



Scientific Advisory Committee on Nutrition

**Subgroup on Folate  
Meeting held on Friday, 10<sup>th</sup> February 2006  
Aviation House, Conference Room 3.**

**Final Minutes**

**Attendees**

**Chair: Professor Sheila Bingham**

**Members: Professor Alan Jackson**

**Dr Anthony Williams**

**Mrs Christine Gratus**

**Dr Anita Thomas**

**Dr Paul Haggarty**

**Secretariat: Dr Alison Tedstone (FSA)**

**Ms Mamta Singh (FSA)**

**Ms Saadia Noorani (FSA)**

**Ms Lynda Harrop (FSA)**

**Mr Cliff Gay (FSA) – pm only**

**Ms Rachel Stratton (FSA) – pm only**

**Dr Theresa Ekong (FSA) – pm only**

**Dr Sheela Reedy (DH)**

**Apologies: Professor Timothy Key**

**Chairs' introduction and welcome**

1. The Chair welcomed members to the fourth meeting of the SACN Subgroup on Folate. It was reported that Prof Timothy Key and Dr Paul Haggarty had been invited to join the Subgroup. The Chair explained that Timothy Key had been invited because of his modelling expertise. He was unable to attend but had provided verbal comments. These would be reported later in the afternoon. Paul Haggarty is now a member of SACN and had been invited to join the Subgroup because of his expertise in folate.
2. It was noted that the report is due to be presented to SACN at their meeting on the 24<sup>th</sup> March for agreement and is due to be presented to the Agency Board in April. The

10/02/06

Subgroup were informed that a consultation on risk management will follow in the summer.

**Agenda Item 1 -Minutes from the last meeting (SACN/Folatemin05/01)**

The Subgroup were invited to comment on the minutes of the previous meeting. The following changes were requested:

3. *Paragraph 15* – to replace “data was a good starting point” with “hospital admission statistics are one means of collecting information about vitamin B12 deficiency”

**Action: Secretariat**

**Agenda Item 2 - Draft report: Folate and disease prevention (SACN/Folate/06/01)**

4. The Secretariat informed the Subgroup that mistakes in vitamin B intakes had been noted in paragraph 14 to 44 of the draft report due to transcription errors from the NDNS.
5. The Secretariat informed the Subgroup that there were inaccuracies in collating the data for NTD affected pregnancies as figures for 2001 were used for England and Wales where as figures for 2002 were used for Scotland. The Secretariat presented the Subgroup with amended figures for NTD affected pregnancies based on 2001 figures for UK, using a correction factor for underreporting as recommended by Boyd et al (2005). The Subgroup was requested to comment on these figures.
6. It was agreed to add a qualifying statement on the uncertainty of figure 56% to paragraph 84. Amendments were also agreed to paragraphs 85, 87, 88 and it was agreed to modify the figure for the number of NTD-affected pregnancies accordingly.
7. The following corrections were also noted:  
Table 6 – Rate needs to be corrected to per 10,000, instead of per 1,000  
Table 8 – Czech republic – voluntary fortification to be corrected with ‘mandatory fortification’

**Agenda Item 3 - Response to consultation  
Summary tables ( SACN/Folate/06/02a)**

8. Members were invited to consider the specific comments received from the consultation period.
9. Members acknowledged the high standard of responses received and agreed that the information providing a historical context for vitamin B12 deficiency was particularly useful.

10. The Secretariat informed the Subgroup that 32 interested parties had commented on the draft report -12 respondents had been in general agreement with the report and 4 were not in agreement with the report.
11. The Secretariat pointed out that there were many comments relating to risk management and the Members would not be asked to consider these. These would be passed to the Agency.

### **General Response- Table 1**

12. The main comments in this section related to:
  - Inconsistency of terminology
  - Possible adverse effects of unmetabolised folic acid
  - Possible risks of high intakes of folic acid in children
  - Reliability of NTD data
  - Possible benefits of folic acid.
  - Vitamin B12 deficiency and risk of delayed diagnosis with folic acid.
13. The Subgroup considered matters raised by respondents in detail.
14. Members agreed to revise the report appropriately, in relation to clarification of terminology around nutrient status and deficiency.

**Action: Secretariat**
15. Members agreed to amend the report to increase the emphasis on at risk groups including diabetic and obese women. It was noted that this was relevant to a fortification strategy in a population with increasing weight.

**Action: Secretariat**
16. Two respondents commented on the approach to work and focus on prospective studies, it was felt that the approach could have been broader. In relation to this comment there was some discussion about the use of animal and human studies and it was concluded that animal evidence is difficult to interpret in humans. It was agreed that a caveat would be inserted to reflect this and more detail on the metabolism of folate would be included in the report.

**Action: Secretariat**
17. It was agreed that relevant data available from the Centres for Disease Control (CDC) would be reviewed and included where appropriate.

**Action: Secretariat**
18. A member of the public had queried whether addition of folic acid would result in bread that was more acidic. The Subgroup was informed by the Secretariat that the individual had already been contacted directly.

**Action: Secretariat**

**Background to the report**

19. The Subgroup was in agreement with the comment that “COMA did not recommend anything”. It was agreed by the Subgroup to reword the report accordingly as “COMA has concluded that universal folic acid fortification of flour at 240µg/100g in food products as consumed would have a significant effect in preventing NTD-affected conceptions and births without resulting in unacceptably high intakes in any group of the population”.

**Action: Secretariat**

20. A response asking what effect folic acid fortification at 280mcg/100g of flour may have on the level of unmetabolised folic acid in the systemic circulation of a UK population was considered to have been already addressed by the Subgroup.

21. Clarification was requested in paragraph 7, where it had been noted that the supplement advice might further increase the level of unmetabolised folic acid. The Subgroup noted this point and agreed to amend the report appropriately.

**Action: Secretariat**

**Folate and neural tube defects**

22. In response to a request for extra emphasis on papers published by Botto et al 2005 and Busby et al 2005. The Subgroup noted that these papers have already been cited in the draft report but it was agreed to amend the report appropriately.

**Action: Secretariat**

23. Two comments were raised concerns about genetic variation. One specifically related to the TCII gene, which may explain the difference rates of NTD's, particularly in Northern Ireland and Scotland. It was also suggested that higher NTD rates in Ireland could also be explained by higher live rates and less choice of terminations. It was agreed to add a new paragraph to the report to address the genetic variation issue with the inclusion of Daly et al 1995 paper.

**Action: Secretariat**

24. It was noted the figures for NTD pregnancies have been underestimated. It was agreed to revise these figures.

**Vitamin B12 deficiency in the elderly**

25. In response to comments received on vitamin B12, the Subgroup agreed that the text relating to vitamin B12 needed more clarity in the report. It was noted that the report needed to be more explicit of what was meant by the term masking. It was agreed to use the term biochemical vitamin B12 deficiency instead of masking (except at the beginning of the report) and rewrite the section on vitamin B12.

**Action: Secretariat**

26. The Subgroup agreed to take into consideration the comments on the underestimation of figures in relation to vitamin B12 deficiency, for the number of elderly people at risk, of neurological damage with fortification.

**Action: Secretariat**

27. It was noted that the reference quoted as Lindenbaum et al 1998 in this summary table was incorrect and should be 1988.

**Action: Secretariat**

28. A response dealing with management strategies for older people with biochemical vitamin B12 deficiency was considered as an issue for risk management and outside SACN's remit. These comments would be passed to the Department of Health.

**Action: Secretariat**

29. A specific comment which disagreed with the summary conclusion "The fortification of flour with vitamin B12 to improve the status of people aged 65 years and over may not be a feasible option" was considered to be an important point. It was agreed by the Subgroup to take this into consideration when redrafting the report.

**Action: Secretariat**

30. A comment suggesting that the dose of folic acid (1mg) which would be spread across meals, following fortification, would result in far less free folic acid circulating in the plasma was noted by the Subgroup. However it was also noted that the points made were unreferenced.

31. A response providing additional explanation for poor vitamin B12 and folate status in older people due to oxidative stress was noted. It was agreed not to include this in the report.

32. Suggestions to review oral or intramuscular vitamin B12 for treatment of vitamin B12 were considered to be outside the scope of the report.

33. It was noted that the last comments in this section related to the lack of evidence to demonstrate that folic acid fortification has any adverse effects.

34. The Secretariat had requested one member of the Subgroup with expertise in the elderly to specifically look at the responses received on vitamin B12 and the elderly.

35. It was noted that clear information was needed on the intake of vitamin B12 and signs of deficiency. A paper by Lindenbaum et al 1988 was highlighted which showed that 20-30% of neurological symptoms occurred in the absence of anaemia. It was noted that levels of MMA were dependent on renal function and need to be adjusted for levels of serum creatinine in the elderly. It was also noted that different studies used different indicators of vitamin B12 status. It was recommended to triangulate data from the General Practice Research Database (GPRD), Centre for Disease Control (CDC) and hospital statistics to generate information on the incidence of vitamin B12 deficiency, macrocytic anaemia, subacute combined degeneration of the cord. The Secretariat agreed to obtain this information where possible and to amend the report accordingly.

Comment:

**Action: Secretariat**

36. The Subgroup was presented with a paper by Solomon 2005, which looked at the response to vitamin B12 treatment for vitamin B12 deficiency. It was noted that there were uncertainties around the appropriateness of current biochemical markers of vitamin B12 status. It was also noted that clarity was needed on the utility, feasibility and validity of vitamin B12 status. It was agreed to reword the report appropriately.

**Action: Secretariat**

37. The Subgroup were presented with a paper by Pfeiffer et al 2005, which looked at the impact of fortification on folate and vitamin B12 status in the US. It was noted that the proportion of older people with low serum vitamin B12 had decreased from 13% to 7%. It was questioned whether increased supplementation had increased vitamin B12 intakes. It was noted from a response received, that vitamin B12 intake had stayed constant (Ray 2004). It was agreed to check these findings. It was noted that this was a reassuring message in relation to the status of older people.

**Action: Secretariat**

38. The Subgroup discussed the level of folic acid associated with risk. It was agreed that 1mg of folic acid supplementary to dietary folate was safe. It was noted that the Expert Group on Vitamins and Minerals (EVM) report stated that a 1mg/day of folic acid or 1.5mg/day of total folates would not be expected to cause adverse effects. It was noted that in the US (Institute of Medicine 1998) 1mg of folic acid was also seen as safe. The majority of adverse effects were seen at doses of 5mg or above. Very few cases were reported at lower doses. The US agreed to apply an uncertainty factor of 5 based on the severity of the neurological complications observed to obtain an upper level of 1mg/day. It was agreed to include this information in the report.

### **Adverse Effects of Folic Acid**

39. Some clarity was requested by a respondent about the metabolism of different forms of folic acid. It was agreed to amend the report appropriately.

**Action: Secretariat**

40. It was noted that it was important to provide increased emphasis on the issue of unmetabolised folic acid in the report. It was agreed to reword the report appropriately.

**Action: Secretariat**

41. The Subgroup noted an error in the inclusion of Emory University response in the summary table under adverse effect of folic acid. It was agreed this would be deleted.

**Action: Secretariat**

### **Folate and Chronic Disease**

42. The main comments in this section included: the effect of exposure of high folate levels on the efficacy of chemotherapy, the effect of folic acid on reducing the risk of cardiovascular disease has been understated and the metabolic effects on unmetabolised folic acid on cell division (accelerating effect).

43. A specific comment on the Clarke et al (1998) study was that the progression of the clinical syndrome of dementia might have had a vascular mechanism. The pathological studies from the CFAS group reveal that much of what is diagnosed clinically as Alzheimer's disease is in fact mixed Alzheimer's and vascular disease. It was agreed to amend the report appropriately.

**Action: Secretariat**

44. The Subgroup did not agree with a comment that the effect of folic acid on reducing the risk of cardiovascular disease had been understated in the report.

45. The Subgroup noted that there was little epidemiological evidence on the effect of folic acid on cancer and comments on the cancer effects referred to animal data. It was suggested that further clarity was needed in this section and to revise the report appropriately.

**Action: Secretariat**

### **Fortification Process**

46. All responses received regarding the fortification process were considered to be risk management issues, including concerns about level of fortification. Taking into account losses during manufacture and manner of labelling required were considered to be a risk management issue.

### **Anaemia**

47. The main comment was on the prevention of folate deficiency anaemia that occurred in the US after fortification. The Subgroup agreed to include this data in the report.

**Action: Secretariat**

### **Co-fortification with folic acid and vitamin B12**

48. It was considered that a suggestion that fortification with high levels of B12 would not cause any problems, had already been covered. However, in order to address this point fully it was agreed to clarify this within the report.

**Action: Secretariat**

Deleted:

### **Overall summary/conclusion**

49. The Subgroup noted there was limited evidence presented to support the comment on the issue of dose response. The Subgroup noted that dose was covered in the report and that this would be checked by cross-referencing with the study by Eussen et al 2005.

**Action: Secretariat**

50. Comments in this category included that patients with mild vitamin B12 deficiency from food malabsorption do not progress to severe B12 deficiency and the report refers to 1000ug folic acid without recognising that this would be taken in three meals a day. It was commented that food malabsorption is not a cause of severe B12 deficiency sufficient to cause irreversible B12 deficiency and is not a cause of peripheral neuropathy.

51. The Subgroup agreed there was a lack of clarity in paragraph 223, it was noted that biochemical vitamin B12 deficiency and the link between irreversible disease is unknown. It was agreed to amend the report to clarify uncertainties.

**Action: Secretariat**

52. It was noted that a paper by Andre et al 2004 was important in relation to paragraph 60, it was agreed to check references 14, 19, 20 and 21 quoted in Andre et al 2004 which may need to be included in the report .

**Action: Secretariat**

### **Recommendations**

53. In response to further information needed to formulate a conclusion regarding fortification and the form of folate to be used, it was agreed to reword paragraph 229 to mandatory fortification of flour with folic acid.

**Action: Secretariat**

54. In response to clarification requested for paragraph 232. It was agreed to reword “more than 30% of the dietary riboflavin in the UK is derived from dairy products” to “more than 30% of dietary riboflavin in the UK is derived from low fat dairy products”.

**Action: Secretariat**

55. A response recommending that folic acid should be made available in doses higher than 0.4mg without prescription was considered to be a risk management issue.

56. Questions raised about whether gluten-free flours will be fortified were considered to be a risk management issue.

57. Specific changes suggested as a result of the consultation period were listed in Table 3. It was agreed for the Secretariat to review the changes and amend the report appropriately.

**Action: Secretariat**

### **Agenda Item 4 - Modelling folic acid doses and risk-benefits (SACN/Folate/06/03)**

58. The Chair welcomed the following FSA officials who have all been working on folate modelling: Rachel Stratton from Nutrition Division, Cliff Gay from Statistics Division and Theresa Ekong from Food Labelling Division to the afternoon session of the meeting.

59. The Subgroup were presented with a paper detailing the current folate intakes by the subgroups of the population and the potential effect of folic acid fortification of flour on dietary intake of folate, NTD numbers and numbers exceeding 1mg folate. The Subgroup was informed that various assumptions had been made as part of the modelling work and these would need to be agreed. The work also models the effect on intake of various levels of flour fortification with folic acid, the doses being 100µg, 200µg and 300µg. It was noted that the Daly papers (Daly et al 1995, Daly et al 1997) had been used to estimate the percentage of NTD reductions.

60. The Secretariat had tabulated specifically the risks and benefits to individuals over 50. One table showed the proportion of elderly people at risk and the second gave the estimated numbers of those that would exceed 1mg/day of folate at 0-300µg/100g flour per day.

61. Members were invited to comment on the assumptions in Annex 1.

62. The Subgroup agreed with the assumptions made about fat spreads, breads, bioavailability, imported flour, and the assumption that fortification applies to all flour and wholemeal flour.

63. A query was raised about the folic acid content 'crumbs' at the bottom of breakfast cereal packets and the Secretariat agreed to find out further information. It was confirmed that the label data had been compared with the analytical data and the results showed the values were the same. It was also confirmed that approximately half of all breakfast cereals on the market are fortified.

64. The assuming unchanged supplement intake since the surveys was queried. The Secretariat agreed to add a clarifying sentence to take into account the elderly data.

**Action: Secretariat**

65. It was queried whether 25% processing loss took into account overages and it was confirmed that it does not.

66. There was some discussion about labelling and enforcement issues. The Secretariat confirmed that this would be taken into account as part of the risk management process.

67. Members requested additional columns to the tables for total folates and folic acid for current intake in Tables 2-5. It was agreed that the Secretariat would add the extra columns.

**Action: Secretariat**

68. It was queried whether it was possible to show the distribution of flour intake by income/socio-economic groups. The Secretariat agreed to consider this.

**Action: Secretariat**

69. All risk/benefit assumptions were agreed by the Subgroup.

70. It was noted that the risk was based on exceeding 1mg of total folate. The Subgroup agreed that this was inappropriate and needed to be modified to 1 mg of folic acid.

**Action: Secretariat**

71. The Subgroup were asked to agree if the data was handled correctly and that the tables listed were accurate.

72. The Subgroup was presented with comments on modelling the effects of folic acid intake on NTD risk.

73. The dose response curve presented in the Daly paper (1995) on the relationship of red cell folate levels to NTDs was discussed. It was noted that the Daly paper used microbiological assay to measure folate which are comparable where as the UK and US assay were different and are not comparable.
74. It was noted that the low red folate levels at 200ng/ml could be distorted, as women with MTHFR genotype are more likely to have low folate levels. Therefore based on the microbiological used in the Daly paper some of the risk could be genetic.
75. It was also noted that the Daly group, based on a red cell analysis, suggested that increasing folic acid intake by 200 µg would result in a 41% reduction in NTD risk. Based on the same population group, Wald et al 2001 suggested on the basis of a plasma folate analysis that increasing folic acid intake by 200µg would result in roughly 20% reduction in NTD risk. It was noted that different metabolites were picked up by microbiological and radioimmunoassay, which could account for the different values proposed.
76. It was noted that American values from the CDC showed a 19-34% reduction of NTD's.
77. The significant contribution made by fortified fat spreads to the intake of elderly people was noted. There was a brief discussion as to whether control of voluntary fortification requires further assessment. The Secretariat reassured the Subgroup that this issue was already being considered as part of the risk management process.

**Initial analysis of children's folic acid intake (SACN/Folate/06/04)**

78. The Subgroup was presented with a paper, which gave an initial analysis of children's folate intake status. The Subgroup was asked to comment on this paper.
79. It was stated that the data had been included due to concerns associated with high folic acid intake on the levels of free blood folic acid in children.
80. Particular concerns were raised about the effects of changing DNA methylation during development. It was pointed out that although the long-term risks are unknown there is no current understanding of optimal methylation status. It was considered that this needed to be taken into account for children and it was agreed that issues associated with methylation would be addressed.

**Action: Secretariat**

81. It was agreed to highlight the hypothetical risk associated with high levels of unmetabolised folic acid within the report.

**Action: Secretariat**

Comment:

82. The importance of monitoring voluntary fortification was re-emphasised.

10/02/06

**Agenda Item 5- Further work programmes**

83. Members were informed that the amendments would be complete by the next meeting on 24<sup>th</sup> March 2006.

10/02/06