

FOLATE AND HEALTH

Executive Summary

1. The Agency's 2005/2010 Strategic Plan includes an overall aim to help reduce diet-related diseases. In this context, the Agency has made a commitment to Health Ministers to provide advice on dietary folate and neural tube defect (NTD) prevention. The Scientific Advisory Committee on Nutrition (SACN) have reviewed evidence that has arisen since the Committee on the Medical Aspects of Food Policy (COMA) advised, in 2000, that universal fortification of flour with folic acid (a synthetic form of folate) would have a significant effect in preventing NTD-affected conceptions and births. SACN advised that there is now further clear evidence available that increasing folate intake would reduce the numbers of NTD-affected pregnancies. SACN also confirmed COMA's earlier advice that flour should be fortified with folic acid.
2. The paper sets out three options for improving the folate status of young women:
 - encouraging the uptake of folic acid supplements and changes to diets to increase the consumption of folate rich foods;
 - further encourage voluntary fortification of foods; or
 - mandatory fortification of foods.
3. The Board is asked to:
 - **note** the background to this issue, including the advice of SACN on reduction of NTD-affected pregnancies;
 - **agree** to consult on the policy options set out in paragraphs 20 – 33;
 - **agree** that mandatory fortification with folic acid be presented as the preferred option at this stage, subject to the finding of the consultation and further information to be collected;

- **note** the work plans to assemble further evidence, including consumer engagement and cost-benefit analysis, set out in paragraphs 37 – 38;
- **identify** any additional information needed to enable the Board to finalise its advice to Ministers; and
- **note** the plans of the Department of Health in relation to vitamin B12.

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FOLATE AND HEALTH

Issue

1. This paper seeks the Board's agreement to consult on its advice to Ministers on how to reduce the number of NTD-affected pregnancies. The issue was previously discussed by the Board in 2002 (FSA 02/05/02).

Strategic Aim

2. The 2005/2010 Strategic Plan includes an overall aim to help reduce diet-related diseases. In this context, the Agency has made a commitment to Health Ministers to provide advice on dietary folate and NTDs.

Background

3. In 2000 COMA advised that universal fortification of flour with folic acid (a synthetic form of the B vitamin folate) would have a significant effect in preventing NTD-affected conceptions and births.¹ In 2002 the Board considered the advice from COMA and agreed not to recommend universal fortification of flour with folic acid, at that time, to Health Ministers. This was largely due to concerns about risks to the elderly but also because of concerns raised by consumer organisations about reducing the freedom to choose unfortified foods. Health Ministers agreed with this assessment and in 2004 asked SACN to update the earlier advice from COMA.
4. SACN have reviewed the earlier work by COMA on folic acid and the new evidence available since 2000. They advise that flour fortification with folic acid would result in a dose dependent reduction in the numbers of NTD-affected pregnancies in the UK (Annex 1, Tables 1 and 2). Fortification would also benefit all age groups by increasing the number of people achieving dietary recommendations for folate.

¹ Department of Health. Folic Acid and the Prevention of Disease. Report on Health and Social Subjects 50. London: TSO, 2000.

5. The background to the SACN report and details of its conclusions and recommendations are given in Annex 1. A fact sheet on folate, folic acid and vitamin B12 is given in Annex 2.

NTD-affected Pregnancies in the UK

6. SACN noted that national data on NTD-affected pregnancies are incomplete but estimated that there are about 700-900 NTD-affected pregnancies in the UK per year. These data do not take into account miscarriages that occur as a result of NTDs but include reported terminations for England, Wales and Scotland, and some estimates of underreporting for England and Wales. Therapeutic terminations are not available in Northern Ireland.
7. The rates of NTDs vary across the UK with the highest levels being reported in Wales and Scotland. The reason for the differences in NTD occurrence is unclear; however it is likely that some differences are due to data collection inconsistencies. In addition, there are a number of factors that affect NTD risk including low folate intake and status, low socioeconomic status, genetic factors (including ethnicity with those of northern European and South Asian decent¹ having the highest prevalence), obesity² and diabetes³. Evidence from clinical trials shows that improving folate intake and status may reduce the risk of an NTD-affected pregnancy by up to 79%.¹

Current Government Policy on Folic Acid

8. Current Government advice to women on folic acid supplements is integrated into general nutrition and pregnancy information. All adults are advised to consume 200 micrograms of folate/day. Women who could become pregnant are advised to take an additional 400 micrograms of folic acid/day from before conception until the 12th week of pregnancy, as a supplement (Department of Health 1992). They are also advised to eat more foods naturally rich in folate, and foods fortified with folic acid, especially breakfast cereals (Department of Health 2000).

² Werler MM, Louik C, Shapiro S & Mitchell AA. Pre-pregnant weight in relation to risk of neural tube defects. *JAMA*. 1996, 275:1089-1092.

³ Bercera JE, Khoury MJ, Cordero JF & Erikson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population based case control study. *Pediatrics*. 1990. 85(1): 1-9.

9. Data on the use of folic acid supplements indicate that about a quarter of women take folic acid as recommended by the Department of Health, i.e. before and after conception.⁴ This relatively low rate of usage is in part due to only about half of all pregnancies being planned.⁴ Although three-quarters of women report taking a folic acid supplement during pregnancy (similar numbers in England, Northern Ireland, Scotland and Wales),⁵ it is unlikely that action only once a pregnancy is recognised will be effective at reducing the risk of an NTD.

Evidence since COMA Report in 2000

Benefits of Increasing Folic Acid intakes through Food Fortification

10. SACN advised that there is now clearer evidence available from countries that have introduced mandatory fortification with folic acid that increasing the folic acid intake of women reduces the risk of NTD-affected pregnancies. It has been demonstrated at a population level by national food fortification programmes in USA, Canada and Chile, that fortifying staple foods with folic acid reduces the numbers of affected of NTD-affected pregnancies by between about 30 – 50%. SACN have therefore confirmed the advice from COMA that fortification of bread or flour with folic acid would reduce the number of NTD-affected pregnancies in the UK. They observed that there have been no consistent reductions in England and Wales over the same period. Data from Scotland suggests that there may have been a reduction in the late 1990s, but the data are unclear.
11. It should be noted that alongside fortification women planning a pregnancy would still need to take folic acid supplements to achieve optimal protection from the risk of NTD. This is similar to the situation in other countries with fortification programmes.
12. SACN also advised fortification of flour with folic acid would benefit older people, as well as women of reproductive age, by increasing the numbers achieving recommended levels of folate intake, substantial numbers of whom currently have low dietary intakes (Annex 1, Table 1).

⁴ Blake M, Herrick K & Kelly Y. Health Survey for England 2002: Maternal and Infant Health. London. TSO, 2003.

⁵ Hamlyn B, Brooker S, Oleinikova K & Wands S. Infant Feeding 2000. A survey conducted on behalf of DH, the Scottish Executive, the National Assembly for Wales and Department of Health, Social Services and Public Safety in Northern Ireland. London: TSO, 2002.

Risk to older people

13. The concerns for older people are related to a potential delaying effect of increased folic acid intake on the diagnosis and treatment of severe vitamin B12 deficiency. In addition, preliminary unpublished research findings suggest that folic acid supplements may increase the risk of progression of pre-cancerous polyps in the bowel.⁶ Both these concerns relate to folic acid intakes in excess of 1000 micrograms. Annex 2 (paragraph 10) explains how folic acid might delay the diagnosis of severe vitamin B12 deficiency.

14. SACN noted that vitamin B12 deficiency is common in older people in the UK, with 5 – 10% people having a low vitamin B12 status and recommend action by Health Departments to address this. They also noted that cases of the irreversible neurological condition associated with severe vitamin B12 deficiency are rare in the UK, with about 28 cases⁷ admitted to NHS hospitals in 2002. This figure represents 0.004% of older people with low vitamin B12 status. Assuming no change in the detection and treatment of less severe vitamin B12 deficiency the number of cases of the irreversible neurological condition associated with severe vitamin B12 deficiency would be expected to increase each year as the population ages (projections suggest that the number of people of pensionable age will increase from about 11 to 14 million over the next 20 years).⁸

15. SACN noted that there are limited data available from countries that have fortified staple foods with folic acid to suggest there have been no concurrent changes in the prevalence of biochemical or clinical signs of vitamin B12 deficiency. Data from the USA⁹ suggests the incidence of low vitamin B12 status has declined in older people post fortification. The preliminary unpublished research findings on folic acid supplements and polyps in the bowel are not clear enough to allow any conclusions to be drawn from them at this time (paragraph 13). There are no data, however, to show that cancer rates have increased in association with folic acid fortification from any country. Data from the USA¹⁰ indicates there has been

⁶ Cole B, Baron J, Sadler R. A randomized trial of folic acid to prevent colorectal adenomas [abstract], 2005. This paper was presented at the American Association for Cancer Research meeting, 2005. The findings have not been peer reviewed or published and there are very few available details.

⁷ Some cases may be re-admissions.

⁸ www.gad.gov.uk

⁹ Pfeiffer C, Caudill S, Gunter E, Osterloh J, Sampson E. Biochemical indicators of B vitamin status in the US population after folic acid fortification: results from the National Health and Nutrition Examination Survey 1999-2000, *The American Journal of Clinical Nutrition*, 2005; 82: 442-50

¹⁰ National Center for Health Statistics (Health, United States, 2005)

a general decline in the incidence of colorectal cancer occurring over the same time period as fortification.

16. SACN advised that there is now evidence that 1000 micrograms/day of folic acid would not be expected to cause delays in the diagnosis of vitamin B12 deficiency. This is consistent with expert opinions from the UK¹¹, EU¹² and USA.¹³ They also noted that the majority of cases of folic acid masking signs of vitamin B12 deficiency have been reported at doses at or above 5000 micrograms/day.

17. SACN estimated up to 15,300 older people are currently exceeding 1000 micrograms/day of folic acid and that 1,200 of these older people also have low vitamin B12 status. Consumption of more than 1000 micrograms/day of folic acid is due generally to consumption of fortified low fat spreads and supplements. They estimated that fortification of flour with folic acid could result in a dose dependent increase in the numbers of older people exceeding 1000 micrograms/day (Annex 1, Tables 1 and 2). SACN, however, also advised that no older people would exceed 1000 micrograms/day of folic acid if low fat spreads were no longer fortified with folic acid, older people limited their consumption of folic acid containing supplements and no significant changes occurred in the fortification of other foods.

18. The factors associated with an increased theoretical risk of delayed diagnosis of severe neurological disease are:

- low vitamin B12 status this can lead to the development of clinical disease (anaemia and / or peripheral neuropathy) associated with severe vitamin B12 deficiency. The proportion who might develop clinical disease is unknown;
- undetected mild neurological disease associated with vitamin B12 deficiency;
- failure to develop anaemia associated with vitamin B12 deficiency; anaemia can act as an early warning sign of vitamins B12 deficiency; the proportion of people with clinical disease who will have symptoms of anaemia, which might

¹¹ Expert Group on Vitamins and Minerals. Safe Upper Levels for Vitamins and Minerals. FSA: London, 2003.

¹² Opinion of the Scientific Committee on Food on the tolerable upper intake level of folate, 2000.

¹³ Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998).

be masked by increased folic acid is unknown; neurological symptoms have been reported to occur without anaemia in 20-30% of cases; and

- intakes of folic acid greater than 1000 micrograms/day.

19. SACN advised that in order to minimise risk to older people a management strategy for vitamin B12 deficiency should be considered. B12 deficiency cannot be managed through the diet (Annex 2, Paragraph 8).

Policy Options

20. This paper recommends consultation on four options. It is recognised that these options are not mutually exclusive and could be developed in combination. The likely benefits in relation to NTD prevention, potential risks to older people and other key issues, including consumer perception and choice issues and impact on industry, are summarised below. Further details and initial views of stakeholders are provided in Annex 3.

*Option 1 - **Do nothing***

21. If no action is taken, there is no reason to expect a significant change to the current population folate status, the prevalence of NTDs or risks to older people.

*Option 2 – **Increase the effort to encourage young women to take supplements and changes to diet to increase the consumption of folate rich foods.***

22. Folic acid supplementation is, in theory, an effective route by which to achieve optimal folate intake among the target group. However, previous messages to women have had limited success in reducing incidence of NTDs, particularly in view of the fact that around half of pregnancies are unplanned. The women most at risk from a NTD-affected pregnancy are also less likely to take up advice, i.e. women who are young, do not plan their pregnancies, come from socioeconomically deprived backgrounds⁴ and have poor dietary patterns¹⁴ (see paragraph 7).

¹⁴ Henderson L, Gregory J, Irving K & Swan G. The National Diet and Nutrition Survey: adults aged 19 to 64 years. London: TSO, 2003.

23. A recent evaluation of the effectiveness of advice to take folic acid across European countries found no examples of the advice being successful at reducing NTD affected births.¹⁵

Option 3 – Further encourage voluntary fortification of foods

24. It is not likely that this option will significantly improve folate status in the target group. Voluntary fortification of foods to help prevent NTD's was encouraged in the 1990's. There are a number of fortified foods and drinks on the market. The only fortified foods that make a notable contribution to folic acid intake are low fat spreads (about a third are fortified) and breakfast cereals (about half are fortified). There are a small number of breads currently fortified with folic acid. Over recent years a number of breads have been fortified with folic acid but these have not remained on the market. Fortified breads and spreads tend to be premium products, which are not likely to be brought by the target group.

25. For voluntary fortification to be effective it must affect foods that are purchased and consumed by the target group on a regular basis. Breakfast cereals and breads are suitable candidates but industry has indicated but they would not be fortified on a voluntary basis to any significantly greater extent.

26. On the other hand increased levels of voluntary fortification may increase the risks to older people posed by high folic acid intakes. SACN have noted that high levels of folic acid intake are commonly associated with the consumption of low fat spreads fortified with folic acid and folic acid containing supplements (Annex 1, Graph 1). It is not clear how voluntary fortification could be managed to maximise benefits and minimise risks.

Option 4 - Mandatory fortification

27. Mandatory fortification of an appropriate food or foods would ensure improved folate status of the target group and a reduction in the number of NTD-affected pregnancies. The fortification of a broad product category would, however, limit choice. The risk to older people is discussed in paragraphs 13 – 19.

¹⁵ Botto LD, Lisi A et al. International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? *BMJ* 2005, 330:571.

28. Bread would be an appropriate vehicle because it has a relatively uniform consumption across subgroups of the population. Fortification will increase folic acid consumption in a predictable way and increase the intake of the target group (Annex 1, Table 3 and Graph 2). This would not be the case for other foods, such as soft drinks, where intakes are seen to vary greatly between individuals. Folic acid is also relatively stable in bread (except for soda bread) unlike in acidic food and drinks. Fortification of bread would also improve the folate status of older people, about a fifth of whom currently have low status.

29. Flour products, including bread, have been successfully used as vehicles for folic acid in countries that have introduced mandatory fortification and seen reduction in NTD rates. Other foods have been seriously considered for mandatory fortification (such as milk in New Zealand)¹⁶ but rejected for technical reasons or because of patterns of consumption.

30. There are the two main potential methods for fortification of bread:

- Fortification of flour at the milling stage (either all flours or all flour except wholemeal).
- Fortification of flour at the bread making stage (either some or all breads).

31. Initial discussion with the bread and milling industry indicates that the fortification of all flour except for wholemeal at the milling stage is their preferred option. This would build upon the existing requirement for the milling industry to fortify all flour except wholemeal in the UK with iron, calcium, thiamine and niacin¹⁷ and so would capitalise on existing technology and regulation in mills. It also would be less technologically challenging for industry than fortification at the bread making stage. The modelling work carried out by SACN has shown that those consumers with the lowest intake of folate would have their intakes improved by the fortification of white and brown flour (Annex 1, Table 2). Choice could be provided to consumers who want an unfortified product through wholemeal bread (which

¹⁶ Green T, Newton R, Bourn D. Estimated folic acid intakes from simulated fortification of the New Zealand food supply. *New Zealand Medical Journal*, 2003; 116(1168):U292

¹⁷ The Bread and Flour Regulations require that flour should contain not less than 0.24 micrograms thiamine (vitamin B1), 1.60 micrograms nicotinic acid and 1.65 micrograms of iron per 100g of flour. These amounts are found naturally in wholemeal flour. White and brown flours must be fortified to restore their nutritional value. In addition calcium carbonate at a level of not less than 235 micrograms and not more than 390 micrograms per 100g of flour is added to all flours except wholemeal (and certain self raising varieties).

provides 40 micrograms/100g folate compared with unfortified white bread, which provides 25 micrograms/100g). Ethnic breads made by using white and brown flour would be included (white, brown and wholemeal chapatti flours are milled in the UK).

32. Fortification of white and brown flour would cause a dose dependent reduction in the numbers of NTD-affected pregnancies in the UK (Annex 1, Table 1). SACN advised that the risk of exposure to high levels of folic acid to older people should be minimised by tightly controlling levels of fortification of bread, as well as controlling the fortification of low fat spreads with folic acid and by advising older people to limit their consumption of folic acid supplements. Initial discussions with the milling and baking industry have indicated that fortification levels are more likely to be effectively controlled at the milling stage rather than at the bread making stage and by controlling in-going fortification rather than levels in bread.
33. People with Coeliac disease who avoid wheat products would not benefit from any fortification policy related to wheat flour. Specific dietary advice to people with Coeliac disease is important and the responsibility of the Health Departments.

View of Interested Parties

34. Annex 4 describes the stakeholder work already undertaken by the Agency. Initial discussions indicate that some public health groups (especially those representing NTD-affected people and their families) are strongly in favour of mandatory fortification. Groups representing older people are concerned that risks to older consumers should be fully taken into account. Consumer groups are keen that issues relating to consumer choice are adequately addressed.
35. The Agency's discussions to date with industry groups indicated that industry is unlikely to oppose mandatory fortification, subject to concerns on labelling and trade being addressed. The milling and baking industry are of the view that the same decision should be reached in all four countries of the UK if mandatory fortification of flour or bread is the preferred option, because of integrated nature of this industry across the UK.

36. The Food Advisory Committees for Wales, Scotland and Northern Ireland have each had preliminary discussions on this issue. Their finalised position will be available for the September Board meeting.

Timetable and Forward Work Programme

37. To inform the Board discussions in September the Agency will:

- consult on the options for increasing folate intake from May to August; (views will be sought on ethics of food fortification, labelling and choice, on costs, market share effects, appropriate legal approaches, trade implications, and race equality issues);
- carry out deliberative research in population representative groups in the four countries of the UK to explore mandatory fortification; participants will be provided with reading material at their initial briefing meeting to discuss the issues and this will be followed up by a second session;
- conduct an economic cost benefit analysis; and
- continue monitoring information from other countries.

38. At the same time the Department of Health will consider the advice by SACN on assessing incidence and prevalence, and management strategies for vitamin B₁₂-deficiency in older people.

Discussion

39. Since the Board last discussed this issue in 2002 experience in other countries has confirmed the substantial potential benefits of improving the folate status of young women and thereby reducing the numbers of NTD-affected pregnancies. New evidence has also enabled the risk assessment for older people to be refined, whilst there remain considerable uncertainties.

40. Continuing with a voluntary approach appears unlikely to affect intakes of the 'at risk' groups and may increase the risks in a hard to control manner. The balance of advantage therefore now appears to favour mandatory fortification as the most certain way of improving intakes in the target group. This approach would

however, raise important issues for consumer and industry, and the next step should be to explore these issues fully including by consulting stakeholders.

Board Action Required

41. The Board is asked to:

- **note** the background to this issue, including the advice of SACN on reduction of NTD-affected pregnancies;
- **agree** to consult on the policy options set out in paragraphs 20 – 33;
- **agree** that mandatory fortification with folic acid be presented as the preferred option at this stage, subject to the finding of the consultation and further information to be collected;
- **note** the work plans to assemble further evidence, including consumer engagement and cost-benefit analysis, set out in paragraphs 37 – 38;
- **identify** any additional information needed to enable the Board to finalise its advice to Ministers; and
- **note** the plans of the Department of Health in relation to vitamin B12.

SCIENTIFIC ADVISORY COMMITTEE ON NUTRITION: DRAFT REPORT ON FOLATE AND DISEASE PREVENTION**Background**

1. The Scientific Advisory Committee on Nutrition (SACN) advises the Agency and Health Departments on matters relating to diet, nutrition and health. In 2001, SACN succeeded the Committee on the Medical Aspects of Food Policy (COMA).
2. In its draft report on *Folic Acid and the Prevention of Disease* (Department of Health, 2000) COMA concluded that the universal folic acid fortification of flour would significantly reduce the number of conceptions and births complicated by neural tube defects (NTD). Following a formal public consultation in 2000, the Agency and Health Departments convened a stakeholder meeting in March 2002 to discuss issues relating to folic acid fortification.
3. The Agency's Board considered the fortification of flour with folic acid at its May 2002 open meeting (FSA 02/05/02). In July 2002 the Agency provided its advice to the Health Ministers, who were responsible for making a decision on folic acid fortification.
4. The Health Ministers replied in June 2004 and agreed with the Agency's advice not to introduce mandatory fortification at that time, due to outstanding concerns about vitamin B₁₂-deficiency. The letter stated that:
 - the wider impact of folic acid fortification, in particular the benefits and risks to older adults, should be assessed;
 - the matter will be reassessed following SACN's consideration and as the evidence becomes available from overseas; and
 - at the same time, options will be considered to increase the usage of pre-conceptual supplements, and increase dietary intakes of folate, for example through the Healthy Start and 5-A-Day Programmes and to address the concerns relating to prevalence and identification of vitamin B₁₂-deficiency.

5. SACN also in 2003 requested an update on the evidence that had arisen since the COMA report on folic acid (Department of Health, 2000). A Subgroup was established in February 2004 to consider the evidence and make recommendations to the Committee. The Subgroup was requested to:
 - Consider the evidence that had arisen since the COMA report, *Folic Acid and the Prevention of Disease* (Department of Health, 2000)
 - Advise on any gaps in the evidence base, with particular reference to the issue of folic acid masking the diagnosis of vitamin B₁₂-deficiency
 - Consider when and how to review the previous COMA risk assessment
6. After initial consideration of the evidence by the Subgroup it was agreed that sufficient new evidence had arisen since 2000 to warrant a full risk assessment.
7. SACN published the draft report *Folate and Disease Prevention* in November 2005 for an 8-week comment period. Thirty-two submissions were received from interested parties. The Committee considered issues raised and the draft report was amended.
8. In addition SACN analysed data from the National Diet and Nutrition Survey (NDNS) to determine current folate intakes and contributions made by foods fortified with and supplements containing folic acid. The Committee has also considered patterns of flour consumption, and the effect of various doses of folic acid in flour (white and brown alone and white, brown and wholemeal) on numbers achieving dietary recommendations for folate, changes in folate intake of low consumers, numbers of NTD affected pregnancies and numbers exceeding intakes of 1000 micrograms folic acid per day.
9. The Committee is now in the final stages of drafting its advice. The SACN report is due to be published in May 2006.

SACN Conclusions and Recommendations

10. The draft SACN report concludes¹⁸, in summary, that:

- There are significant percentages of women of child-bearing age and people of 65 years and over who currently have poor folate intake and /or status.
- Current advice to reduce the incidence of NTD-affected pregnancies by advising women to take folic acid supplements (pre- and post-conception) is not being followed by large numbers of women. About half of all pregnancies in the UK are unplanned.
- There are about 700 – 900 NTD-affected pregnancies in the UK per year.
- Countries that have introduced mandatory fortification of flour with folic acid have seen a 30 – 50% decline in NTD affected pregnancies. No reduction has been seen in England and Wales. Data from Scotland suggests there may have been a reduction in NTDs in the late 1990 but the data are unclear.
- It is estimated that if fortification of flour with folic acid at doses ranging between 100 and 450 micrograms/100g there would be a reduction in the numbers of NTD-affected pregnancies in the UK by 40-370 per year. This would also benefit all age and sex groups by reducing the number of the population not achieving dietary recommendations for folate (see Tables 1 and 2).
- Folic acid from supplements or fortified foods may lead to free folic acid appearing in the blood. The long-term effects of this are unknown. Doses of folic acid above 1000 micrograms/day may delay the diagnosis and treatment of vitamin B12 deficiency.
- Vitamin B₁₂ deficiency is relatively common in people aged 65 years and over in the UK and is usually caused by a failure of the gut to digest and absorb vitamin B₁₂ which means it cannot easily be managed by using a food-based approach. People aged over 65 years and young women, are also likely to have low intakes of the B vitamin riboflavin.

¹⁸ At this time the SACN report has not been finalised.

- Clinical signs of vitamin B12 deficiency are anaemia and peripheral neuropathy (the most extreme form of which is irreversible). High doses of folic acid improve the anaemia (which is easily detected) and so lead to a delay in the diagnosis and treatment of B12 deficiency, which could potentially lead to irreversible neurological damage.
- Intakes of folic acid below 1000 micrograms/day are not associated with adverse effects. This is consistent with the expert opinions from the UK¹¹, EU¹² and USA¹³. Countries that have mandatory fortification of flour with folic acid have not systematically collected and reported evidence on incidence related vitamin B₁₂ neurological damage. In the USA there has been a decline in the numbers of older people with low vitamin B12 status since fortification was introduced.
- It is estimated that 15,000 older people currently have intakes of folic acid above 1000 micrograms/day. This number includes 1,200 who have low vitamin B12 status.
- It is estimated that at doses of folic acid in the range of 100-450 micrograms/100g flour, up to about 24,200 –133,100 older people may have intakes exceeding 1000 micrograms; of those, about 1,700-8800 people may also have a low vitamin B12 status (Table 1 and 2). However, not all these individuals will develop clinical disease associated with vitamin B12 deficiency and the proportion that will develop clinical symptoms is unknown. Historically, anaemia was the basis for diagnosing vitamin B12 deficiency because recognition of anaemia usually preceded the finding of vitamin B12 deficiency, however not all older people with symptoms of neurological impairment caused by vitamin B12 deficiency have symptoms of anaemia.
- It is estimated that no people aged over 65 years would exceed 1000 micrograms/day of folic acid with fortification in the range of 100-450 micrograms/100g, if folic acid was removed from low fat spread, older people stopped using supplements containing folic acid and no other foods were fortified with folic acid.
- It has been proposed that increasing folate intake would decrease the risk of a number of chronic diseases (e.g. cardiovascular disease, certain cancers and bone disease). There is insufficient evidence to draw conclusions on this.

- In the US, typical folic acid intakes have increased post fortification by more than twice that originally intended, presumably due to overage (the practice of adding nutrient above the recommended level to allow for losses during storage). Overage needs careful consideration, as does voluntary fortification and supplement use.
- The potential benefit to the health of the UK population of the mandatory fortification of flour with folic acid is substantial; whereas the available evidence suggests the potential risks are uncertain. To minimise potential risks, fortification must be accompanied by measures to address the widespread vitamin B₁₂ deficiency in people aged 65 years and over.

11. SACN therefore:¹⁹

- endorses the earlier recommendation for women who could become pregnant to take 400µg/d folic acid;
- recommends the mandatory fortification of flour with folic acid in the UK;
- recommends mandatory fortification of flour should be accompanied by greater control of voluntary fortification of other foods, particularly low fat spread; the consumption of vitamin supplements also needs to be considered;
- recommends further consideration be given to the level of fortification and the issue of overage in food fortification;
- recommends that action is taken to assess the incidence, prevalence and management strategy for vitamin B₁₂-deficiency in older people; and
- recommends that the prevalence of poor riboflavin status in the UK population should be addressed.

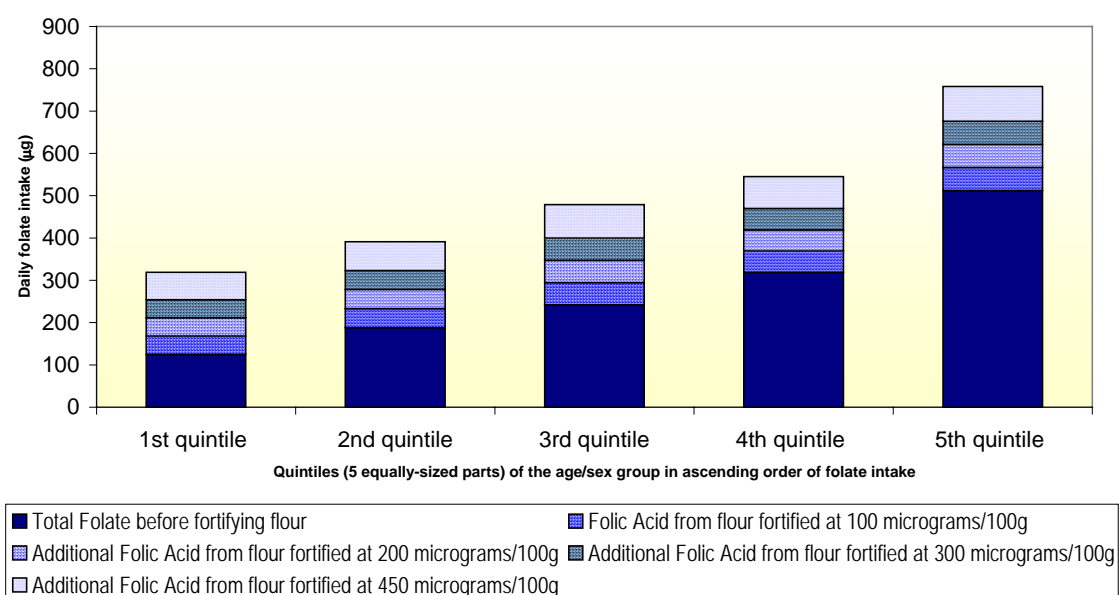
¹⁹ These recommendations are not finalised at this time.

Detailed Analysis of Current Folate Intakes and the Effect of Fortification of Flour

The effect of fortification on the folate intake of women of childbearing age

12. Population folate intakes for women of childbearing age are represented by 19 – 34 year old women in Graph 1. Each quintile (five equally sized sections of the population sorted in ascending order of current folate intake) increases in folate status as a result of flour fortification, including the lower quintiles, representing poor initial folate status. A similar situation is seen for all other women of childbearing age.

Graph 1: Mean total folate intake for women aged 19 to 34 shown in equal fifths of the population



13. Tables 1 and 2 illustrate how each level of fortification progressively reduces the percentage of individuals with folate intakes below the reference nutrient intake (RNI).²⁰ Again this indicates that individuals with poor folate intakes are reached through flour fortification. It can be seen that as the level of fortification increases, the numbers of NTD-affected pregnancies prevented also increase.

²⁰ The reference nutrient intake (RNI) is the amount of a nutrient that is considered sufficient to meet the requirements of 97.5% of the population.

Table 1: Summary table to show the effect of fortifying all flour INCLUDING wholemeal flour with folic acid

		Current consumption of folate from all sources (including estimates of overage)				Current consumption of folate excluding consumption of supplements and voluntary fortified spreads ²¹			
Fortification level µg/100g of flour	Average additional folic acid from flour µg/day ²²	Average % below RNI of 200µg/day ²³	No. of NTD pregnancies prevented ²⁴	Estimated number of individuals aged 65 years and over exceeding 1mg folic acid per day	Estimated number of individuals aged 65 years and over exceeding 1mg folic acid per day with low vitamin B12 status ²⁵	Average % below RNI of 200µg/day	No. of NTD pregnancies prevented	Estimated number of individuals aged 65 years and over exceeding 1mg folic acid per day	Estimated number of individuals aged 65 years and over exceeding 1mg folic acid per day with low vitamin B12 status
0	0	38	0	15300	1200	39	0	0	0
100	56	18	49-99	24200	1700	19	49-99	0	0
200	113	9	91-198	53100	3600	9	91-198	0	0
300	169	4	126-288	67200	4700	4	126-288	0	0
450	253	2	175-378	133100	8800	2	175-378	0	0

²¹ Folate from voluntarily fortified breakfast cereals was included in this analysis due to complications involved with its removal from the data.

²² Average additional folic acid intake as a result of fortification of flour across all population groups

²³ Average percentage of individuals with intakes below RNI across all population groups

²⁴ In order to calculate the number of NTD-affected pregnancies prevented, the risk reduction due to folic acid fortification was multiplied by the current level of NTD-affected pregnancies (700-900 a year, 2003 figures for UK see main report).

²⁵ Prevalence of biochemical vitamin B12 deficiency is estimated to be as high as 5% of 65-74 year olds and 10% of 75 year olds and over (SACN draft report, 2005).

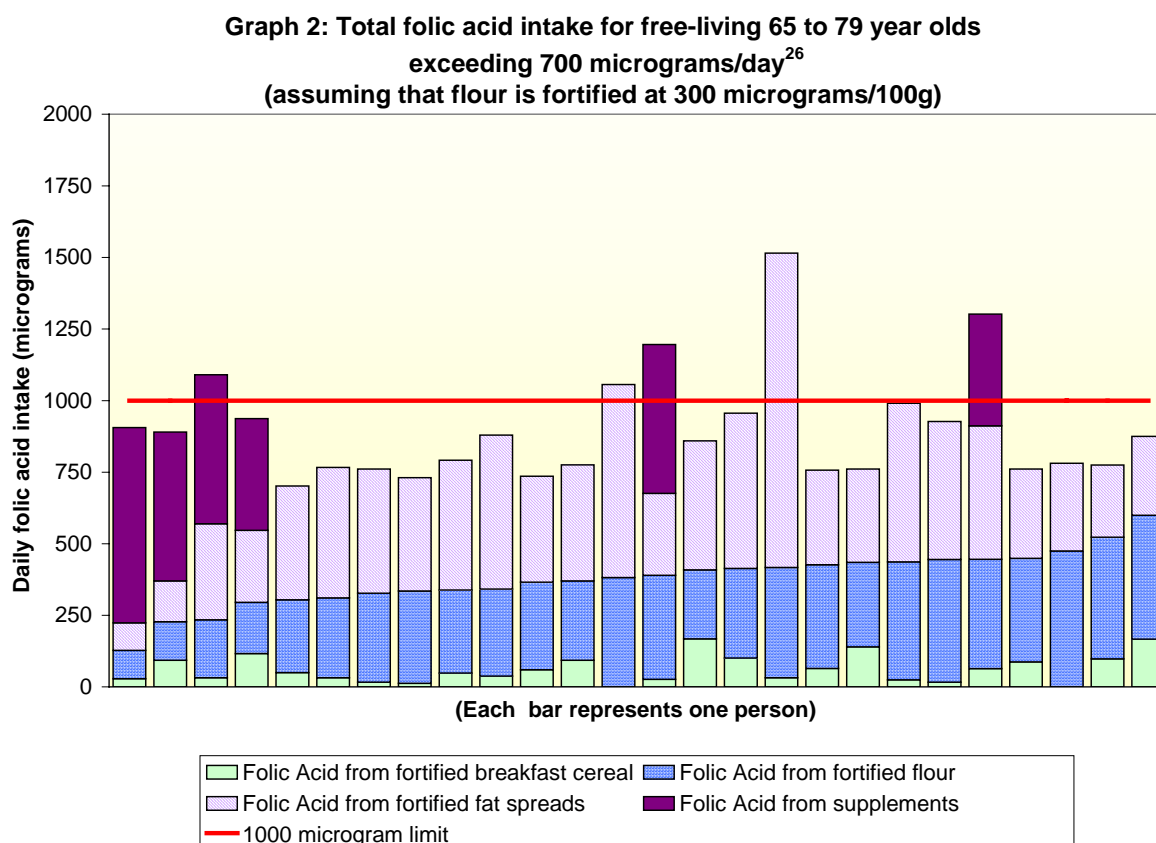
Table 2: Summary table to show the effect of fortifying flour with folic acid EXCLUDING fortification of wholemeal flour

		Current consumption of folate from all sources (including estimates of overage)				Current consumption of folate excluding consumption of supplements and voluntary fortified spreads			
Fortification level µg/100g of flour	Average additional folic acid from flour µg/day	Average % below RNI of 200µg/day	No. of NTD pregnancies prevented	Estimated number of individuals aged 65 years and over exceeding 1mg folic acid per day	Estimated number of individuals aged 65 years and over exceeding 1mg folic acid per day with low vitamin B12 status	Average % below RNI of 200µg/day	No. of NTD pregnancies prevented	Estimated number of individuals aged 65 years and over exceeding 1mg folic acid per day	Estimated number of individuals aged 65 years and over exceeding 1mg folic acid per day with low vitamin B12 status
0	0	41	0	15300	1200	42	0	0	0
100	49	21	42-90	24200	1700	21	42-90	0	0
200	98	10	84-180	37800	2400	11	84-180	0	0
300	147	5	112-261	48900	3200	6	112-261	0	0
450	220	4	161-369	108400	6700	4	161-369	0	0

People aged 65 Years and Over

14. Tables 1 and 2 show up to 1200 individuals aged 65 years and over with low vitamin B12 status currently exceed 1000 micrograms folic acid per day. These high intakes are generally due to consumption of fortified fat spreads and supplements.

15. As an example Graph 2 illustrates the dietary contributors to folic acid intakes in the elderly post flour fortification. It illustrates how fortification of flour could result in relatively uniform increases in folic acid intakes across the population, reaching nearly all individuals to roughly the same extent. Compared to supplement use or consumption of fortified fat spreads, which are seen to sporadically contribute to high folic acid intakes amongst individuals.



²⁶ 700 micrograms was chosen to illustrate those individuals approaching the 1000 microgram level.

Wholemeal Flour

16. It can be seen in Table 2 that excluding wholemeal flour from fortification would have a small effect on the numbers of individuals with folate intakes below the RNI, the number of NTD pregnancies prevented and the number of elderly with biochemical vitamin B12 deficiency exceeding 1000 micrograms folic acid per day.

Flour and Bread Consumption

17. Table 3 describes flour and bread consumption in Britain (NDNS 1998²⁷, 2000²⁸, 2003²⁹) COMA commented that flour would be an appropriate staple food for use in fortification, because of the near universal, consistent consumption of flour in the population.¹ This is reflected in table 3, which shows little variation in the amount of flour consumed per day and percentage of food energy consumed as flour across different age groups. Another potential fortification strategy considered was to fortify bread. Table 3 also indicates relatively uniform levels of bread consumption across all age groups.

Table 3: Table to illustrate consistent flour and bread consumption population groups.

Age/Sex Category	Flour consumed per day* (g)	% Food energy from flour	% Food energy from bread	% Flour consumed as bread
14-18 yr old females (NDNS 2000) (n=269)	68	15	13	71
19-34 yr old females(NDNS 2003) (n=287)	66	15	14	76
35-49 yr old females (NDNS 2003) (n=379)	67	15	13	74
50-64 yr old males and females (NDNS 2003) (n=536)	84	16	14	73
65-79 yr old free living males and females (NDNS 1998) (n=828)	82	18	14	70
65-79 yr old Institutional males and females (NDNS 1998) (n=121)	87	16	12	64
80+ free living males and females (NDNS 1998) (n=447)	75	18	14	67
80+ Institutional males and females (NDNS 1998) (n=291)	75	16	11	60
Mean (n=3158)	76	16	13	69

²⁷ Finch S, Doyle W, Lowe C, Bates CJ, Prentice A, Smithers G & Clarke PC. National Diet and Nutrition Survey: people aged 65 years and over. Volume 1: report of the diet and nutrition survey. London: TSO, 1998.

²⁸ Gregory J, Lowe S, Bates CJ, Prentice A, Jackson LV, Smithers G, Wenlock R & Farron M. National Diet and Nutrition Survey: young people aged 4 to 18 years. Volume 1: report of the diet and nutrition survey. London: The Stationary Office, 2000.

²⁹ Henderson L, Gregory J, Irving K & Swan G. The National Diet and Nutrition Survey: adults aged 19 to 64 years. London: TSO, 2003.

FOLATE, FOLIC ACID AND VITAMIN B12***Folate***

1. Folate is a water-soluble B vitamin found naturally in some foods. The term 'folate' is also used as an umbrella term for all the different forms of this vitamin, of which there are many, including folic acid, which is used in the fortification of food and in supplements.
2. Foods rich in folate are green leafy vegetables such as spinach, Brussel sprouts and broccoli; beans and peas; and liver (women who are pregnant or thinking of having a baby should avoid eating liver or liver products because these are very high in vitamin A).³⁰ In the UK other important sources of folate are cereal and cereal products, in particular breakfast cereals (many of which are fortified on a voluntary basis) and vegetables including potatoes. Both groups each contribute about one-third to total intakes.
3. Folate is required for cell division and cell maintenance. The amount of folate recommended during early pregnancy is particularly high to ensure that needs of the rapidly growing embryo are met, in particular to ensure the appropriate development and closure of the neural tube, up to about day 26 post conception. Failure to close the neural tube leads to neural tube defects (NTDs), such as spina bifida. Folate is also important for the metabolism of the amino acid homocysteine.
4. The reference nutrient intake (RNI)²⁰ for folate for adults in the UK is 200 micrograms/day. There are different needs for folate at different stages of the reproductive process. As such women are advised to take an additional 400 micrograms from before conception until 12 weeks after conception, an additional 100 micrograms thereafter and if breastfeeding an additional 60 micrograms.

³⁰ High vitamin A intake is associated with teratogenic risk (causes malformations of an embryo of foetus)

Vitamin B12

5. Vitamin B12 is a water-soluble vitamin that is needed by the body to form healthy nerve and red blood cells. The metabolism of folate and vitamin B12 are closely related because vitamin B12 is needed for the production of active folate inside cells.
6. Vitamin B12 is found in virtually all meat products and certain algae such as seaweed. Good sources include meat, salmon, cod, milk, cheese, eggs, yeast extract, and some fortified breakfast cereals.
7. The RNI for adults in the UK is 1.5 micrograms/day, during lactation the requirement increases to 2 micrograms/day.
8. Vitamin B12 deficiency is not commonly associated with low dietary intakes of vitamin B12 in the UK, except in the case of vegans. Deficiency is more commonly associated with a reduced ability of the gut to release vitamin B12 from food and then absorb it into the body. The latter is sometimes caused by a condition known as pernicious anaemia (an autoimmune disease that causes damage to the wall of the intestine). Impaired digestion of vitamin B12 becomes more common throughout old age. It is not clear what proportion of this age-related decline in vitamin B12 impaired digestion is caused by pernicious anaemia.
9. There are two clinical symptoms of vitamin B12 deficiency: megaloblastic anaemia and peripheral neuropathy, the most severe form of which (subacute combined degeneration of the spinal cord) is irreversible. The latter is associated with severe deficiency and is rarely seen in the UK. Patients with vitamin B12 related neuropathy do not always have vitamin B12 related anaemia.
10. Case reports suggest that a high dose of folic acid improves megaloblastic anaemia but not neurological impairment. This could in theory lead to a delay in the treatment of severe vitamin B12 deficiency and irreversible neurological damage. 1000 micrograms/day of folic acid is regarded as a safe level of intake with the majority of cases of adverse effects reported at doses at or above 5000 micrograms/day;

<p>Option 1 – Do Nothing</p> <ul style="list-style-type: none"> ▪ Current Government advice to women on supplement use would remain in place. ▪ No further legislative requirements ▪ Current encouragement for voluntary fortification would remain in place 		
<p><u>Pros</u></p> <ul style="list-style-type: none"> ▪ No additional costs to industry. ▪ No additional exposure to potential risks associated with high folate intake. ▪ Maintains current level of consumer choice 	<p><u>Cons</u></p> <ul style="list-style-type: none"> ▪ Current level of about 700-900 neural tube defect (NTD) affected pregnancies each year will continue. 	<p><u>Views of Stakeholders</u></p> <ul style="list-style-type: none"> ▪ This option would be strongly opposed by some public health and consumer groups, including groups supporting NTD sufferers and their families such as ASBAH (Association of Spina Bifida and Hydrocephalus) and Society for Research into Hydrocephalus and Spina Bifida (SRHSB). ▪ Industry likely to be neutral to this option.
<p>Option 2 - Public information campaign to encourage greater uptake of supplements and changes to diet in the target group.</p> <ul style="list-style-type: none"> ▪ Government funded consumer education campaign, to promote current advice to women about supplement use. Possibly targeted specifically at those sub-groups most at risk of poor folate status. 		
<p><u>Pros</u></p> <ul style="list-style-type: none"> ▪ Campaign can be targeted specifically to women of childbearing age, therefore not likely to increase the risks to the elderly associated with high folate intake. ▪ No additional costs to industry. ▪ Maintains current level of consumer choice 	<p><u>Cons</u></p> <ul style="list-style-type: none"> ▪ Unlikely to achieve significant reductions to current NTD rates as no evidence of success elsewhere. ▪ Women in lower income groups who have poorer folate status, and are at a greater risk of NTD affected pregnancies, are hard to reach with consumer education messages and are less likely to consume supplements. ▪ Will have no impact on the estimated 50% of pregnancies that are unplanned. 	<p><u>Views of Stakeholders</u></p> <ul style="list-style-type: none"> ▪ Public health groups and consumer groups (e.g. ASBAH) would be expected to strongly oppose this option as a missed opportunity to reduce NTD affected pregnancies. ▪ Supplement manufacturers expected to support this option. ▪ Views of other industry groups are likely to depend on the potential effect on sales of individual products.

<p>Option 3 – Strategy to encourage further voluntary but structured fortification of foods</p> <ul style="list-style-type: none"> Work with industry stakeholders to develop incentives for manufacturers to produce fortified products, e.g. “folate flash” (previously developed by the Health Education Authority) or similar logo. Supported by consumer education campaign to encourage uptake among target population of newly fortified products. 		
<p><u>Pros</u></p> <ul style="list-style-type: none"> There is no evidence that voluntary approach in the UK or other countries has been successful at reducing NTD risk. Appearance of a greater range of fortified products would increase current level of consumer choice. Does not place a statutory requirement (with ensuing burdens) on businesses. 	<p><u>Cons</u></p> <ul style="list-style-type: none"> Likely that this option will not deliver an equal benefit to all consumer groups. Voluntary fortification has potential to leave “pockets” in the market: if there is increased fortification in categories for which consumption is variable across the population (e.g., fat spreads, dairy products etc), the target group may not benefit. Target group consumers may not purchase fortified brands. Given the likelihood that fortification will be reflected in the price of products, this may disadvantage low-income consumers, who are those most at risk of poor folate status Consumption of bread and flour is consistent across all population groups. This is not the case for the vast majority of other food categories; for example fortified low fat spreads. A voluntary regime will inevitably be less structured than statutory requirements, making it more difficult to predict and manage the risk. In the event of limited uptake by industry, will achieve little reduction to the current level of about NTD-affected pregnancies each year. 	<p><u>Views of Stakeholders</u></p> <ul style="list-style-type: none"> The Industry believes that few new fortified products would be launched, given that companies are free to fortify products and make claims on them at the moment. Those public health and consumer groups (such as ASBAH and SRHSB), who support mandatory fortification could be expected to oppose this option as a missed opportunity.

Option 4 - Mandatory Fortification of Flour

- New legislation making fortification with folic acid mandatory for specified products or categories (requirements would apply to wheat flour)

NB – the first part of the discussion below examines the arguments for and against mandatory fortification in general terms. The second part of the discussion focuses on four sub-options for how the requirements might apply.

<u>Pros</u>	<u>Cons</u>	<u>Views of Stakeholders</u>
<ul style="list-style-type: none">▪ Would be successful in reducing NTD rates. Fortification would result in a dose dependent reduction of NTD's (Annex 1, Table 1).▪ Consumption of bread and flour is consistent across all population sub-groups. All groups will therefore derive benefit from increases in folate uptake although evidence suggests that those women most at risk will derive most benefit. Ethnic flours are subject to the same regulations as other flours.▪ Will reduce NTD risk in the estimated 50% of unplanned pregnancies.	<ul style="list-style-type: none">▪ More people exposed to the potential risks associated with higher folate intake. Modelling work described in Annex 1 estimates the numbers of older people exposed to increased risk at different doses of folic acid (Annex 1, Table1).▪ Increased costs to industry (<i>NB – Industry estimate costs at around £700K a year if their preferred option is implemented alongside current legal fortification requirements, although this will vary depending on the scope of the requirements</i>).▪ Might lead to export issues for some companies.▪ General ethical population concerns about prospect of “compulsory” or “mass medication” issues.	<ul style="list-style-type: none">▪ Public health groups and some consumer groups (such as ASBAH and SRHSB), strongly support this option.▪ Early indications from consumer groups such as Which? and NCC suggest that they would like to know the views of consumers and may have concerns over some issues of consumer information and choice.▪ Milling and baking industries are unlikely to oppose the option, subject to the requirements being implemented in line with current fortification requirements and the rules applying consistently throughout the UK countries. However, they do have some practical concerns, particularly around labelling and export issues.

Fortification of all flour – at the milling stage	
<p><u>Pros</u></p> <ul style="list-style-type: none"> Ensures that folic acid is present in all bread and flour products, therefore ensuring that all population groups, and consumers of all types of bread and flour products derive benefits of increased folate intake. 	<p><u>Cons</u></p> <ul style="list-style-type: none"> Offers restricted choice for consumers who wish to eat non-fortified bread and flour products. Would require the fortification of flours (i.e., wholemeal and those produced using traditional stoneground techniques)) that are exempt from current fortification requirements. This would require significant and expensive changes to current milling practice. Affected businesses would include a large proportion of SME's (Small and Medium Enterprises) producing stoneground flours, and who are not currently required to fortify their flour (this might include “tourist” watermills and windmills). Ensuring accurate fortification in these types of mill would be difficult, and installing machinery would not be a viable option.
Fortification of all flour for bread-making use – at the milling stage	
<p><u>Pros</u></p> <ul style="list-style-type: none"> Removes any concern about export of bakery products. 	<p><u>Cons</u></p> <ul style="list-style-type: none"> Significant practical difficulties in defining “flour for bread use”. Would include some flours (i.e., “wholemeal flours for bread use”) that are exempt from current fortification requirements. This would require significant and expensive changes to current milling practice. Offers restricted choice for consumers who wish to eat non-fortified bread products.
Fortification of all flours other than wholemeal – at the milling stage (i.e. in line with current requirements of Bread and Flour Regulations).	
<p><u>Pros</u></p> <ul style="list-style-type: none"> The most practicable approach, and least costly for industry to implement. Machinery for fortifying flour is already in place allowing folic acid to be added to existing nutrient mix. Would allow choice for consumers, while still covering over 90% of bread produced in the UK. 	<p><u>Cons</u></p> <ul style="list-style-type: none"> Would not deliver benefits to consumers of wholemeal bread. Consumers may have a difficult choice between benefits of wholegrain foods, and benefits of increased folate intake.

Fortification of Bread Products – at the bakery	
<p><u>Pros</u></p> <ul style="list-style-type: none">▪ Could be used to ensure that folic acid is present in all bread products, covering all population groups (i.e., as in the “all flour” options above).	<p><u>Cons</u></p> <ul style="list-style-type: none">▪ Significant practical difficulties in ensuring accurate and consistent levels of fortification.▪ Practical difficulties described above would be exacerbated for SME’s (including craft and specialist bakers) and in-store bakeries working with small quantities of dough.

STAKEHOLDER ENGAGEMENT

Stakeholder meetings

1. In recent months Agency officials have held two small meetings with key members of the milling and baking industries, followed by a meeting with Association for Spina Bifida and Hydrocephalus (ASBAH), and two larger scale stakeholder meetings for consumer and industry representatives.
2. The aims of the consumer and health NGO's stakeholder meeting were to identify the key issues relating to fortification and to gather initial views. This meeting included representatives from the following organisations: Age Concern, ASBAH, British Nutrition Foundation, Consumers for Health Choice, Nutrition Society, Which and academics from various UK institutions.
3. The purpose of the industry stakeholder meeting was to identify any key technical issues relating to fortification and to gather initial views. Attendees included: Food and Drink Federation, Biscuit Cake, Chocolate and Confectionery Alliance, National Association of British and Irish Millers, Food Additives and Ingredients Association and breakfast cereal manufacturers.

Consultations

4. An 8-week comment period on SACN's risk assessment was completed on 18 January. 32 organisations and individuals responded. There were a significant number of risk management comments received and these will usefully inform later stages in the process.
5. It is expected that a consultation on policy options will be launched simultaneously with publication of the SACN report, in May.