



SUMMARY OF RESPONSES RECEIVED TO REQUEST FOR COMMENTS ON FOLATE AND DISEASE PREVENTION DRAFT REPORT

Response

32 responses were received and are available, in full, in the attached file (Annex 1).

Responses were received from the following organisations & individuals:

1. Association for Spina Bifida & Hydrocephalus (ASBAH)
2. British Dietetic Association (BDA)
3. British Nutrition Foundation (BNF)
4. Co-operative Group (Co-op)
5. Diabetes UK
6. Folic Acid Action (FAA)
7. Food and Drink Federation (FDF)
8. Hennock Industries
9. Institute of Food Research (IFR)
10. McDaddon, Andrew
11. MRC Human Nutrition Research (MRC HNR)
12. National Public Health Service for Wales
13. NHS Wales
14. Nichols, John
15. Rollins School of Public Health of Emory University, USA
16. Rowett Research Institute
17. Royal Free Hampstead, NHS
18. Society for Research into Hydrocephalus and Spina Bifida (SRHSB)
19. St Patrick's Centre for Community Health
20. Sydney West Area Health Service, Australia
21. The Federation of Bakers
22. The Incorporated National Association of British and Irish Millers Limited (NABIM)
23. The Nutrition Society (NS)
24. The University of Sheffield
25. Thrower, Jan
26. University of Newcastle, Australia
27. University of Western Ontario, USA
28. University of Oxford
29. Vos, Eddie
30. Wilson, J.D
31. Wolfson Institute of Preventive Medicine
32. University of Ulster

An overview of the responses received is provided in Table 1.

Of the respondents who expressed an opinion those in general agreement with the conclusions of the report:

SRHSB
Birmingham Community Nutrition and Dietetic Department
Sydney West Area Health Service
The Federation of Bakers
NS

Wolfson Institute of Preventive Medicine
ASBAH and SSBA
BDA
BNF
Co-op
Diabetes UK
FAA
MRC HNR
National Public Health Service for Wales
Rollins School of Public Health Emory University

4 respondents in disagreement with the conclusions of the report

Hennock Industries
University of Sheffield
Jan Thrower
IFR

The concerns raised by respondents are summarised, for discussion, in Table 2 and specific comments on the text are listed in Table 3.

Table 1: Overview of responses received to Folate and Disease Prevention draft report

General response	Comments	Organisation
<i>General comments on the report and other options to consider</i>	The draft report is very welcome and we wish to support the recommendation that “Mandatory fortification of flour with folate should be introduced in the UK”. Hopefully the vitamin B12 deficiency argument will now be put to rest and that there will be a better awareness for the need for monitoring of the elderly through the Primary Care Services.	SRHSB
	The presentation of the evidence is well balanced and we support the final recommendations. It is very important that paragraph 231 on vitamin B12 deficiency remains in the final document.	Birmingham Community Nutrition & Dietetic Department
	<p>The report is excellent and look forward to the UK introducing mandatory fortification of flour with folic acid. Australia is going through the same process of considering mandatory fortification and the decision made in the UK would have a positive impact in Australia. Other EU countries would find it easier to introduce mandatory fortification as well.</p> <p>Education campaigns to increase consumption of folic acid are expensive because they must be ongoing in order to be effective. Educational campaigns bring about very little change in dietary habits except in a small percentage of the better educated groups.</p>	Sydney West Area Health Service
	If the Government proposes mandatory fortification of flour that will be supported by the plant baking industry. We would not support or recommend implementation of a voluntary scheme.	The Federation of Bakers
	The Society acknowledges the significance of SACN’s contribution in providing a very well constructed and highly comprehensive report on the evidence available concerning folate and disease prevention. In general terms the Society agree with the conclusions summarised in the report and support the recommendations SACN has specified, which are of considerable public health importance.	NS

<p><i>General comments on the report and other options to consider</i></p>	<p>It's not whether we should fortify, but by how much. Given the choice however, I would opt for a staged approach:</p> <p>a) Increase levels of awareness of folate health benefits combined with the existing level of discretionary folate fortification (i.e. maintaining the status quo on voluntary permissions). I would urge the UK to monitor the effect of this policy first.</p> <p>b) As above, but with increased permissions for voluntary folate fortification.</p> <p>c) Aim for a lower target figure of 200µg folate intake from mandatory fortification. This would reduce the likelihood of anyone group receiving too much unmodified pteroylmonoglutamic acid (PGA). The health benefits in terms of NTD reduction and homocysteine lowering could then be evaluated prior to moving on to a target figure of 400µg folate intake from mandatory fortification if required.</p> <p>Clearly I urge a fairly conservative approach to this issue.</p>	<p>University of Newcastle, Australia</p>
	<p>The report is important in concluding that mandatory fortification of flour with folate should be introduced in the UK. This is to be welcomed and supported.</p>	<p>Wolfson Institute of Preventive Medicine</p>
	<p>Strongly welcome the report's clear recommendations. COMA-recommended rate of fortification of 240µg/100g flour too low and therefore recommend fortification of 280µg/100g to achieve target levels.</p> <p>Recommend that DH, together with ONS, should re-emphasise to hospitals and neurological centres the importance of reporting all NTD births.</p> <p>Welcome SACN's recognition of the evidence of NTD reduction in countries that have mandated flour fortification and wish to see a similar application in the UK, fortifying flour at the rate of 280µg/100g.</p> <p>Supplements – The government should be continually informing and educating the public, so those girls of child bearing age are informed and encouraged to supplement their diet at the appropriate time. This should occur <u>in addition</u> to flour fortification. All women should be given access to a 5mg supplement.</p>	<p>ASBAH and SSBA</p>

<i>General comments on the report and other options to consider</i>	Commend the excellent review of public health options on folate presented in the report, which provides a sound basis for discussion and decision. In particular support of recommendations on p.43 (paras 228-231).	BDA
	Support SACN's recommendation of mandatory fortification of flour with folic acid in the UK, in the light of SACN's review of recent evidence.	BNF
	Welcome the report and do not have any specific comments on the scientific background to the recommendations in the report.	Co-op
	Women with diabetes have a much higher risk of giving birth to a child with neural tube defect than a woman without the condition (3-4 fold).	Diabetes UK
	<p>Folic acid supplementation is as important as flour fortification. Even with fortification of flour, many women of childbearing age are still unlikely to achieve the recommended level of 400ug and should take a folic acid supplement.</p> <p>Concerns that women might be given false assurance that they can obtain the recommended level of folic acid through diet alone. The programme should be run alongside a comprehensive government public health campaign to promote benefits of folic acid supplementation, perhaps a re-run of the campaign during 1996-99 by the now defunct Health Education Authority</p> <p>Key healthcare groups should routinely discuss and recommend folic acid supplementation to all women who are ovulating and sexually active – this was the conclusion of the FAA's report 'Improving awareness and uptake of folic acid (2004)'. </p> <p>DH should develop Primary Care Trusts (PCT) targets to increase folic acid supplementation and also monitor offer, uptake and outcome in women of childbearing age.</p>	FAA

<p><i>General comments on the report and other options to consider</i></p>	<p>This is a thorough review of studies in relation to folic acid intakes and status and various associated diseases. There are however, some omissions of published prospective cohort studies, which would offer a more comprehensive review of the evidence. (See table 4).</p> <p>Support the need to consider the scientific evidence base in order to protect public health and safety, and since mandatory food fortification interventions result in an increased nutrient exposure of everyone who consumes fortified food(s), it is therefore a fundamental public health nutrition issue.</p>	MRC HNR
	<p>Congratulate SACN on the draft report and concur with the sense of the recommendation in the para 229. Mandatory synthetic folic acid fortification is urgently needed and should be required in the UK no later than January 1, 2007 at 280µg/100g of flour.</p>	Rollins School of Public Health of Emory University
	<p>Report does an excellent job of reviewing the current literature. However, there is further relevant data available from the Centres for Disease control (CDC). A full review of the CDC trends should be carried out.</p>	Rowett Research Institute
	<p>The document does not raise new compelling data to support mandatory fortification of flour with folic acid.</p>	University of Sheffield
	<p>Oppose the proposal for folic acid fortification on the following grounds:</p> <ul style="list-style-type: none"> • It is an over response to the problem of birth defects. • It is wasteful and bad environmentally, as the vast majority of the folic acid incorporated will at best do no good, and at worst harm (both during production processes and by entry into the food chain). • It has known negative effects in terms of masking other problems. • In the future it is quite possible that other negative effects will become known to due excess folic acid, with potential litigation against the government as a result. <p>A more sensible and economic approach would be to educate pregnant women, or even women likely to become pregnant, of the benefits of supplements.</p>	Hennock Industries Ltd

<p><i>General comments on the report and other options to consider</i></p>	<p>It would not be a good thing, as thousands like myself, suffer from interstitial cystitis, a condition where part of the bladder lining is missing, where it is essential to follow a diet with no acid. If folic acid is added to bread and flour, I would not be able to consume this.</p>	<p>Jan Thrower (member of the public)</p>
	<p>In the absence of a sufficiently comprehensive picture we conclude that a true assessment of benefit / risk cannot presently be made, and that the current case for a policy of mandatory folic acid fortification encompassing the whole population is therefore unproven.</p>	<p>IFR</p>

Table 2: Issues for discussion arising from responses received to report

Subject	Comments	Organisation	Action
<p>SACN process i.e. methodology, review of evidence</p>	<p>Whilst it is a matter for SACN to give a final opinion/recommendation on mandatory folic acid fortification, we believe that an initial “scoping consultation”, aimed mainly at researchers with an interest in folate, would have been valuable in ensuring at the outset that all significant evidence and issues potentially relating to such a policy decision were anticipated and identified.</p> <p>The evidence base was largely restricted to prospective cohort studies and randomised controlled trials in humans. In doing so they failed to consider some pertinent scientific observations, reports and hypotheses.</p> <p>Plausible metabolic arguments that excess unmetabolised folic acid might either precipitate or exacerbate hypomethylation, thus affecting <i>inter alia</i> the efficiency of neurotransmitter synthesis (cognition) and DNA methylation (gene expression), have not been adequately addressed.</p> <p>A rigorous benefit/risk analysis of mandatory folic acid fortification must include age-subgroups (foetus, babies, infants, children, adolescents, adults, elderly and the aged) and both genders of the population.</p>	IFR	
	<p>The report needs to mention in vitro data suggesting human folate has been vastly underestimated.</p>	Rollins School of Public Health of Emory University	
<p>Background of the report</p>	<p>COMA did not “recommend” anything. As made clear in the preface of the COMA report, and in its paragraph B (Interpretation of Remit) on page 1, the Committee carried out an options appraisal and examined only some of the many aspects that would have had to be considered in making policy recommendation. Moreover, the designated fortification level was a specific (achieved) level not a target level and the still unsolved problems of overage were noted. Hence, there was no way in which the results of the options appraisal would have been appropriate as a policy recommendation. The overage problem is not considered where the estimates based on COMA are considered (e.g. Para 111 and 130).</p>	University of Oxford	
	<p>Paragraph 6 notes that the (recalculated) UK COMA recommendation was for 280µg folic acid /100g flour (i.e. <u>double</u> the US level of fortification) it seems pertinent to ask what level of unmetabolised folic acid this may lead to in the systemic circulation of a UK population.</p>	IFR	

Background of the report	<p>Paragraph 7 states that “<i>In addition to recommending folic acid fortification of flour, COMA recommended that all women should increase their folate prior to conception.</i>” Presumably this is a call for additional self-supplementation with 400µg/day folic acid. Bearing in mind the issues raised in the paragraph above, what even greater proportion of unmetabolised folic acid may this lead to in the systemic circulation of UK females prior to conception? Further, can this unmetabolised folic acid be passed to the developing foetus? (Sweeney <i>et al.</i>, 2005)</p>	IFR	
Folate	<p>Paragraph 13 states that “<i>Folates are metabolised on absorption (in the gut mucosa and liver) to 5-methyltetrahydrofolate (5-MTHF), which is usually the only form found in the plasma.</i>” Strictly speaking, this should read “Folates are metabolised on absorption (in the gut mucosa and liver) initially to 5-methyltetrahydrofolic acid, which is usually the only form found in the plasma.” [Folates are deconjugated (at the mucosal brush border) to their monoglutamate form prior to being absorbed and initially biotransformed to 5-methyltetrahydrofolic acid (the name explicitly indicating the monoglutamate structure). “5-methyltetrahydrofolate” is a generic name pertaining to an undisclosed glutamate chainlength.]</p> <p>Paragraph 13 also states that “<i>Oral folic acid, in excess of about 260µg, can lead to the appearance of unmetabolised folic acid in the systemic circulation (Kelly et al., 1997).</i>” The implied corollary of this statement is that, provided that any consumption of folic acid is below this threshold, there should be no concern that unmetabolised folic acid will enter the systemic circulation to be taken up by cells and to exert any metabolic effects. This is exemplified in such statements as that promulgated by Hoffbrand (2005) in a recent ‘Symposium on Folic Acid and Health’ viz, that because “single oral doses of folic acid of less than 300µg are ... converted by the gut during absorption ... to ... 5-methyltetrahydrofolic acid ... fortification of the diet with levels of folic acid giving less than ca. 300µg would be predicted to have no effect on the anaemia or red cell macrocytosis due to B₁₂ deficiency.”</p>	IFR	

Folate	<p>Whilst pre-1983 there was already a reasonable degree of agreement that a significant portion of physiological doses of folic acid would undergo conversion to 5-methyltetrahydrofolic acid in the intestine (Rosenberg, 1976), it was being accepted post-1983 (following publication of the paper of Tani & Iwai, 1983) as axiomatic. However, the initial site of folic acid biotransformation <u>in humans</u> has been challenged recently, leading to a re-evaluation of the Kelly et al. 1997 paper in which results were obtained from acute studies in fasted volunteers that had not been subject to folic acid supplementation/fortification, the implied oral threshold (260-300µg) for the plasma appearance of unmetabolised folic acid, in the context of mandatory day-in day-out fortification, being hypothesised (eventually) to be significantly lower.</p>	IFR	
	<p>The report has insufficient attention to folate deficiency in those over 65. This evidence should be reported. The report also fails to mention prevention of folate deficiency anaemia that occurred in the US after fortification (Ganji & Kafai, 2006).</p>	Rollins School of Public Health of Emory University	
Folate & neural tube defects	<p>It would be worth asking DH to consider recommending that all women planning a pregnancy take a 4 or 5mg supplement rather than 0.4mg, and it would be worth facilitating this by recommending that the appropriate licensing authority consider making the 5mg dose available without prescription.</p>	Wolfson Institute of Preventive Medicine	
	<p>Two very important papers were published in March (Botto <i>et al.</i>, 2005 & Busby <i>et al.</i>, 2005). Although both are cited in the draft report, have their findings been dealt with as explicitly as they should be in the document. The papers show that current folic acid recommendations in the UK and in several European countries are simply not working. In contrast, in the US, Canada and Chile, the policy of mandatory fortification of grain foods with folic acid ensures a more optimal folate status in the general population, and has proven itself in terms of lowering the prevalence of NTDs. These findings make a strong case for mandatory fortification in the UK. These papers perhaps deserve more prominent treatment (e.g. in Recommendations) in the report.</p>	NICHE, University of Ulster	

<i>Folate & neural tube defects</i>	<p>In respect of reducing the incidence of NTDs, it is of interest to note that supplementation with vitamin B₁₂ may be warranted in its own right, aside from supplementation with folate (Afman <i>et al.</i>, 2001). These authors deduced that some mothers with NTD-affected offspring probably had a reduced affinity of the systemic plasma carrier-protein transcobalamin II, which may be explained by genetic variation in the TCII gene.</p> <p>Additionally, folic acid supplementation by itself may not be sufficient to minimise uracil misincorporation into DNA if serum B₁₂ concentration is low (Kalemba <i>et al.</i>, 2005).</p>	IFR	
	<p>Although prevalence rates for NTD are given in the report (p21 Table 9), is it stated anywhere that Irish and Scottish rates are particularly high? This could be part genetic, but also almost certainly reflects the higher live birth rates in Ireland generally because terminations are not available/offered to parents of NTD cases diagnosed pre-natally. This is evident from the Botto <i>et al</i> (2005) paper, which very visually displays NTD rates on a country-by-country basis and includes both live births and terminated cases. With Irish NTD rates as high as they are, there may be particular benefits from mandatory folic acid fortification for Northern Ireland compared with the UK as a whole.</p>	NICHE, University of Ulster	
	<p>The annual number of neural tube defect pregnancies in the UK is under-estimated (para 219). In 2002 there were about 1,200 NTD pregnancies in Britain, not about 600 as stated.</p>	Wolfson Institute of Preventive Medicine	
<i>Folate & B vitamins status</i>	<p>Nutrition status requires further expansion in order to establish continuity throughout the text. Several different terms are used e.g. folate deficiency, risk of folate deficiency, low or marginal status, risk of low or marginal status, the use of these terms has not been categorically defined in the draft report and could be misinterpreted.</p> <p>It would be helpful to be explicit regarding what outcomes are used to define these terms e.g. plasma or red cell concentration of folate or homocysteine, haemoglobin, or any other marker. Important that such terms should be used with care when applying them to populations rather than individuals, or vice versa.</p> <p>The issue of categorisation of status when applied to micronutrients needs to be addressed. In several places various cut off values have been used to distinguish between levels of status. From this approach it is not always clear whether these values are to be applied to populations where they might indicate <i>risk</i> of deficiency or to individuals where they might directly distinguish deficient from adequate (however defined).</p> <p>Would like to clarify in what respect are the quoted levels 'marginal' – i.e. what outcome is at increased risk? Furthermore, the marginal risk is quoted as below a range, this begs the question whether marginal is below the upper or lower end of this quoted range?</p>	NS	

<p><i>Vitamin B12 deficiency in the elderly</i></p>	<p>It doesn't look as though we understand more about the likelihood of the occurrence of neuropathies and irreversible degeneration of the spinal cord with vitamin B12 deficiency in the elderly with folic acid fortification than we did in 2000.</p> <p>Estimates of biochemical vitamin B12 deficiency (plasma B12) in the elderly give a modest 5-10% (is this really 'high' as stated in the report?), or higher (around 23% when using the more functional MMA measurement), but the clinical significance of this statistic is not known.</p> <p>There are no data available from countries that have introduced mandatory fortification, regarding effects on biochemical markers of B12 status or of functional effects.</p> <p>If mandatory fortification is to be recommended it should be on the condition that such steps are taken to monitor B12 deficiency in the elderly and to determine the effects on neurological damage.</p> <p>The report estimates that the fortification strategy would prevent about (204-236) NTD-affected pregnancies, whilst putting a potential 2921-5844 elderly people at increased risk of neurological damage associated with B12 deficiency. This latter estimate should probably be higher if deficiency statistics are based on reports of MMA levels. There should be a clearer justification of the recommendation on the basis of these statistics alone.</p>	<p>University of Sheffield</p>	
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<p><i>Vitamin B12 deficiency in the elderly</i></p>	<p>The evidence base has recently been updated in the Banbury B12 study of 1000 community-dwelling older people who were screened for clinical and biochemical correlates of vitamin B12 (Hin et al).</p> <p>A major omission in the report is the failure to appraise management strategies for older people with biochemical evidence of vitamin B12 deficiency. There are 4 possible options (1) No action; (2) Screen high-risk older people for vitamin B12 deficiency and treat those identified with biochemical evidence of vitamin B12 deficiency; (3) Consider co-fortification of vitamin B12 with folic acid; and (4) A combination of folic acid fortification with some means of non-selective B12 supplementation for older people. Co-fortification has been considered in several countries and is an important area to commission research.</p> <p>Eussen et al (2005) carried out a dose-finding trial of incremental oral doses of vitamin B12 supplements. The results of short-term trials assessing oral doses of vitamin B12 are required to assess whether co-fortification of vitamin B12 with folic acid is a realistic solution.</p> <p>We are pessimistic about the utility of any of the available biochemical markers of vitamin B12 status to provide a cost-effective population-based screening strategy for vitamin B12 deficiency in older people. We compared single and dual testing with vitamin B12 and holotranscobalamin to detect individuals with elevated MMA concentrations (as a surrogate for vitamin B12 deficiency) and do not believe that any such screening approach for vitamin B12 deficiency will be cost-effective.</p>	<p>University of Oxford</p>	
	<p>The report does not provide sufficient emphasis on the evidence about the proportion of older people with biochemical evidence of vitamin B12 deficiency that have clinical signs of anaemia, cognitive impairment and dementia (Lindenbaum et al., 1998).</p>	<p>University of Oxford, University of Sheffield</p>	
	<p>The report is too circumspect and inconclusive on B12. The evidence is clear in showing that folic acid fortification is extremely unlikely to affect B12 levels or anaemia or neuropathy caused by B12 deficiency or pernicious anaemia.</p>	<p>Wolfson Institute of Preventive Medicine</p>	
	<p>The definition of vitamin B12 deficiency based on a "normal range" (i.e. the population mean + 2 SD, or variants of such definitions) is entirely inappropriate, since when defined metabolically, by elevation of methylmalonic acid or homocysteine, approximately 20% of the elderly are B12 deficient. This means that the "normal range" includes people with B12 deficiency.</p>	<p>University of Western Ontario, USA</p>	

<p><i>Vitamin B12 deficiency in the elderly</i></p>	<p>The strong impression given by SACN that B₁₂ deficiency is <u>only</u> correctable with high dose treatment, and the summary conclusion that “<i>the fortification of flour with vitamin B₁₂ to improve the status in people aged 65 years and over may not be a feasible option</i>”, is challenged. We would accept completely that paragraphs 66, 67 and summary paragraph 71 would be applicable to the B12 deficiency of pernicious anaemia (the minority cause of deficiency). However, given that the majority cause of deficiency is the inability to release food-bound B12 (associated with gastric atrophy/hypochlorhydria), where intrinsic factor remains unimpaired, and given that the Institute of Medicine (2000) infers that those over 50 years of age can meet their RDA (2.4µg) by obtaining their B₁₂ from dietary supplements (of ‘free B₁₂’), it would seem arguable that the fortification of flour with vitamin B₁₂ to improve the status in people aged 65 years and over <u>is</u> a feasible option.</p> <p>Wider consideration of the potential effects of mandatory folic acid fortification on the 10-30% of elderly with B₁₂ depletion/deficiency should be given, rather than a narrow focus on whether the haematological clinical signs of B₁₂ deficiency due to pernicious anaemia (the minor cause of deficiency) can be ‘masked’. In particular since, the presentation of haematological abnormalities is often absent, and indeed inversely related to neurological complications, which may proceed in their absence.</p> <p>The suggested incidence of B₁₂ deficiency, and estimates of the number over 65 years of age likely to be exposed to folic acid in excess of 1,000µg/day, may have been markedly underestimated. It should be considered that the US population was actually exposed to double the projected intake of folic acid.</p>	IFR	
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<p><i>Vitamin B12 deficiency in the elderly</i></p>	<p>The prevalence of B12 deficiency in the elderly, whether due to malabsorption or lower dietary intake, and the difficulties associated with diagnosing and treating it, needs to be dealt with as a separate issue, which should not hinder or delay the introduction of mandatory fortification of appropriate food vehicle with folic acid. Folic acid does not cause B12 deficiency. While it is necessary to keep in mind that megaloblastic anaemia and total homocysteine levels are common biomarkers of both B12 and folic acid levels, it is no reason to conclude that B12 deficiency cannot be unmasked in the presence of a higher than current level of serum folic acid due to mandatory fortification.</p> <p>The solution to the problem of masking of B12 can be sorted out by:</p> <ol style="list-style-type: none"> 1. Being more aware of the problem of B12 deficiency in the elderly 2. More aware of the difficulties involved in the diagnosis of B12 deficiency 3. Taking a thorough case history of neuropsychiatric symptoms in the elderly which could serve as an indication of B12 deficiency, even in the presence of normal serum levels of B12 4. Determining serum B12 and folic acid level as initial screening test 5. Not interpreting normal serum B12 level as lack of B12 deficiency 6. Ruling out folic acid deficiency in the presence of macrocytic anaemia and higher levels of tHcy. 7. Using more specific markers of B12 deficiency - methylmalonic acid (MMA) and holotranscobalamin (holoTC) and interpreting results taking the effect of renal impairment into consideration 8. Using Intrinsic Factor Antibody test and Schilling test to determine the cause of B12 deficiency rather than the presence of it 9. Using tHcy and MMA levels as follow up tests. <p>Public education targeted for those over 40, about risk of B12 deficiency in the elderly, so that they have the opportunity to store up on their reserves of B12 before the inevitable problems of old age set in. Make folic acid and B12 estimation after age 40 routine examination at regular intervals, just as one would test for blood sugar levels.</p> <p>Encourage 'medical instrument' companies and those involved in that area of research to come up with cheaper and more accurate B12 and folic acid estimation kits.</p>	<p>Sydney West Area Health Service</p>	
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<p>Vitamin B12 deficiency in the elderly</p>	<p>(Pg 22: 109-111) The report does not distinguish between folic acid given in a single dose therapeutically, e.g. 1000µg and an intake of 1000µg of folic acid daily which might occur in a very small percentage of subjects resulting from fortification. The dietary intake of 1000µg folic acid a day as a result of fortification would be spread across several meals not as a single dose. This is extremely important since the gut converts low single doses of folic acid, e.g. up to 260µg to methyltetrahydrofolate during the absorption process. Thus there would be far less free folic acid circulating in the plasma of individuals eating 1000µg of folic acid daily spread across several meals compared to those given a single therapeutic dose of folic acid.</p> <p>(Pg 24: 118) The statement that folic acid can maintain DNA synthesis in megaloblastic anaemia is vague. Do the authors mean in folate deficiency? Low doses, e.g. as little as 200µg daily does in folate deficiency but not in vitamin B12 deficiency. Folic acid might only do this in B12 deficiency if present in very high concentrations. There is no evidence that the amounts of free folic acid that might circulate following three meals a day containing even as much as 1000µg of folic acid in one day would affect the anaemia of B12 deficiency. The maximum dose in a single meal would be of the order of 400µg and this amount by mouth does not produce a haematological response in B12 deficiency.</p>	<p>Royal Free Hampstead, NHS</p>	
	<p>Recognise the importance of folate in protecting against NTD. US fortification ensures that those least likely to achieve an extra 400µg/d via grain products do so. As a consequence of this, those of us who eat a lot of grain products will readily achieve the 1mg tolerable upper limit threshold on a daily basis. This raises issues in the elderly where atrophic gastritis is common, leading to B12 deficiency. The first symptom of B12 deficiency will be megaloblastic anaemia due to a secondary 'functional' deficiency of folate induced by a lack of B12 for the conversion of 5-methyl-H4folate into H4folate by B12 dependent methionine synthase. However, if individuals are folate replete, as they would be if mandatory fortification were in place, then megaloblastic anaemia, the presenting sign of B12 deficiency would be masked, and the first sign of B12 deficiency would be potentially fatal pernicious anaemia. By the time this is picked up with fortification in place, it may be too late.</p>	<p>University of Newcastle, Australia</p>	
	<p>Pleased to see parallel recommendation about the need to monitor and act on concerns about B12 deficiency in the elderly. This should be tackled regardless of the policy decision on folic acid.</p>	<p>BNF</p>	
<p>Vitamin B12 deficiency in the elderly</p>	<p>An additional potential explanation for poor vitamin B12 and folate status in older adults should be taken into consideration. Both vitamins are susceptible to the effects of 'oxidative stress', an important feature of the ageing process (Zhou & Banerjee, 2005; McCaddon <i>et al.</i>, 2002; Fuchs <i>et al.</i>, 2001; Pezacka <i>et al.</i>, 1990; Shane & Stokstad, 1985; Widner <i>et al.</i>, 2002; McCaddon <i>et al.</i>, 2004).</p>	<p>Andrew McCaddon</p>	

	Review on oral or intramuscular vitamin B12 for the treatment of vitamin B12 should be included (Vidal-Alaball <i>et al.</i> , 2005).	National Public Health Service for Wales	
	<p>The term “masking” B12 deficiency with folic acid was intended to alert physicians to the fact that folic acid was not a treatment for B12 deficiency and remission of the anaemia should not suggest that folic acid was beneficial. This combination of circumstances is not going to come about again due to:</p> <ol style="list-style-type: none"> 1. The relatively low incidence of new cases of pernicious anaemia 2. The common GP practice of checking serum b12 in patients with macrocytic anaemia 3. Clinicians are unlikely to treat macrocytic anaemia with very high doses of folic acid without proper investigation 4. Lesser degrees of b12 deficiency commonly detected in the elderly are not adversely affected by fortification 5. Fortification proposed is too low a dose to affect the anaemia of B12? <p>I am therefore in complete agreement with your conclusions and also quite sure that general practices is ready to deal with the consequences in terms of vigilance for B12 deficiency.</p>	John Nichols	
	There is no controlled evidence that has shown that folic acid therapy in persons with vitamin B12 deficiency in any way affects the course of untreated vitamin B12 deficiency disease (Oakley, 2002 & Dickinson, 1995).	Rollins School of Public Health of Emory University	
	There have been no reports of adverse effects as a result of the introduction of mandatory fortification with folic acid. If anything, there is a growing concern that the level of fortification in the US at 140 micrograms of folic acid per 100 grams of flour was too low and needs to be increased for better results in the prevention of NTD.	Sydney West Area Health Service	
<i>Adverse effects of folic acid</i>	The form of folic acid that is used as a supplement, is always PGA. This form of the vitamin is not natural, but is cheap and stable, unlike native forms of the vitamin. Research carried out (Lucock <i>et al.</i> , 1989) shows that a single dose of 400µg (or less) PGA is converted efficiently into 5-methyl-H4folate during absorption. However, the absorption and biotransformation process is saturated at this 400µg dose, and anything higher will lead to unmodified PGA appearing in the blood. The question arises; 'what is the potential detrimental effect, if any, of unnatural folic acid metabolites when they are absorbed into the body'? The answer is; 'we simply don't know'. There are possible interactions that one can speculate upon. We need to know more about the effects of chronic exposure to PGA before instituting mandatory fortification. We need to ask the right questions and undertake appropriate research. It is quite likely that there will be no adverse effects from chronic, even a lifetime exposure to PGA - but the point is we do not know this for certain.	University of Newcastle, Australia	

<i>Unmetabolised folate</i>	<p>New experimental research in humans, re-assessment of old research, and recent observations all combine to suggest that the anticipated exposure of the systemic blood plasma circulation to unmetabolised folic acid may have been underestimated.</p> <p>We draw attention to the effects of mandatory fortification on anti-folate chemotherapy, and new research showing that unmetabolised folic acid can be passed to the developing foetus – thus raising concerns of unintended influences during human embryonic development (Sweeney <i>et al.</i>, 2005).</p>	IFR	
	<p>The report fails to understand that exposure to unmetabolised folic acid has been widespread and almost universal for all foetuses that developed in the United States for the last 50 years (Huber <i>et al.</i>, 1998).</p>	Rollins School of Public Health of Emory University	
<i>Epilepsy</i>	<p>(pg 24: 120) The only double blind trial of whether folic acid therapy might affect epilepsy control showed no effect. Reynolds statement that folic acid might aggravate fit frequency is not based on any prospective randomised evidence. In this connection the summary in paragraph 132 could also be modified; as it stands it implies the possibility of a risk when there is in fact no evidence of there being one. The impact of high levels of folic acid (5mg/day) on the anticonvulsant effects of phenytoin has been studied and no effect has been found (Norris & Pratt, 1971; Ralston <i>et al</i>, 1970; Grant & Stores, 1970; Bowe <i>et al.</i>, 1981; Houben <i>et al.</i>, 1971).</p> <p>At 1mg/d, folate would likely interfere with anticonvulsant drug therapy. Folate interferes with the control of epilepsy by drugs such as phenytoin in particular, but it also interacts with valproic acid and carbamazepine. 2% of the population has drug controlled epilepsy, so this is no small thing.</p>	<p>Wolfson Institute of Preventative Medicine, Royal Free Hampstead, NHS</p> <p>University of Newcastle, Australia</p>	
<i>Folate and chronic disease</i>	<p>The report considers several possible adverse effects, and concludes, rightly, that possible effects on neurological function in the elderly has the strongest evidence base. However, it would have been wise to consider concerns that increasing folic acid intake might accelerate the progression of premalignant lesions. The data to support this contention are limited but the concern should be aired in the report.</p>	University of Sheffield	
	<p>“progression of Alzheimer’s disease” (para 185) – Alzheimer’s disease is a pathologically defined disease of the brain. What was observed was actually progression of the clinical syndrome of dementia that 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.</p>	University of Oxford	

<i>Cardiovascular disease</i>	<p>The evidence indicating that folic acid has a modest effect in reducing the risk of cardiovascular disease has been understated. It might be worth pointing out that the advantage of the MTHFR studies is that they avoid the confounding that can affect cohort studies so that they are in effect natural randomised experiments capable of testing whether moderately raised serum homocysteine levels cause IHD. It is also worth pointing out that the two meta-analyses performed (Wald et al., 2002 & Lewis et al., 2005) obtained the same quantitative results, a statistically significant odds ratio of 0.84 (that is a 16% lower risk of IHD).</p> <p>It is misleading (Para 162) to say that the randomised controlled trials have failed to demonstrate a beneficial effect of folic acid. From the serum homocysteine reductions achieved, the expected reduction in IHD events is only about 10%. The trial data are consistent both with this 10% reduction and with no reduction. A better conclusion would be as follows: "Existing randomised trials alone and collectively lack the statistical power to be able to demonstrate the expected reduction in risk from increasing serum folate based on predictions from observational epidemiology".</p>	Wolfson Institute of Preventive Medicine	
<i>Cancer</i>	<p>Plausible metabolic arguments that excess unmetabolised folic acid might up-regulate dihydrofolate reductase enzyme activity, which may be accompanied by increased pyrimidine production, have also not been adequately addressed. This may potentially increase cells' capacity for division, thus predisposing to an 'accelerating' effect, which may be detrimental in the context of cancer.</p>	IFR	
<i>Fortification process</i>	<p>Strongly recommend that the most practical means of adding folic acid to flour is at the milling stage. The most practical means of legislating for the addition of folic acid to flour is under the Bread and Flour regulations. Costs would have to be established i.e. the addition of folic acid and the cost of initiating the process.</p> <p>Folic acid will have to be added as part of a mix, manufacturers of mixes such as those used to add other nutrients to flour will need to be involved in discussions. Folic acid should be added to the same flours, as other nutrients already added to white and brown flours, otherwise the installation of extra mills would be required, increasing the cost. Folic acid is expensive, the cost will almost certainly not be recoverable from the marketplace. Current rules do not require the labelling of nutrients added to flour, would this apply to folic acid? The organic sector opposes the addition of nutrients to flour, including existing statutory nutrients.</p>	<p>The Federation of Bakers</p> <p>NABIM</p>	<p>Risk management</p> <p>Risk management</p>

	The report does not make it clear whether the recommendation is for mandatory fortification of all flours (with the concomitant loss of consumer choice) or some flours (with a loss of effectiveness but a reduction in any risks associated with masking B12 deficiency in the elderly).	University of Sheffield	Risk management
	What those arguing potential harm in sub groups overlook is that, for example, standard 70% extraction flour loses >50% of its vitamin B2 and folate and >80% of its B6 from milling. These amounts are later lowered further by storage, boiling, light and/or heating. The 'first do no harm principle' should really start at the refining, processing and handling stages and replacing known lost or low nutrients should not require decades of contemplation when the current 'draft' report confirms, once again, long-known harm from deficiency.	Eddie Vos	Risk management
	Mandatory fortification should be restricted to processed foods e.g. refined not wholemeal flour, so that advocates of 'pure food' have a choice.	Sydney West Area Health Service	Risk management

<p>Fortification process</p>	<p>Bread manufacturers and flour millers would tolerate the mandatory fortification of flour. Flour rather than bread fortification is preferred by bakers, as regulations already exist on mandatory fortification of flour with several other nutrients¹ and this position should be followed for the addition of folic acid.</p> <p>To fortify on a voluntary basis may mean that industry fortifies (with the associated cost) only to find that new UK or EU regulations forbid a claim for fortification to be made, for example if the product is deemed to be too high in fat, salt or sugar. In addition, the millers and bakers have indicated that Government must accept responsibility for the medical impact of fortification e.g. in the event that fortification leads to an increase in neurological damage caused by the masking of B12 deficiency.</p> <p>However, some FDF members have concerns that mandatory fortification will lead to trade barriers with other countries, which do not tolerate fortification. This would particularly be the case if the fortificants have to be labelled.</p> <p>The labelling issue needs to be considered, i.e. would all products that use, say fortified flour, need to declare that they contain fortified folic acid? Bread manufacturers have indicated that using the existing Bread and Flour Regulations would overcome the need to label folate separately in flour.</p> <p>A decision will need to be made about fortifying wholemeal flour with folic acid. Currently there is no provision set up for fortifying wholemeal flour, and to do so would involve significant cost to the industry.</p> <p>It should be noted that the organic sector is against any form of fortification.</p> <p>Some FDF members already fortify food with folic acid on a voluntary basis, for example breakfast cereals and some margarines. Some of these members want to maintain the option of fortifying with folic acid on a voluntary basis. FDF hopes that such products will be allowed to continue to claim that they contain folic acid and therefore may offer health benefits. Current trends in defining foods in terms of 'good or bad' may mean that such valuable sources of folate will no longer be able to make this claim.</p> <p>A modelling exercise has shown that if flour was fortified to a level of 280µg/100g, total folate intake at current voluntary folate fortification levels (with current supplement use) would not lead to excessive folic acid consumption. The results show that intakes by all age groups remains below 1000µg/day.</p>	FDF	Risk management
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¹ The Bread and Flour Regulations require that flour should contain not less than 0.24mg thiamine (vitamin B1), 1.60mg nicotinic acid and 1.65mg 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 235mg and not more than 390mg per 100g of flour is added to all flours except wholemeal (and certain self raising varieties).

<i>Dose</i>	Recommend that women with diabetes should take a dose of 5mg/d to achieve the same protection – this issue needs to be addressed in the report.	Diabetes UK	
	Concerns about level of fortification to ensure sufficient increase in folic acid (taking into account losses during manufacture), and the manner of labelling required.	Co-op	
<i>Anaemia</i>	The report does not mention the prevention of folate deficiency anaemia that occurred in the United States after fortification. There was a dramatic increase in RBC folate and serum folate concentrations and a concomitant reduction in those judged to be folate deficient. It is well known that one has to be folate deficient to have folate deficient anaemia (Ganji & Kafai, 2006).	Rollins School of Public Health of Emory University	
<i>Co-fortification with folic acid and vitamin B12</i>	Due to the possible consequences of masked vitamin B12 deficiency from folate fortification, it would be far better to fortify with both folate and B12. Fortification with both has the potential for major reductions also of vascular disease, dementia and possibly falls in the elderly (due to impaired position sense from subacute combined degeneration).	University of Western Ontario, USA	
	<p>Point 71 of the report suggests that simultaneous fortification with B12 to satisfy needs in some elderly may be impractical because 400x RNI amounts may be required [that would be ~0.5 mg/d]. Since B12 is entirely without toxicity in any practical amount, what is wrong adding a target amount of 50 µg/d to processed foods to be fortified? Although one may propose that this will not resolve deficiency in 100% of over 65 year olds (my guess is that it will), one cannot argue cost and safety of B12. B12 with folate can be added at RNI amounts at a material cost of about £0.05/year, per person.</p> <p>The Centres for Disease Control and Prevention in the U.S. reported a 300% rate decline for stroke and heart disease deaths, comparing the 3 years prior with those post folate fortification. As further 'unintended side-benefit' [USB], others reported a 60% reduction in a neonate brain cancer. Adding some B12, if not B2 and B6, should increase these figures at minuscule cost while adding to the list of USB's.</p>	Eddie Vos	

<p><i>Co-fortification with folic acid and vitamin B12</i></p>	<p>Treatment of disease states such as pernicious anaemia and other types of malabsorption due to disease conditions other than the results of the natural ageing process, requiring large doses of B12 supplementation, should not be attempted through mandatory fortification with B12 meant for the whole population.</p> <p>Although the case may not be urgent, a recommendation for voluntary (to begin with) co-fortification with B12 at a low level - 2.5-4.0 µg/ 100 gm flour - could be made for the benefit of the general population, if one were to aim for optimum health, characterised by genomic stability, rather than absence of deficiency diseases.</p> <p>Co-fortification with B12 would enhance the effect of mandatory fortification with folic acid. B12, having no upper limit for intake nor any known toxicity, would not harm any segment of the population who would be exposed to higher than the RDI level. Being stored in the liver and made available for many years, the excess B12 could serve as a good backup for the elderly to fall back on.</p> <p>The additional cost involved for fortification with B12, once the technical arrangement for fortification with folic acid is in place, is negligible.</p> <p>Co- fortification with B12 would benefit risk groups other than the elderly - vegetarians and alcoholics. The number of elderly who suffer from mild B12 deficiency due to atrophic gastritis and the resulting achlorhydria far outnumber those who suffer from malabsorption like pernicious anaemia. In those with deficiency due to achlorhydria, it is expected that lower doses of B12 supplementation would be sufficient to reverse the deficiency and co-fortification could possibly delay the onset of the deficiency state by several years.</p>	<p>Sydney West Area Health Service</p>	
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<p>Overall summary /conclusions</p>	<p>(pg 41:217) In the discussion of this point it is important that irreversible subacute combined degeneration of the cord only occurs with extremely severe vitamin B12 deficiency. In the older literature it was found only in patients with serum vitamin B12 levels of 50ng/l or less measured on the Euglena Gracilis assay. Food malabsorption is not a cause of severe B12 deficiency sufficient to cause irreversible B12 deficiency and is not a cause of peripheral neuropathy which again occurs only in severe B12 deficiency, e.g. associated with pernicious anaemia.</p> <p>(pg 42:223) This point is completely wrong. It refers to 1000µg folic acid daily without recognising that this would be taken in three meals a day. It does not recognise that patients with mild B12 deficiency as from food malabsorption do not progress to severe B12 deficiency. The deficiency remains mild because the enterohepatic circulation for B12 is not broken as it is in pernicious anaemia. Mild deficiency is irrelevant in terms of irreversible neurological damage. It is this spurious issue raised by the finding of frequent minor degrees of biochemical B12 deficiency in the Oxford area that has delayed the fortification of flour with folic acid in the UK as recommended by COMA in the year 2000. The incidence of these biochemical abnormalities depends on where the upper limit of normal ranges are placed in the old age group for e.g. serum methyl malonic acid or homocysteine. These minor degrees of possible B12 deficiency are not relevant to B12 neuropathy or indeed megaloblastic anaemia.</p> <p>(pg 42:226) It would be a relevant problem if manufacturers put in substantially more folic acid into flour than recommended. This could be monitored. This point applies in all countries, which have already fortified with folic acid and no increase of vitamin B12 neuropathy has been reported.</p>	<p>Royal Free Hampstead, NHS</p>	
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Recommendations	<p>Welcome the report's recommendations as highlighted in paras 228 - 232, in general. However, it is necessary at least to identify what further information would be required to formulate a conclusion regarding the level of fortification and the form of folate to be used. In the absence of this information it is not possible to implement the recommendation laid out in para 229, which detracts substantially from its value.</p> <p>It is not clear why the issues identified (vitamin supplements, fortification and overage) have not been considered as information already exists (and some is quoted in this report) in order to come to a more precise recommendation. Finally, the information stated in para 232 suggests that promotion of a healthy diet to correct riboflavin deficiency but as this may not be effective alternative options should also be considered.</p>	NS	
	<p>Recommendation 5 (para 232) needs clarification. A diet that is 'low in salt, and saturated and total fat and rich in fruits, vegetables and complex carbohydrates' is unlikely to have a significant impact on riboflavin intake. More than 30% of the dietary riboflavin in the UK is derived from dairy products and riboflavin deficiency is endemic in those regions of the world in which diets are low in dairy and meat products.</p>	University of Sheffield	

<p>Recommendations</p>	<p>Strongly support the recommendation in para 229, however it should be specific for folic acid as recommended by COMA and on which nearly all the evidence on NTD prevention is based.</p> <p>The recommendation covered in para 228 should come second, and that on flour fortification first, to emphasise that all women who could become pregnant take a folic acid supplement should be maintained after fortification, so that people do not think fortification replaces the need for supplement use.</p> <p>Suggest that SACN recommend that the appropriate licensing authority consider allowing folic acid to be available in doses greater than 0.4mg without prescription, as is the case in many other countries, such as France, Italy, Spain and Australia. It is not logical to recommend the 5mg dose for women who have had an affected pregnancy but only 0.4mg to women at average risk. The higher dose would reduce the risk of an NTD pregnancy by about 80%, the lower dose by about 40%. A WHO Euro Working Group has recommended that all women planning a pregnancy should take 5mg. This is of particular importance since over 95% of NTD pregnancies occur in women with no history of affected pregnancies. Both doses are safe and inexpensive. The main reason that the lower dose was recommended in the UK was that it required no prescription so it would be more accessible. If this restriction were removed there would be a simple uniform recommendation to all women planning a pregnancy that would be more effective in preventing NTDs.</p> <p>The recommendation to further consider the level of fortification and the form of folate should be removed (para 230). It will further delay the introduction of fortification in Britain. Detailed implementation of the recommendation can be left to discussion between the Food Standards Agency, the Department of Health and the food industry. The report should specify the level based on COMA as modified in this report, namely 280µg per 100g flour. It would be unwise to open a debate over the use of different forms of folate.</p> <p>The uncertainty over the incidence, prevalence and management strategy for B12 deficiency in older people is a completely separate issue from folic acid fortification and should not feature as a recommendation in this report.</p> <p>The recommendation on riboflavin (Para 232) is out of place in this report, however valid the suggestion made in the recommendation. It should therefore not feature as one of the listed recommendations.</p>	<p>Wolfson Institute of Preventive Medicine</p>	
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Recommendations	<p>Specific comments on para 229: How do levels suggested (240 or 280mcg/100g flour) compare to the US mandatory levels (140µg/100g food as consumed)? How is flour defined? Is the intention to include wholemeal and non-wheat flours into the provision? Are gluten-free flours to be fortified? If not, will additional measures be needed to target women on gluten-free diets? The 1992 Department of Health report 'Folic Acid and the Prevention of Neural Tube Defects' recommended that there should continue to be a choice of unfortified bread and breakfast cereals. The BDA feels that this should be considered in further discussions.</p> <p>Specific comments on para 230: The 'higher than required' level of fortification observed in the US attributed to overages is likely to occur in the UK as well. The high proportion of US children aged 1-8 years reported to be consuming folic acid intakes above Upper Levels defined in the US, indicates some basis for the restriction of further voluntary fortification of foods marketed specifically to children, if fortification of flour becomes mandatory.</p>	BDA	
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Table. 3 Specific changes to the text/report

Paragraph /Table	Comments	Organisation
Para 13	The oral folic acid dose noted (260µg) is presumably referring to the dose per day?	NS
Para 13	It is worth adding that for half a century pregnant women have been taking folic acid supplements in pregnancy with no indication of harm and that free folic acid in maternal circulation may be an advantage in preventing neural tube defects since the folic acid in this form will readily pass into the fetal circulation.	Wolfson Institute of Preventive Medicine
Para 13	<i>“Folates are metabolised on absorption (in the gut mucosa and liver) to 5-methyltetrahydrofolate (5-MTHF), which is usually the only form found in the plasma.”</i> Strictly speaking, this should read “Folates are metabolised on absorption (in the gut mucosa and liver) initially to 5-methyltetrahydrofolic acid, which is usually the only form found in the plasma.”	IFR
Para 13	It should be mentioned that folic acid is an artificial substance not occurring in nature (not mentioned until paragraph 212). It is also important to point out that there have been no follow-up studies of babies whose mothers took high doses periconceptually.	University of Oxford
Para 22	Second sentence “The amounts of folate required to prevent NTDs are above the RNI for folate” is clearly not true for most women, though the effective dose for reducing risk of NTDs is above the RNI. The Society would recommend the following sentence as an alternative: "Although most pregnancies in women consuming folate at the RNI will not be affected by NTD, the risk can be reduced by increasing folic acid consumption to levels above the RNI".	NS
Para 22	Makes no mention of genetic differences in requirements, an issue that is not raised until paragraph 138.	University of Oxford
Para 25	Use of the term ‘normal’ requires clarification in the context of the sentence “For all age ranges from 4 years and above, the <i>normal</i> range for red cell folate concentrations is considered to be 422-1463 nmol/L...” It is not clear whether the reference is a reflection of usual intakes or whether it is what would be considered a desirable level.	NS
Para 28	It is not clear what is meant by an “increased risk of marginal status”. Requires clarification.	NS
Para 29	Not sufficiently clear what is meant by the term "intermediate risk" in the context of having NTD- affected pregnancies i.e. intermediate between what? In addition, is it difficult to interpret how the conclusion in this point is reached when considering the figures for "normal" values under <i>para 25</i> .	NS
Para 36	For the lay reader there should be some explanation of why there is a discrepancy between recommended intake and folate status.	University of Oxford
Para 36	Suggest the point could be phrased more clearly to "Although average folate intake was above RNI in all age groups, the RBC folate concentrations were low [or marginal if defined] in young women and in people aged 65 years and older, with frank deficiency in a substantial proportion of the latter who were in institutional care. Average RBC folate concentrations in women aged 18-49 years are below those associated with low risk of NTD".	NS
Para 45	The explanation offered in this paragraph as to why there is an unexpectedly high proportion of people apparently riboflavin deficient, i.e. an inappropriate cut off offers one explanation. An alternative explanation is that large numbers of people are deficient. The Society suggests that this discrepancy should be explained as to why the former is deemed correct and not the latter.	NS
Para 46	This paragraph explains how the value of 2.00 is arrived at for pyridoxine. The Society recommends that the justification for this value be clarified in the light of the concerns highlighted in the report in <i>para</i>	NS

	45 regarding riboflavin status.	
Para 62	Uses both the terms 'sensitive' and 'specific' in respect of MMA's value in detecting vitamin B ₁₂ -deficiency. It would be worth emphasising that it is indeed both terms sensitive and specific, if that is what is intended.	NS
Para 63	States that after applying various criteria, that for instance xx% of adults aged 65+ were <i>at risk of</i> deficiency. However as these cut offs apply to the individuals and not the group, the Society suggests it should say that xx% had low status or were deficient - i.e. this is a measure of status in individuals not of risk in a group; it could also be noted that a certain number fell below the quoted threshold.	NS
Para 67	It is not clear whether the range of lowest effective dose of vitamin B ₁₂ (647-1032µg/d) applies to individuals or whether it was an average for a group. Either way the implications might be clearer if an explanation of the experimental design was provided.	NS
Para 68	Tables 1-4, where the number of patients seen in hospitals is stated only refers to admissions and will therefore exclude any out patient activity, which might be considerable. It also states that it excludes those seen in the primary care setting, though it seems likely that those admitted to hospital will have already been seen in primary care. The relevance of the peripheral neuropathy category is unclear as vitamin B ₁₂ deficiency might be amongst the rarer causes compared to for example diabetes.	NS
Para 71	The conclusion in this paragraph not to recommend these high doses of vitamin B ₁₂ may well be sensible but other than the high dose the rationale is not given. The Society believes that it would be helpful to provide a more detailed explanation of why a high dose is not recommended.	NS
Para 73, line 5	"an additional" should be replaced by "a"	Wolfson Institute of Preventive Medicine
Para 75	Reference is made to both folic acid supplementation and to diet change in order to increase folate intake in mothers whom reported planning their pregnancy. The Nutrition Society believes that there should be some discussion regarding the merits or otherwise of such approaches as diet change is much less likely to achieve an adequate folate intake with respect to NTD risk.	NS
Para 83	The following should be added to the end of the paragraph, as the text does not adjust for under reporting. "However the extent of under-reporting of NTD births and NTD terminations are different so an aggregate correction figure will not remain constant over time when NTD terminations are increasing and NTD births decreasing".	Wolfson Institute of Preventive Medicine
Para 84 & 85	Replace paragraphs 84 and 85 with: Morris and Wald ⁷ showed that the total number of NTD terminations (allowing for under-reporting) can be estimated by applying a multiple of 2.3 (1/0.44) to the reported <u>CNS</u> terminations (before 1995 terminations were only reported CNS for all abnormalities not separately for NTD), and the equivalent multiple to apply to reported <u>NTD</u> terminations (as published from 1995) is 3.4 (1/0.29) (since 67% of CNS terminations are NTD terminations (0.44 x 0.67 = 0.29)). In 2002 there were 278 notified NTD terminations in England, Wales and Scotland, so the estimated total is 945 cases (278 x 3.4). Boyd et al ⁸ estimated that only 68% of NTD births were reported (1991-99). 143 NTD births were reported in England, Wales and Scotland in 2002 so the estimated total number was 213 cases (143 x 1/0.68). Taking account of under-reporting there were, therefore, an estimated 1,158 NTD (945 + 213) pregnancies in England, Wales and Scotland in 2002.	Wolfson Institute of Preventive Medicine

Para 99	The list of countries shown in Table 8 is not complete list so the text should say that it refers to <i>some</i> of the countries that have introduced fortification.	Wolfson Institute of Preventive Medicine
Para 104	Anencephaly rates 'fell from 8.19/10,000 in 1990-2000 to 3.18/10,000 in 2001-2002' which is a 61% fall. However, in line 6 it is described as a 42% fall, a value which in the original paper by Lopez-Camelo takes into account the data from 1982-1989, where the anencephaly rates were 6.39/10,000.	MRC HNR
Para 109	Defines the term 'masking' of vitamin B ₁₂ deficiency as both the correction of anaemia and the progression to irreversible neurological damage; this is confusing. It seems most sensible to define "masking" as the correction of anaemia, which allows but does not necessarily result in the progression of neurological symptoms. It is not clear if the 1000µg daily threshold stated in this paragraph applies to progression of neuropathy or to the correction of anaemia.	NS
Para 111	Figures given under this paragraph provide numbers exposed to folic acid in excess of 1000 µg/d, but it is important to note that this does not take account of the overage issue expounded in <i>paras 105 and 106</i> .	NS
Para 123	line 5: '20µg/d of vitamin B1' - should be vitamin B12	MRC HNR
Para 133	It would be more accurate to say that there is no evidence to indicate that folic acid fortification is associated with multiple births and that there is evidence to suggest that it is not.	Wolfson Institute of Preventive Medicine
Para 135	The Society believes that it would be helpful to know how the Panel judges the likely causality of the association between homocysteine and cardiovascular disease as this is a controversial area, as noted under this paragraph.	NS
Para 136	The maximal or near maximal plasma homocysteine lowering doses of folic acid is 400-800µg per day, not 200-400µg per day.	Wolfson Institute of Preventive Medicine
Para 139	Penultimate line: it may be clearer if the words 'by folate supplements' were inserted after 'tHcy concentration'.	MRC HNR
Para 140	Line 4 - 'C677T MTHFR genotype and risk of coronary heart disease' – please clarify that this refers to the TT genotype here.	MRC HNR
Para 147	Please clarify that all of these are daily supplements of the vitamins	MRC HNR
Para 161 & fig 1	Three out of the 6 studies quoted found a significant association in one or more groups in fig 1, therefore does this tally with the conclusion: 'generally not shown a significant association'?	MRC HNR
Para 164	Last line: 'described in 25' – should be 125.	MRC HNR
Para 192	"correlated" – presumably inversely?	University of Oxford
Para 194	Final sentence: 'after adjustment for folate and plasma tHcy concentrations...only low plasma folate concentrations predicted cognitive decline'. This should be clarified, as folate was adjusted for plasma tHcy, vitamin B6 and B12) and vitamin B6 for tHcy, folate and B12)	MRC HNR
Para 198	Last line: suggest insert 'other' before 'B vitamins'?	MRC HNR
Para 200	Suggest either separate this, as depression is not the same as cognitive decline or dementia, or label section as mental health.	MRC HNR
Para 202	"Sastre" not "Satre"	University of Oxford
Para 221	Has this been adjusted for the difference in flour concentration?	University of Oxford
Para 229	Should be rewritten to read: "Mandatory synthetic folic acid fortification is urgently needed and should be required in the UK no later than January 1, 2007 at 280 micrograms per 100g flour".	Rollins School of Public Health of Emory University

Para 230	Suggests deletion of this paragraph, as the only feasible form of folate is pteryl-monoglutamic acid (PGA). Therefore also suggest amending para 229 to read “synthetic folic acid or pteryl-monoglutamic acid (PGA)”.	Rollins School of Public Health of Emory University
Table 9	As there is a continuing decline in NTD rates in unfortified countries, comparable time trends should be give for these too.	NS
Table 18	Does not add any further information to that shown in table 17, and has an error for the vitamin B6 entry for men and women.	University of Sheffield
References	Sastre reference missing.	University of Oxford

Table. 4 Suggested references

No	Reference	Organisation
1	Abrahamsen B, Madsen JS, Tofteng CL, Stilgren L, Bladbjerg EM, Kristensen SR, Brixen K, Mosekilde L. Are effects of MTHFR (C677T) genotype on BMD confined to women with low folate and riboflavin intake? Analysis of food records from the Danish osteoporosis prevention study. <i>Bone</i> 36:577-83 (2005)	MRC
2	Abrahamsen B, Jorgensen HL, Nielsen TL, Andersen M, Haug E, Schwarz P, Hagen C, Brixen K. MTHFR c.677C>T polymorphism as an independent predictor of peak bone mass in Danish men-results from the Odense Androgen Study. <i>Bone</i> . (2005) [Epub ahead of print]	MRC
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