provided) in the whole group ( $n=607$ ) and 2.40 (CI, 1.20-4.80;  $p$  value not provided) in the group who continued treatment.
  - In the first phase of the study 1021 participants were randomised to receive placebo (with or without aspirin) or folic acid (with or without aspirin) and 987 (97%) completed the first colonoscopic examination. In the second phase, the aspirin treatment was discontinued and participants were allocated to either placebo or folic acid. Although 926 (90.6%) participants consented to extended follow-up, only 607 (59.5%) actually completed a second colonoscopic examination and only 501 (49%) continued to take study pills (placebo group,  $n=254$ ; folic acid group,  $n=247$ ). The loss of so many participants to follow-

up and the considerable proportion of subjects who discontinued taking tablets mean that the results of the two time intervals may not be directly comparable.

- The study was carried out in a folate replete population and the results of the trial may have been affected by fortification of the food supply which began in 1996 and became mandatory in 1998 (recruitment for the study took place from 1994-1998). Fortification may have affected the impact of the supplement.
- At baseline, the dietary folate intakes of the study population were 320-325 µg/day (compared to 302 µg/day in the UK). It has been estimated that as a consequence of mandatory folic acid fortification in the USA, typical folic acid intakes increased by 215-240 µg/day. Since folic acid fortification was mandatory by the time of the second phase, the folic acid group would have had substantially higher folic acid intakes than the 1mg/day provided in the study. This is much higher than the estimated increase in population average daily intake in folic acid if mandatory fortification is introduced in the UK.
- The Agency's recommendation for mandatory folic acid fortification is with the proviso that there are controls on voluntary fortification and clear guidance on the appropriate use of supplements containing folic acid. In the USA there were no controls on voluntary fortification following the introduction of mandatory folic acid fortification. If mandatory fortification is introduced in the UK there would be legislation to ensure that voluntary fortification is controlled and advice would be provided on supplement use.
- The actual amount of folic acid to be used has not yet been decided but the Agency Board agreed that it should be at a level that will reduce NTD pregnancies by 11-18% without increasing the number of people with high intakes. It is estimated that the overall effect of the combined approach of mandatory fortification with controls on voluntary fortification will be to increase folic acid intakes by 80-100 micrograms per day. This is considerably less than the increase in folic acid intakes in the United States following mandatory fortification.

**Table 1. Risk of Adenoma in the intention to treat population & those consenting to continued treatment (unadjusted RR)**

End Point	First follow-up interval (n=987)				Second follow-up interval (n=607)				Second follow-up interval (n=501 continued treatment)			
	Number (%) of participants		Unadjusted RR (95% CI)	P value	Number (%) of participants		Unadjusted RR (95% CI)	P value	Number (%) of participants		Unadjusted RR (95% CI)	P value
	Placebo (n=486)	Folic Acid (n=501)			Placebo (n=304)	Folic Acid (n=303)			Placebo (n=254)	Folic Acid (n=247)		
Any adenoma	206 (42.4)	221 (44.1)	1.04 (0.90-1.20)	0.58	113 (37.2)	127 (41.9)	1.13 (0.93-1.37)	0.23	92 (36.2)	106 (42.9)	1.18 (0.95-1.47)	0.13
Advanced lesion	42 (8.6)	57 (11.4)	1.32 (0.90-1.92)	0.15	21 (6.9)	35 (11.6)	1.67 (1.00-2.80)	0.05	18 (7.1%)	29 (11.7%)	1.66 (0.95-2.90)	0.08
No. adenomas												
1-2	168 (34.6)	174 (34.7)	1.00 (0.85-1.19)	0.66	100 (32.9)	97 (32.0)	0.97 (0.77-1.22)	0.02				
≥3	38 (7.8)	47 (9.4)	1.20 (0.80-1.81)		13 (4.3)	30 (9.9)	2.32 (1.23-4.35)		11 (4.3%)	27 (10.9%)	2.52 (1.28-4.98)	0.008

**Table 2. Risk of adenoma in intention to treat population (unadjusted and adjusted for age, sex, study centre, length of follow-up, lifetime number of adenomas at baseline, aspirin treatment assignment)**

	First Follow-up Interval		Second Follow-up Interval	
	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Any Adenoma	1.04 (0.90-1.20)	1.05 (0.90-1.21)	1.13 (0.93-1.37)	1.14 (0.93-1.39)
Advanced Adenoma	1.32 (0.90-1.92)	1.32 (0.90-1.93)	1.67 (1.00-2.80)	1.68 (0.95-2.78)
Number of adenomas				
1-2	1.00 (0.85-1.19)	1.01 (0.85-1.20)	0.97 (0.77-1.22)	0.99 (0.78-1.26)
≥3	1.20 (0.80-1.81)	1.21 (0.81-1.81)	2.32 (1.23-4.35)	2.30 (1.21-4.35)

**Table 3. Risk of adenoma in the intention to treat population & those consenting to continued treatment (unadjusted & adjusted for 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])**

	First Follow-up Interval (n=987)		Second Follow-up Interval (n=607)		Second Follow-up Interval (n=501) (continued treatment)	
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Any Adenoma	1.04 (0.90-1.20)	1.03 (0.89-1.20)	1.13 (0.93-1.37)	1.13 (0.92-1.39)	1.18 (0.95-1.47)	1.19 (0.95-1.50)
Advanced Adenoma	1.32 (0.90-1.92)	1.26 (0.85-1.86)	1.67 (1.00-2.80)	1.57 (0.92-2.67)	1.66 (0.95-2.90)	1.57 (0.88-2.81)
Number of adenomas						
1-2	1.00 (0.85-1.19)	1.00 (0.84-1.19)	0.97 (0.77-1.22)	0.99 (0.78-1.25)	1.00 (0.78-1.30)	1.03 (0.79-1.34)
≥3	1.20 (0.80-1.81)	1.16 (0.78-1.75)	2.32 (1.23-4.35)	2.20 (1.15-4.21)	2.52 (1.28-4.98)	2.40 (1.20-4.80)

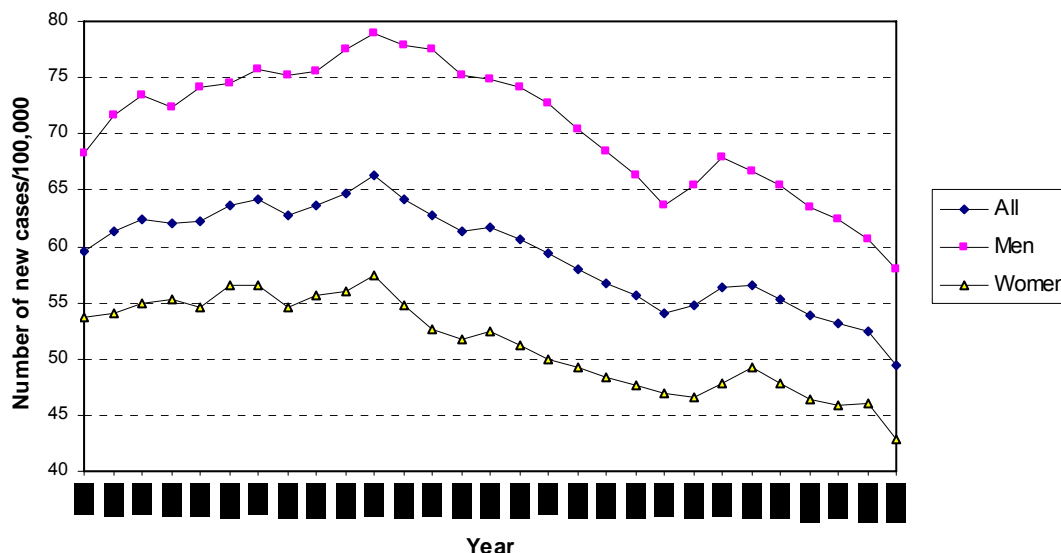
**Table 4. Risk Ratios comparing folic Acid vs placebo by randomised aspirin treatment in the intention to treat population in the first and second follow-up interval (unadjusted & adjusted for *age, sex, study centre, length of follow-up, lifetime number of adenomas at baseline*)**

	<u>FIRST FOLLOW-UP INTERVAL</u>		<u>SECOND FOLLOW-UP INTERVAL</u>
	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)	Unadjusted* RR (95% CI)
<u>Any Adenoma</u>			
Aspirin Placebo	1.20 (0.95-1.51)	1.20 (0.95-1.52)	1.14 (0.82-1.58)
Aspirin 81 mg/d	0.88 (0.66-1.17)	0.90 (0.68-1.21)	1.09 (0.76-1.55)
Aspirin 325 mg/d	1.03 (0.81-1.30)	1.05 (0.82-1.34)	1.16 (0.82-1.64)
<u>Advanced Adenoma</u>			
Aspirin Placebo	1.86 (1.01-3.41)	1.79 (0.98-3.29)	1.72 (0.74-3.98)
Aspirin 81 mg/d	1.09 (0.47-2.50)	1.01 (0.40-2.50)	0.84 (0.29-2.42)
Aspirin 325 mg/d	1.01 (0.55-1.86)	1.04 (0.56-1.92)	2.59 (1.06-6.31)

**ANNEX 3****Trends in cancer risk in the USA and Canada following mandatory fortification****USA**

45. In the USA, voluntary fortification of food products with folic acid was first authorised in March 1996 and mandatory fortification became effective from January 1998. For all populations combined, age-adjusted overall trends in colorectal cancer incidence in the USA<sup>7</sup> between 1975-2003 (National Cancer Institute, 2005) (see figure 1) show there was a significant increase in colorectal cancer incidence of 0.8% per year from 1975 until 1985, a significant decline of 1.8% per year between 1985-1995, a non-significant increase of 1.2% per year between 1995-1998, followed by a significant decline of 2.1% per year between 1998-2003. The incidence rate after 1998 continued to decline at approximately the same rate as before 1996.

**Figure 1: Colorectal cancer incidence rates, USA 1975-2003:** (per 100,000/year, age-adjusted to the 2000 US population)



46. The temporary increase in rates of CRC incidence after several years of decline occurred around the same time as fortification of food products with folic acid, raising the possibility that fortification might be implicated in the increase in CRC incidence between about 1996-1998. Food manufacturers began fortifying foods in 1996 (when voluntary fortification was permitted) and CRC incidence began to increase in the same year. Colorectal tumours usually develop from benign polyps or adenomas over a period of 10-15 years (Tomeo *et al*, 1999). If the increase was caused by fortification then the effect of folic acid on tumour progression would have to have been instantaneous. Longer periods of exposure are generally expected before an increase in cancer or precancerous lesions can be detected, for example, up to 3 years in polyp recurrence intervention trials (Martinez *et al*, 2006).
47. If the trends are considered by sex, it can be seen from figure 1, that the increase in CRC incidence occurred in 1996 for men and in 1997 for women. A more detailed consideration of the trends shows that they also varied by age (see figures 5-8, Annex 8): for ages 20-54 years, CRC incidence increased in 1995 for men and in

<sup>7</sup> Information on cancer incidence was based on data collected by cancer registries participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program and represents 10-14% of the population (Edwards *et al*, 2005).

1997 for women; for ages 55-64 years, CRC incidence increased in 1996 for men and in 1997 for women; for ages 65-74 years, CRC incidence increased in 1996 for men and in 1997 for women; for ages 75 years and over, CRC incidence increased in 1997 for men and in 1996 for women. The greatest increases occurred in those aged 75 years and over, suggesting that the overall trend (figure 1) is largely driven by the pattern for 75 years and older age-groups. Precursor high risk polyps are more common in this age group than in younger age groups (Williams *et al*, 1982; Clark *et al*, 1985).

48. Average plasma and red cell folate concentrations in the USA increased following folic acid fortification (Pfeiffer *et al*, 2005) peaking in 1999-2000 before starting to decrease in 2001-2002 (Ganji and Kafai, 2006). However, it can be seen from figure 1, that CRC incidence rates (for men and women combined) started to decline after 1998, i.e. before the decrease in population blood folate concentrations.
49. If the increase in CRC incidence was caused by folic acid fortification it is not clear why it should occur at different times in the various age groups and for men and women or why the change in rates was not clearly consistent with changes in folate status.
50. The increased incidence might be explained by improved screening for colorectal cancer: in 1995, the US Preventive Services Task Force (USPSTF)<sup>8</sup> reversed earlier position statements and endorsed screening with fecal occult blood testing (FOBT) and sigmoidoscopy for people at average risk for colorectal cancer (Frame *et al*, 1997; Levin & Bond, 1996). Examination of trends in cancer screening practices (Breen *et al*, 2001) based on data from the National Health Interview Survey (NHIS)<sup>9</sup>, shows that the proportion of the population aged 50 years or older who reported recent use of screening endoscopy<sup>10</sup> increased from 12% in 1992 to 19% in 1997 for men and from 7% to 10% in women; use of FOBT increased from 24% in 1992 to 29% in 1998 for men and from 25% to 26% for women. Use of colorectal cancer screening using either FOBT or endoscopy increased from 29% in 1992 to 37% in 1997 for men; and from 28% to 30% in women.
51. Screening for CRC may lead to increased incidence since cancers are detected earlier than they would be otherwise. It may also lead to decreased incidence since premalignant lesions can be identified and removed before they develop into cancer. This makes it difficult to make inferences about the effect of screening on incidence rates, particularly as different tests are recommended which may have differing effects on incidence, and trends in their use appears to vary for men and women and over time. The overall marked decline in CRC incidence rates in the 1990s has been attributed to increased screening (Cress *et al*, 2006).
52. There are no clear temporal changes in the incidence of other cancers such as breast, lung, and prostate following mandatory folic acid fortification.

### **Canada**

53. In Canada, fortification of food with folic acid was permitted in December 1996 and became mandatory in November 1998. Age-adjusted trends in CRC incidence in

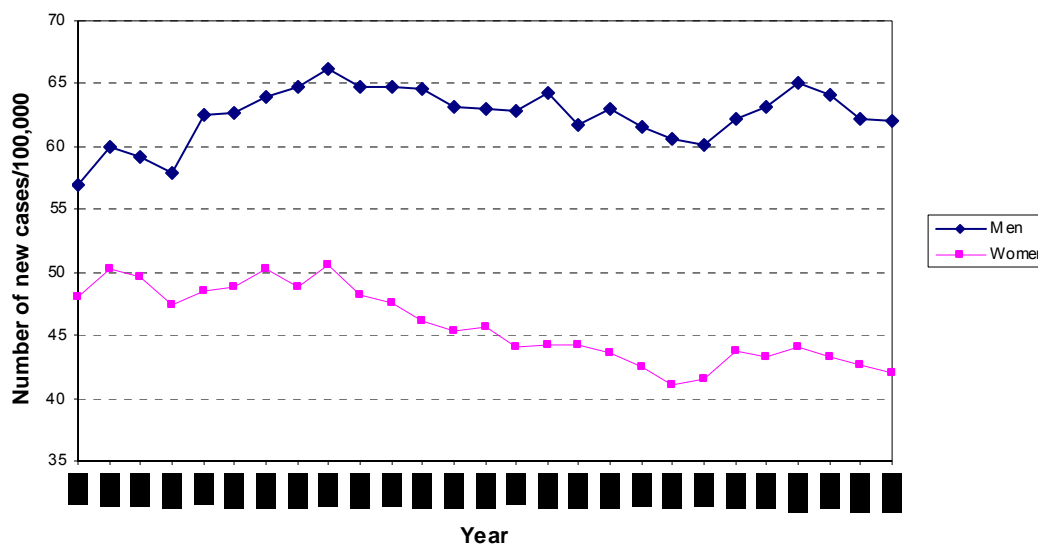
<sup>8</sup> The USPSTF is an independent expert advisory panel convened by the US Public Health Service, Department of Health and Human Services, that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services.

<sup>9</sup> The NHIS is conducted annually by the National Center for Health Statistics of the Centers for Disease Control and Prevention. It is a continuing, nationwide in-person survey of approximately 40,000 households in the civilian non-institutionalised population.

<sup>10</sup> The term *endoscopy* refers to screening procedures that may have consisted of rigid procto-sigmoidoscopy, flexible sigmoidoscopy, or colonoscopy.

Canada<sup>11</sup> for 1977 to 2003 (see figure 2) show non-significant increases of 1.7% per year after 1997 for men and 1.2% per year after 1996 for women (Canadian Cancer Society/National Cancer Institute of Canada, 2006). Since 2000, rates have reverted to the previous longer time trend showing a decline in CRC incidence for men and women.

**Figure 2: Colorectal cancer incidence rates, Canada 1977-2003** (per 100,000/year, age-standardised to the 1991 Canadian population)



54. As in the USA, the timing of the increase in CRC incidence differed for men and women; however the increase in Canada occurred earlier for women than for men, whereas the reverse was observed in the USA.
55. There are no nationally representative data available on blood folate concentrations in Canada before and after fortification. A retrospective study which analysed clinical samples obtained from Canadian women aged 65 years and older from Ontario and British Columbia reported a 64% increase in mean serum folate concentration: from 14.8nmol/L (6.5µg/L) before fortification (January 1996-December 1997) to 24.2nmol/L (10.7µg/L) postfortification (January 1998-December 2000) (Ray *et al*, 2003). Analysis of clinical samples obtained from women aged 18-42 years in Ontario reported that mean RBC folate concentration increased by 41%, from 527nmol/L (232.7µg/L) prefortification to 741nmol/L (327µg/L) postfortification (Ray *et al*, 2002). Caution should be applied in the interpretation of these results as they are based on clinical samples from 1-2 provinces. It is not known if the decline in CRC incidence after 2000 coincided with a decline in blood folate concentrations as there are no data on folate status in Canada after 2000.
56. Survey data on the use of colorectal cancer screening are available for only a few regions.<sup>12</sup> which may not be representative of the Canadian population and there are no data on trends in cancer screening practices.
57. Examination of trends for the incidence of other cancers shows that after 1996 there was a significant decline in the incidence of lung cancer (1.6%) for men and a

<sup>11</sup> Incidence data were available for all the provinces and territories. Incidence rates are estimates for Quebec 2002 and 2003 and for Ontario 2003.

<sup>12</sup> British Columbia, Newfoundland and Labrador covered 100% of the population, Saskatchewan (covered 63% of the population) and Ontario (covered 27% of the population; Toronto not included).

significant increase in the incidence of prostate cancer (3.4%); for women, there was a non-significant decline (1.0%) in Non-Hodgkin's lymphoma after 1997.

**Annex 4****The potential impact of mandatory fortification of flour with folic acid****Modelling exercise**

1. The effect of fortifying flour with different doses of folic acid on the total folate intake (taking account of current levels in fortified foods, supplement use, processing losses, overage) of different population age groups was investigated by modelling intake data from the National Diet and Nutrition Survey series.
2. Flour was considered the most appropriate vehicle for fortification because of its near universal and narrow variability of consumption in the population.
3. The purpose of the modelling exercise was to explore the effect of mandatory folic acid fortification of flour on the:
  - average intakes of folic acid;
  - proportion of the population with folate intakes below the recommended nutrient intake (RNI<sup>1</sup>);
  - risk of NTD-affected pregnancies;
  - total numbers in the population who might be exposed to doses of folic acid above the tolerable upper level (UL) per day set for folic acid<sup>2</sup>;
  - number of people aged 65 years and over, with low vitamin B<sub>12</sub> status, who might be exposed to doses of folic acid above 1 mg/day.
4. In the UK, a Guidance Level<sup>3</sup> (GL) of 1 mg/day for folic acid was set for adults, however no GLs were set for children. ULs were set for children in Europe and the USA, which were extrapolated from the UL for adults on the basis of body weight. The ULs were therefore used for the purpose of the modelling exercise in order to estimate the total proportion of the UK population (including children) who might be exposed to high intakes of folic acid.
5. The potential effects of mandatory fortification of flour with folic acid were assessed at four different levels/100g of flour: 100, 200, 300 and 450 µg. After processing losses this would result in actual levels of 75, 150, 225 and 338 µg/100 grams food respectively.
6. The modelling exercise also considered the effect of mandatory fortification of flour with folic acid *excluding* the contribution of folic acid intakes from:
  - fortified breakfast cereals and fortified fat spreads but *including* the contribution from supplements;
  - fortified breakfast cereals, fortified fat spreads, and supplements.

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<sup>1</sup> The RNI is the amount of a nutrient that is considered sufficient to meet the requirements of 97.5% of the population. The RNI for adults & children: 100µg/d for 4-6y; 150µg/d for 7-10y; 200µg/d for 11y and above.

<sup>2</sup> The UL represents the highest level of daily nutrient that is likely to pose no risk to health. UL for adults (≥18y) : 1mg/d; UL for children (Europe): 300µg/d for 4-6y; 400µg/d for 7-10y; 600µg/d for 11-14y; 800µg/d for 15-17y.

<sup>3</sup> The Guidance Level is an approximate indication of intakes that would not be expected to cause adverse effects.

## Results of modelling exercise

**Table 1: Effects of mandatory fortification of flour with folic acid (excluding fortification of wholemeal flour)**

Level of folic acid ( $\mu\text{g}/100\text{g}$ flour (level in food after processing))	Average increase in folic acid intake ( $\mu\text{g}/\text{day}$ ) <sup>4</sup>	Estimated mean total folate intakes ( $\mu\text{g}/\text{day}$ )	Estimated % of people with intakes below RNI <sup>5</sup>	Estimated number of people exceeding the UL/day of folic acid <sup>6</sup>	Estimated number aged 65y+ with low vitamin B <sub>12</sub> status exceeding 1 mg/day folic acid	Estimated NTD pregnancies prevented / year (% risk reduction)
<b>Includes folate and folic acid from all sources (including estimates of overage)<sup>7</sup></b>						
0	0	302	23	127,000	900	0
100 (75)	51	353	11	225,000	1,700	42-93 (6-10%)
200 (150)	102	403	6	404,000	2,000	82-180 (12-20%)
300 (225)	152	454	3	773,000	2,500	114-261 (16-29%)
450 (338)	228	530	2	2,200,000	6,300	163-369 (23-41%)
<b>Excluding folic acid from fortified breakfast cereals and fat spreads</b>						
0	-74	232	36	18,000	800	-70 (-10%)
100 (75)	-24	283	17	38,000	800	-14 (-2%)
200 (150)	27	334	9	52,000	900	35-63 (5-7%)
300 (225)	78	385	5	115,000	900	77-162 (11-18%)
450 (338)	154	461	3	559,000	900	126-279 (18-31%)
<b>Excluding folic acid from fortified breakfast cereals, fat spreads and supplements</b>						
0	-85	217	38	0	0	-91 (-13%)
100 (75)	-34	267	18	0	0	-35 (-5%)
200 (150)	17	318	9	0	0	21-36 (3-4%)
300 (225)	68	369	6	55,000	0	63-126 (9-14%)
450 (338)	144	445	3	470,000	0	112-252 (16-28%)

To note: the figures in brackets in the first column represent the actual levels in food after processing losses.

### Effects of mandatory fortification including current levels of folic acid intake from voluntary fortification and supplements

- See first section of table, headed: *Includes folate and folic acid from all sources*.
- It can be seen from Table 1 (line 1: fortification level, 0) that at current levels of folic acid intake in the UK (from voluntary fortification and supplements):
  - The average folate intake of the population is approximately 302  $\mu\text{g}/\text{day}$ ;
  - Approximately 23% of the population (13,261,000 people) have intakes below the RNI for folate;
  - Approximately 127,000 people are exceeding the UL/day set for folic acid (the largest proportion are children aged 4-10 years [57% or 72,000 children] as the ULs / day are much lower for these age groups [300-400  $\mu\text{g}/\text{day}$ ] than for adults [1 mg/day]);
  - Approximately 900 adults aged 65 years and over with low vitamin B<sub>12</sub> status are exceeding folic acid intakes of 1 mg/day.
- It can be seen that mandatory fortification at increasing levels of folic acid would progressively reduce NTD risk and the percentage of the population with intakes below the RNI for folate. However it would also progressively increase the proportion of the

<sup>4</sup> Across all population groups.

<sup>5</sup> For each age group (DH, 1991)

<sup>6</sup> For each age group (European Scientific Committee on Foods, 2001).

<sup>7</sup> Mean of values for overage applied and not applied.

population with intakes above the UL/day for folic acid and the number of adults aged 65 years and older with low vitamin B12 status exceeding folic acid intakes of 1 mg/day.

*Effect of mandatory fortification excluding folic acid intakes from fortified breakfast cereals/fortified spreads and including folic acid intake from supplements*

10. See second section of Table 1, headed: *Excluding folic acid from fortified breakfast cereals and fat spreads*.
11. It can be seen that, in the absence of mandatory fortification, removing the contribution of folic acid intakes from fortified breakfast cereals and fortified fat spreads (but including intakes from supplements) would increase the NTD risk and the percentage of the population with intakes below the RNI for folate but would reduce the percentage of the population with intakes above the UL/day for folic acid and the number of adults aged 65 years and over with low vitamin B12 status and folic acid intakes above 1 mg/day:
  - The average folate intake of the population would decrease by 74 µg/day.
  - Approximately 70 more pregnancies would be affected by NTDs (10% increase in risk).
  - The percentage of the population with intakes below the RNI for folate would increase from 23% to 36%.
  - Approximately 18,000 people would exceed the UL/day for folic acid intake (decrease of 86%).
  - Approximately 800 adults aged 65 years and over, with low vitamin B<sub>12</sub> status, would exceed folic acid intakes of 1 mg/day (decrease of 11%).
12. The lowest level of mandatory fortification with folic acid required to overcome the increased NTD risk caused by removal of folic acid from fortified breakfast cereals and fortified fat spreads would be 200 µg/100 grams flour. Mandatory fortification at 300 µg/100 grams flour would further reduce the risk of NTD-affected pregnancies (by 11-18%) without increasing the number of people with intakes above the UL (115,000 compared to the current level of 127,000) or the number of adults aged 65 years and over with low vitamin B12 status, exceeding intakes of 1 mg/day. The proportion of people with intakes below the RNI would be reduced from the current level of 23% to 5%. Mandatory fortification with folic acid above this level would further reduce the risk of NTD-affected pregnancies and the proportion of the population with intakes below the RNI, however the numbers with intakes above the UL/day would be substantially increased.

*Effect of mandatory fortification of flour with folic acid excluding the contribution of folic acid intakes from fortified breakfast cereals, fortified spreads, and supplements*

13. See third section of Table 1, headed: *Excluding folic acid from fortified breakfast cereals, fat spreads and supplements*.
14. Without folic acid intakes from fortified breakfast cereals, fortified fat spreads, and supplements:
  - The average folate intake of the population would decrease by approximately 85 µg/day.
  - Approximately 91 more pregnancies would be affected by NTDs (13% increase in risk).

- The percentage of the population with intakes below the RNI for folate would increase from 23% to 38%.
  - Unlikely that anyone would exceed folic acid intakes above the UL/day.
  - Unlikely that any adults aged 65 years and over, with low vitamin B<sub>12</sub> status, would exceed folic acid intakes of 1 mg/ day.
15. Mandatory fortification with folic acid at a minimum level of 200 µg/100 grams flour would be required to overcome the increased risk of NTD-affected pregnancies caused by removing the contribution of folic acid intakes from fortified breakfast cereals/fortified spreads and supplements.

*Comparison of the effects of excluding folic acid intakes from fortified breakfast cereals and fat spreads only with excluding folic acid intakes from fortified breakfast cereals, fat spreads, and supplements*

16. Including or excluding folic acid intakes from supplements would result in little difference in the number of people with intakes below the RNI for folate: 36% including supplements and 38% excluding supplements. This suggests that compared to fortified foods, supplements do not make an important contribution to helping people achieve the RNI for folate intake.
17. The increased risk of NTD-affected pregnancies is lower if folic acid intakes from supplements are included (10% increased risk) than if they are excluded (13% increased risk), indicating that supplements make an additional contribution to reducing NTD risk.
18. Approximately 127,000 people in the UK are currently exceeding the UL/day for folic acid. Out of this total, 14% can be attributed to supplement consumption (18,000 people) and 86% (109,000 people) to consumption of fortified foods. This suggests that folic acid intakes above the UL / day for folic acid are largely due to consumption of foods fortified with folic acid.

*Summary*

19. Current intakes of folic acid above the UL/day for folic acid intake are largely due to consumption of foods voluntarily fortified with folic acid. Present consumption patterns of supplements and foods voluntarily fortified with folic acid contribute to the highly variable intakes of folic acid, resulting in large sections of the population with intakes below the RNI for folate and considerable numbers of people with intakes of folic acid above the UL/day.
20. Results from the modelling exercise suggest that, without the contribution of folic acid from voluntary sources, mandatory fortification of flour with folic acid would confer a more even distribution of folic acid intakes across the population compared to current voluntary fortification and supplement use. The redistribution of folic acid intakes would mean that women at greatest risk of NTD-affected pregnancies, i.e. those with the lowest folate intakes, would be reached through mandatory fortification.
21. If no foods were voluntarily fortified, the option that appears to provide the optimum balance between benefits and possible risks is mandatory fortification at a level of 300 µg of folic acid/100 grams flour (excluding wholemeal flour); the actual level in food after processing losses would be 225 µg/100 g food. At this level it is estimated that: average folic acid intake would increase by 78 µg/day; the estimated mean total folate intake would be 385 µg/day (compared to the current average intake of 302 µg/day). 77-162 NTD-affected pregnancies per year could be prevented (11-18% risk reduction)

without increasing the number of people with folic acid intakes above the UL/day or the number of adults aged 65 years and over, with low vitamin B<sub>12</sub> status, exceeding intakes of 1 mg/day; and the proportion of the population with intakes below the RNI would be reduced from 23% to 5%.

***Comparison of results from the SACN modelling exercise with the experience in the USA and Canada following mandatory fortification of flour with folic acid***

22. There are a number of difficulties in making comparisons with countries that have mandatory folic acid fortification policies. This is because:
- different countries have fortified different groups of food products with varying levels of folic acid (see Table 2);
  - there are differences in the available data for the estimated effects of folic acid on NTD incidence;
  - the effect of folic acid on reducing NTD risk is dependent on background blood folate concentrations so at a particular dose of folic acid the proportional reduction in NTD risk will be higher in populations with lower initial blood folate concentrations.
23. There are also difficulties in comparing the fortification levels modelled by SACN which would be equivalent to the increase in folic acid intake observed in other countries with mandatory fortification because SACN considered a number of scenarios (i.e. mandatory fortification: including current intakes of folic acid from voluntary fortification and supplements, excluding voluntary fortification but including supplements; excluding voluntary fortification and supplements) with and without wholemeal flour. The comparisons below are therefore of the estimates from the SACN modelling which include the effects of mandatory fortification of all flour and include folic acid intakes from voluntary fortification and supplements as this most closely resembles the situation in other countries.
24. SACN's recommendation for mandatory fortification of 300 µg/100g flour excludes fortification of wholemeal flour and folic acid from voluntary sources, so the estimated increase in folic acid/day and the corresponding NTD risk reduction is lower than observed in the USA and Canada and predicted for the Republic of Ireland.

USA

25. Mandatory fortification with folic acid at an average level of 140 µg/100g cereal product was intended to increase average intakes of folic acid by approximately 100 µg/day. It has been estimated that mandatory fortification has actually increased folic acid intakes by approximately 215-240 µg/day. This is mainly because controls apply at final food level and to ensure minima are met there has been over addition at ingredients level. The additional increase in folic acid of 215-240 µg/day has resulted in a 27% decline in NTD-affected pregnancies. Data from the SACN modelling exercise suggest that to achieve an increase in folic acid intake equivalent to that observed in the USA, would require fortification of all flour (including wholemeal flour) at a level somewhere between 300 and 450 µg/100 grams (because fortification at 300 µg would be too low and 450 µg would be too high). This would result in an additional folic acid intakes of somewhere between 172 µg/day and 258 µg/day and reductions in NTD-affected pregnancies somewhere between 18 and 42%.

CANADA

26. Mandatory fortification with folic acid at an average level of 150 µg/100 grams flour was intended to increase average intakes of folic acid by approximately 100 µg/day. There are no nationally representative data for the estimated daily increases in folic acid intakes in Canada, however it has been estimated that folic acid intakes increased by approximately 70 µg/day for women (aged 19-44 years) in Newfoundland which

resulted in a 78% decline in NTD rates. This decline in NTD rates is higher than observed for other provinces in Canada (Ontario, 51%; Nova Scotia, 54%; Quebec, 32%). Data from the SACN modelling exercise suggest that the increase in folic acid intake observed in Newfoundland is roughly equivalent to fortification at a level somewhere between 100 and 200 µg/100 grams flour (including wholemeal flour) which would result in an additional intake of folic acid somewhere between 50 and 100 µg/day for women of childbearing age (not shown in Table 1, which is for the whole UK population) and reductions in NTD-affected pregnancies somewhere between 7 and 22%.

27. In Ontario, it has been estimated that mandatory fortification increased average folic acid intake by 150 µg/day (for the whole population), which resulted in a 51% decline in NTD rates. (However measurement of blood folate levels were from clinical samples and may differ from folate blood levels in the general population). Data from the SACN modelling exercise suggest that the increase in folic acid intake observed in Ontario is roughly equivalent to fortification at a level somewhere between 200 and 300 µg/100 grams flour (including wholemeal flour) which would result in an additional intake of folic acid somewhere between 115 and 172 µg/day and reductions in NTD-affected pregnancies somewhere between 13 and 32%.

#### **Comparison of results from the SACN modelling exercise with proposed fortification level in Republic of Ireland**

28. The National Committee on Folic Acid Food Fortification (NCF AFF) in Ireland estimated that fortification at 120 µg/100 grams bread would provide women of child bearing age with an average additional daily intake of 110 micrograms folic acid and reduce NTD risk by 24%. Results from the SACN modelling suggest that this is equivalent to a fortification level somewhere between 200 and 300 µg/100 grams flour (including wholemeal flour). This which would result in an additional folic acid intake of somewhere between 100 and 150 µg/day for women aged 14-49 years (not shown in Table 1, which is for the whole UK population) and reductions in NTD risk somewhere between 13 and 32%.
29. The most likely explanation for the differences in NTD risk reduction predicted by SACN & NCF AFF is that SACN used a more developed model which accounted for losses in the food chain and used 2 different approaches to model NTD risk because of uncertainties in the available data. The two methods provided an estimated range of NTD-affected pregnancies which could be prevented at the different fortification levels. SACN compared the NTD risk reduction estimated from the modelling exercise with the reduction in NTD risk observed in the USA following mandatory fortification and found that the change in NTD rates in the USA falls within the range of values for NTD risk reduction estimated by the modelling. The predicted NTD risk reduction in Ireland of 24%, in response to an increase in folic acid intakes of 110 µg/day following mandatory fortification, is similar to the actual reduction in NTD risk observed in the USA (27%) after an increase in folic acid intakes of approximately 215-240 µg/day.

**Table 2: Comparison of results from SACN modelling exercise with proposed fortification in Republic of Ireland and with experience in USA & Canada following mandatory fortification**

Country	UK (SACN predicted estimate)	Republic of Ireland (NCF AFF predicted estimate)	United States (measured estimate)	Canada (measured estimate)
Fortification level	<ul style="list-style-type: none"> <li>300µg/100g cereal flour (equivalent to 225µg/100g of food)</li> </ul>	<ul style="list-style-type: none"> <li>120µg/100g bread</li> </ul> <p><i>(exclusion of some minor bread products)</i></p>	<ul style="list-style-type: none"> <li>154µg/100g cereal flours</li> <li>95µg/100g enriched bread, rolls, buns</li> <li>154-308µg/100g</li> </ul>	<ul style="list-style-type: none"> <li>150µg/100g cereal flours</li> <li>100µg/100g enriched bread</li> <li>200-270µg/100g pasta</li> </ul>

	<i>(excluding wholemeal flour and excluding folic acid from voluntary sources)</i>	<i>(voluntary fortification also permitted)</i>	<ul style="list-style-type: none"> <li>enriched rice</li> <li>198-265µg/100g macaroni &amp; noodle products</li> </ul> <i>(voluntary fortification also permitted)</i>	<i>(voluntary fortification also permitted)</i>
Estimated increase in folic acid intake (µg/day)	78 <sup>8</sup> <i>(whole population)</i>	110 <i>(women of childbearing age)</i>	215-240 <sup>9</sup> <i>(whole population)</i>	National data unavailable
Reduction in NTD risk <sup>10</sup>	11-18%	24%	27%	Ontario: 51% Nova Scotia: 54% Quebec: 32% Newfoundland: 78%

<sup>8</sup> The estimated daily increase in folic acid intake is lower than other countries because it excludes fortification of wholemeal flour and folic acid from voluntary sources.

<sup>9</sup> It was anticipated that mandatory fortification would increase folic acid intakes by about 100 µg/day.

<sup>10</sup> Comparison of NTD risk is complicated because of differences in ascertainment of NTD data and completeness of data can be affected by methods of collation. The effect of folic acid on reducing NTD risk is also dependent on background blood folate concentrations so at a particular dose of folic acid the proportional reduction in NTD risk will be higher in populations with lower initial blood folate concentrations.