Update report on folic acid:
Responses received to the scientific consultation (16 February – 2 March 2107)

Responses were received from the following organisations & individuals:

1. British Nutrition Foundation (BNF)
2. NHS Health Scotland
   (N Hay, Senior Communications and Engagement Officer)
3. E Carter
4. Professor A V Hoffbrand
   Department of Haematology, Royal Free Hospital, London
5. Dr A Sobczyńska-Malefora
   Lead Clinical Scientist; Nutristasis Unit; Honorary Senior Lecturer (King's College London); Haemostasis & Thrombosis, St. Thomas' Hospital, London
6. J Nichols
   Visiting Research Fellow, University of Surrey
7. Propriety Association of Great Britain (PAGB)
   (Tracy Callis, Food Supplements Regulatory Manager)
8. Dr E H Reynolds MD FRCP FRCPsych
   Former Consultant Neurologist to the Maudsley and King's College Hospitals;
   Honorary Senior Lecturer, Department of Clinical Neurosciences, King's College, London.
9. Professor A D Smith *FMedSci*
   Professor Emeritus of Pharmacology, University of Oxford; Founding Director, Oxford Project to Investigate Memory & Ageing (OPTIMA); Founding Director, MRC Anatomical Neuropharmacology Unit.
10. Dr M R Sweeney
    Dublin City University
11. Professors Sir Nicholas Wald, Joan Morris, Malcolm Law
    Wolfson Institute of Preventive Medicine, Queen Mary University of London
12. Royal College of Obstetricians and Gynaecologists (RCOG)

Table 1: General comments (chapters and paragraph numbers refer to those in the draft report)

Comments	Org/ Individual	Action agreed by SACN
BNF welcomes SACN's expert review of the recent evidence relating to folic acid and health, in the context of recommendations made previously by the Committee. We do not know of any further studies to be considered.	BNF	Comments welcomed.
NHS Health Scotland welcomes SACN's draft report which provides a concise and systematic review of the evidence since the 2006/2009 risk assessments. NHS Health Scotland supports the scientific content of the report and has no further evidence to add to this consultation.	NHS Health Scotland	Comments welcomed.
Folic acid fortification: Fact or folly - This review of 1992 US FDA decision & process leading to fortification in 1996 and experience *of in vivo* trial on whole 250 million USA population (comparable to UK) with 10y follow up of huge benefit and little harms re cancers and B12 deficiency masking. Also attached: article (2001) by Suzanne White Junod, FDA historian (Folic acid fortification: Fact or folly); abstract of cross-sectional study (Folate status of Ghanaian population; Owusu et al, 2010); 2009 website article, *Folate And Cancer* (by Dr S Duthie).	E Carter	No new or relevant evidence provided.
Shame SACN never thought to prepare update of evidence before being asked to by Scotland. And then a draft isn't produced in time to inform parliament as the Bill has passed over the year through Lords and now Commons. Consultation very brief period and timing to end after the Commons Bill Vote on 24 February 2017.	E Carter	The Committee continues to keep a watching brief on the issue of folic acid fortification and, as explained in the draft report (see para 15), SACN wrote to Health Ministers in October 2015 to alert them to evidence from other countries on the safety of folic acid fortification at the levels proposed in 2006 and the associated improvements in folate status and decrease in the prevalence of neural tube defects.
Report covers literature well but over cautious in concluding possible harm associated with fortification of flour with folic acid & understates benefits of fortification. The imposition of 1mg/day upper limit of folic acid intake is questionable and could have perverse effect of blocking fortification. Taking all the evidence as a whole there is, in my view, no evidence that fortification will be harmful and clear evidence that it will be of benefit. Concerns about possible effects of fortification of the diet in the UK on cancer incidence or progression, or on safety for vitamin B12 deficient subjects and for those with cognitive impairment are not scientifically justified. At the levels used internationally fortification is harmless in normal and vitamin B12 deficient subjects. Delay in fortification since it was recommended by COMA in 2000 has allowed substantial numbers of NTD affected pregnancies (Morris et al, 2016).	Professor A V Hoffbrand	Opinion noted. SACN was not asked to reassess the Tolerable Upper Intake Level (UL) for folic acid (1 mg/d) (Guidance Level [GL] of 1 mg/d in UK) and the assessment of the evidence did not provide grounds to disregard the UL/GL which was set by other expert scientific committees with that remit[1]. Agreed to include fuller explanation of the UL/GL in report.
Politicians will want to know outcome of fortification at population level (Chile & N America). Could not find a reference to this but USA CDC must have some data? Although there will be confounding factors, it will reflect general trends.	J Nichols	Information about benefits of fortification at a population level included in report (see para 8). Trend data from the USA and Canada covering the period before and after fortification was discussed extensively in the SACN 2006 report and 2009 update.
Whilst not within SACN's remit to consider economic & social implications of health policy, these should be acknowledged. A systematic review of economic burden of NTDs (2011[2]) found all studies suggested use of folic acid in preventing NTDs was,	PAGB	SACN 2006 report made detailed assessment of benefits. Current update also makes a clear case for beneficial effects

[1] Institute of Medicine, USA; European Scientific Committee on Food, Europe; Expert Group on Vitamins & Minerals, UK.
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3197907/

Comments	Org/ Individual	Action agreed by SACN
overall, cost effective. A study in 2017[3] found that if UK had implemented folic acid fortification in 1998, about 2014 fewer pregnancies would have been impacted by NTDs..		on NTDs of mandatory fortification.
Report correctly concludes there is clear evidence that increasing folic acid intake reduces NTD risk & no evidence of harm from either folic acid supplementation or fortification but language used too equivocal. Summary statements describe "inconsistent evidence" rather than "no evidence". This is misleading. In a literature review there will be apparent inconsistencies due to random variation, confounding & bias. Report makes detailed reference to the literature but is overly cautious in interpretation of results of individual studies. Tends to interpret associations as possibly causal when there is evidence that they are unlikely to be causal.	Professors Wald, Morris, Law/RCOG	Do not agree that there is '*no evidence'* of possible harms from folic acid intakes and that the language is equivocal. SACN was very careful with the terminology used. Consider that observational data are described in an appropriately cautious way. Agreed to provide further clarification in the report on the terminology used to describe the evidence.

[3] http://adc.bmj.com/content/early/2015/11/13/archdischild-2015-309226.long

Table 2: Specific comments on health outcomes (chapters and paragraph numbers refer to those in the draft report)

Comments	Org/Individual	Action agreed by SACN
COGNITIVE HEALTH: MASKING OR EXACERBATION OF LOW VITAMIN B12 STATUS; COGNITIVE DECLINE IN OLDER INDIVIDUALS		
Note that SACN acknowledges that where evidence exists in relation to folate intakes impacting on vitamin B12 deficiency, such evidence indicates that this relates to interventions in excess of 1mg/d. Evidence from NDNS years 5 & 6[4] indicates that even at the 95th percentile intakes fall far below that. Unlikely that contributions from fortification will lead to intakes exceeding 1mg/day of folic acid.	PAGB	Considered in detail in the modelling exercise commissioned by Food Standards Scotland.
Based on observations from studies and my daily work, it is evident that an excessive intake of folic acid leads to an increased utilization of vitamin B12, resulting in the depletion of vitamin B12 and probably exacerbating clinical symptoms. The same is observed when B12 is given in excess without folate supplements. Folate deficiency is prevalent in the UK, but a similar prevalence is reported for excessive intake. For example, in our recent audit of patients (n=17 875) from primary care, we found serum folate below our deficiency cut-off of 7 nmol/L in 14% patients but the elevated folate concentrations (>45.3 nmol/L) were also highly prevalent, 10.3%.	Dr A Sobczyńska-Malefora	Considered in detail in the modelling exercise commissioned by Food Standards Scotland.
Para 41 states "*Cohort studies consistently report either no significant relationships or that relatively higher folate status is associated with lower risks of cognitive decline and dementia*." This statement not entirely accurate. A systematic review (Smith & Refsum, 2016) referred to first report of cognitive decline in large cohort of older people in relation to folate intake (Morris et al. 2005) which found that folate intake in top quartile (median 742 µg/d) was associated with a doubling of rate of cognitive decline over 6 years compared with those in lowest quartile (median 186 µg/d). An Australian study (Faux et al. 2011) found that red cell folate levels displayed inverted U-shaped relationship with several cognitive outcomes such that '*cognitive performance improved as red cell folate levels rose to a threshold of about 1500 nmol/L for females and about 1200 nmol/L for males, whereas higher levels of red cell folate were associated with worse cognitive performance*'. Studies from Tufts University have shown that older people with low vitamin B12 status may be particularly at risk of cognitive impairment if exposed to high folate status. This outcome found in the NHANES cohort (Morris et al. 2007) for those with serum folate > 59 nmol/L, where those with low B12 status had a 5-fold increased odds of cognitive impairment, whereas those with normal B12 status had a reduced odds of cognitive impairment compared with subjects with folate and B12 in the normal range. Likewise, in a Framingham cohort (Morris et al, 2012) rate of cognitive decline for those with low B12 status was greater in those who took folic acid supplements than in non-supplement users. Another Australian study also found that red cell folate levels above 90th centile (> 1594 nmol/L) were associated with increased risk of cognitive impairment in the elderly (Moore et al. 2014). It was not only those with low B12 status (< 250 pmol/L) who showed increased risk of cognitive impairment with high folate status but also those in normal range of B12 (median 383 pmol/L). Finally, for people who carry the common (23% in USA) 19 bp *del/del* polymorphism of dihydrofolate reductase it has been reported that those with plasma folate > 40.3 nmol/L had worse memory scores than those with normal folate levels (Philip et al. 2015). Authors concluded that in a population with a similar frequency of the DHFR *del/del* polymorphism & similar folate levels, for every 4 individuals who would benefit from high folate, one person would risk memory impairment.	Professor A. David Smith	Statement in report summarises conclusions from the available systematic reviews and meta-analyses which were considered. Agreed to clarify this point in the report and note that differing evidence is cited in narrative reviews. Interactions with vitamin B12 are addressed in report. Smith & Refsum (2016) is not a systematic review. Regarding cognitive health specifically, it states *'in spite of much evidence, which will not be reviewed here, of the beneficial cognitive effects of a good folate status (2; 14; 17), there have also been several reports that high intake or high blood concentrations of folate may be detrimental to some cognitive functions. We will briefly review these reports here'.*
Para 45 states: "*The high levels of systemic folate at which the adverse associations are reported most likely occur from intake of folic acid supplements exceeding 1 mg/d.*" Helpful to have references for this statement. In Chicago study (Morris et al. 2005) those in top folate intake quintile who showed more rapid cognitive decline consumed 400–1200µg/d. In Australian study (Moore et al. 2014), only 23% of those with high folate and increased risk of cognitive impairment took folic acid supplements, while in the Framingham study (Morris et al, 2012) majority of folic acid supplements were in form of multi-vitamin tablets, usually containing ≤ 400 µg. In the NHANES survey (Bailey et al. 2010), the total folic acid intake from fortified food and supplements ranged from 220 to 421 µg/d at different ages, with a no more than 5% exceeding 1 mg/d. Therefore unlikely that supplementary folic acid intakes > 1mg/d are an important cause of high folate status in elderly.	Professor A. David Smith	Agreed to clarify in report.

[4] https://www.gov.uk/government/statistics/ndns-results-from-years-5-and-6-combined

Comments	Org/Individual	Action agreed by SACN
Para 47 states: "*Intervention studies with folic acid supplementation (with or without vitamin B12), have generally found no significant effects on cognitive performance and risk of dementia*." We recently reviewed these trials & related meta-analyses (Smith & Refsum, 2016) & have given several reasons why many trials have apparently failed. Main reasons: placebo group did not show cognitive decline, trial too short & population studied had adequate B vitamin status at start. Two trials without these deficiencies showed folic acid supplementation slows age-related cognitive decline in people with raised homocysteine (Durga et al. 2007) and that a supplement combining folic acid, B6 & B12 slows brain atrophy and cognitive decline in people with Mild Cognitive Impairment who have raised plasma homocysteine (VITACOG trial, summarised in above review).	Professor A. D Smith	Shortcomings in the intervention trials are acknowledged in the report.
No discussion relating to markers of vitamin B12 status in people with high folate status. We reviewed this topic in supplement to our review (Smith & Refsum, 2016). Two studies in USA reported U-shaped relationship between markers of poor B12 function (homocysteine & methylmalonic acid) & serum folate (Selhub et al, 2007; Miller et al. 2009); e.g., plasma homocysteine concentration fell as serum folate rose from 7 nmol/L to 20 nmol/L but started to increase again as serum folate further increased towards 44 nmol/L (Selhub et al, 2007). Similar result found in Australia for relation between red cell folate and plasma homocysteine (Faux et al. 2011). It was speculated that these U-shaped relationships were consequence of oxidative damage to vitamin B12 so inhibiting its function as a co-factor for methionine synthase. More direct evidence of impaired B12 availability at high folate levels is the markedly decreased concentration of holotranscobalamin in those with low B12 and high folate (Miller, 2009). These results provide evidence that high folate status impairs the functioning of vitamin B12.	Professor A D Smith	Report has acknowledged and expressed caution about intakes of folic acid above the UL of 1 mg/d.
Paras 38 & 42-44. The statement that "*Folic acid treatment can alleviate the anaemia and, as a consequence "mask" the vitamin B12 deficiency*" is an incomplete and potentially very misleading statement. This can occur in a small minority of patients but SACN continues to overlook the fundamental point that excess folic acid in the presence of vitamin B12 deficiency can eventually lead to relapse of the anaemia as well as neurological deterioration. At 5 years (Schwartz et al 1950) and 10 years (Will et al 1959) follow-up, relapse of the anaemia is as common as neurological relapse. In latter study, only 3 of 36 patients remained well and all 3 had v low vitamin B12 levels. In vitamin B12 and folic acid deficiency there is often a dissociation between the neurological & haematological manifestations. Likewise in B12 deficiency in presence of excess folate the haematological and neurological relapses are often dissociated. The dose of excess folate is relevant i.e. the greater the dose the greater the risk, but so is duration of exposure to nervous system which is important in relation to fortification policies.	Dr E H Reynolds	The term *'masking'* included because it is still referred to in the literature. Evidence on folic acid exacerbation of low vitamin B12 status has also been considered. Agreed to make this clearer. Report has recognised concern and expressed caution about intakes of folic acid above the UL of 1 mg/d.
Para 39. As pointed out in my review (Reynolds 2016) already some evidence in the pre-fortification era that prolonged exposure to doses of folic acid < 1mg could be harmful to the nervous system in the presence of vitamin B12 deficiency (Savage & Lindenbaum, 1995). Furthermore doses < 1mg can sometimes trigger a haematological response.	Dr E H Reynolds	Report has recognised concern and expressed caution about intakes of folic acid above the UL of 1 mg/d.
Para 44. Why refer only to study by Qi et al (2014) reporting prevalence of low B12 levels in absence of anaemia & macrocytosis has not increased since folic acid fortification? Why not mention study by Wyckoff & Ganji (2007) in which prevalence was higher? However, both studies completely missed point that they should have included patients with macrocytosis & anaemia since excess folate can lead to relapse of anaemia. This oversight arises from misguided preoccupation with "masking", even though in the era of fortification in otherwise healthy elderly US subjects with low vitamin B12 status, high serum folate was associated with anaemia and cognitive impairment (Morris et al 2007). In those with serum vitamin B12 levels < 148 pmol/L total homocysteine and methylmolonic acid concentrations increased with increasing serum folate levels, whereas the opposite occurred in those with normal vitamin B12 status (Selhub et al 2009). This is separate issue from "masking".	Dr E H Reyolds	Agreed to consider study by Wyckoff & Ganji (2007) and others on this point.
Paras 45-47. These paragraphs and the very few studies referred to in Annex 2 suggest SACN is not well informed about neurology of folic acid deficiency. I attach a recent review (Reynolds 2014). The Committee appears puzzled that folic acid can have beneficial effects on cognitive and neurological function in certain folic acid deficiency situations but harmful effects in the presence of vitamin B12 deficiency. These two scenarios should be viewed quite separately. I also draw the Committee's attention to the large Australian study in the pre & post fortification period by Moore et al (2014) reinforcing the potential risks to cognitive function of high folate levels in the presence of low vitamin B12 levels.	Dr E H Reynolds	Potential adverse effects of folic acid were carefully considered in report.

Comments	Org/Individual	Action agreed by SACN
By limiting scope of present review & over-emphasising "masking" SACN is ignoring evidence that was consistently documented in pre-fortification era and is being rediscovered in post-fortification era (Reynolds 2016). The Committee therefore continues to neglect fundamental concept that prolonged excess folic acid can be harmful both to the nervous system & the blood in the presence of B12 deficiencies. By reaffirming its earlier advice that 1mg is the safe upper intake level for folic acid (contrary in my view to the evidence), SACN continues to underestimate risk of prolonged excess folate to the nervous system and blood, especially in elderly subjects in whom the prevalence of vitamin B12 deficiency rises from 5% age 60 years to 20% over the age of 85 years. I wish to acknowledge undoubted benefits of folic acid fortification in reducing NTD prevalence by about 1/3, but have suggested there is a better way to improve these outcomes while reducing the above and perhaps other risks (Reynolds 2016).	Dr E H Reynolds	The concerns expressed here are acknowledged in report.
No evidential basis for setting an upper limit of 1mg/day of folic acid intake. This recommendation appears to rest on possibility that high folate levels might exacerbate B12 deficiency neuropathy & high folate levels, in presence of low B12 level, might lead to cognitive decline. Both these interpretations unjustified. The first because the historical evidence linking folic acid with B12 neuropathy relates to folic acid being used instead of B12 as a treatment for neuroblastic anaemia & early sub-acute combined degeneration of the spinal cord. If folic acid used instead of B12, the anaemia may resolve but neuropathy will progress. Review of all relevant papers & case reports comes to conclusion that there is no direct evidence of a causal association between folic acid and neurotoxicity. Reynolds (2016) provides no evidence for folic acid neurotoxicity. His paper is an expression of his view there may be neurotoxicity. This arises from data in the '60s in which people with sub-acute combined degeneration had high folate levels (e.g. Waters & Molin, 1961). Not surprising since folic acid was often iused as treatment in misguided view that it was correct treatment. Such associations are not evidence of causality. Also, treating anaemia of B12 deficiency with folic acid should not be regarded as "masking" (e.g. Wald & Bower, 1994; Oakley, 1994). Also, the macrocytic anaemia that can be found in B12 deficiency is not needed to make the diagnosis of B12 deficiency early enough for treatment. The theoretical possibility that fewer patients with B12 deficiency may present with anaemia as well as with neurological symptoms instead of neurological symptoms alone is therefore unimportant.	Professors Wald, Morris, Law	SACN's assessment of the evidence did not provide grounds to disregard the UL/GL.
Concerns relating to cognitive decline unjustified because the relevant papers simply show an association between high blood folate, low B12 and cognitive decline. Blood levels indicate that high folate levels are likely to be, at least in part, associated with folate supplementation. Likely that adults with early cognitive decline may take folic acid supplements in belief that this may be of value. A paper cited on this association (Morris et al, 2012) states that association is not likely to be causal. They suggest likely explanation for association is that in individuals with early cognitive decline who take vitamin supplements including folic acid and a small amount of B12, the folic acid is absorbed but not B12 due to relative lack of intrinsic factor & intestinal malabsorption. This upper limit should be removed from report. Retaining it will have the undesirable effect of discouraging both folic acid supplementation and fortification since both will lead to an upward shift in the distribution of blood folate levels such that some people will exceed 1mg/day. We believe that there is not an upper limit to other water-soluble vitamins such as B12 and no reason to have one for folic acid.	Professors Wald, Morris, Law/RCOG	Concerns about observational studies addressed in report. SACN was not asked to reassess the appropriateness of the UL/GL which was set by other expert committees with that remit. SACN's assessment of the evidence did not provide grounds to disregard the UL/GL.

Comments	Org/Individual	Action agreed by SACN
Question raised in report whether free folic acid in plasma has harmful effects in those who are vitamin B12 deficient & quotes safe upper limit of 1mg/d. I consider that fortification is entirely safe in these subjects and do not consider this upper limit meaningful in the context of dietary fortification. Evidence as follows: • Single doses of folic acid of 5mg/d or more were reported in the literature in 1940s/1950s to produce haematological response in anaemic subjects with severe vitamin B12 deficiency (Reynolds 2016). This response now thought to be due to extremely high concentrations of unmetabolised folic acid in plasma. These very high plasma levels may partly overcome the block in folate coenzyme synthesis caused by vitamin B12 deficiency, allowing DNA synthesis and so red cell formation in the bone marrow to resume. No data for 'masking' by correction of the red cell size (mean corpuscular volume, MCV) or by causing a durable haematological response at 1mg/d as a single dose in vitamin B12 deficiency. There are no reports of this amount of folic acid precipitating a vitamin B12 neuropathy. • Imposition of safe upper limit of 1mg/d daily is invalid. Amount of free circulating folic acid, if any, caused by levels of folic acid added as dietary fortification cannot be compared with those produced by single daily oral or parental doses of crystalline folic acid. Dietary fortification spreads extra folic acid across 3 meals/day. Ingestion of single amount of 200-400ug, will be totally or almost totally converted to MTHF by gut. Gut has capacity to convert this amount as a single intake but not larger doses completely to methylfolate. Amount of folic acid ingested at any fortified meal which enters the circulation therefore as unmetabolised folic acid rather than as MTHF, will be zero or a very minor fraction of that ingested. Therefore levels of folic acid added to flour will result in either zero or extremely low levels of free folic acid in plasma. No data showing that these extremely low plasma levels will cause any 'masking' by correcting the anaemia or lowering the raised mean corpuscular volume (MCV), or precipitate vitamin B12 neuropathy in vitamin B12 deficient subjects. • Natural folates of any amount, like small amounts of folic acid (200-400ug), will be entirely converted by the gut into MTHF. MTHF unable to correct DNA defect & therefore anaemia or raised MCV in vitamin B12 deficiency (Hoffbrand & Jackson, 1993). • Consistent with these data is that free folic acid resulting from levels of fortification used internationally do not affect the anaemia in vitamin B12 deficiency, fortification since 1998 in the USA has not lead to an increase in subjects with low serum vitamin B12 levels and no anaemia (Mills et al; Qi et al 2014). Moreover there are no reports of an increased incidence of vitamin B12 neuropathy in any of the countries which have introduced fortification. • Vast majority of older subjects with subnormal serum vitamin B12 levels do not have degree of vitamin B12 deficiency sufficiently severe to cause a neuropathy or a haematological abnormality. They have malabsorption of food vitamin B12 which is mild and does not progress because they have intact entero-hepatic circulation of the vitamin. In contrast, in pernicious anaemia, vitamin B12 absorption is essentially nil because of an autoimmune gastritis and total lack of intrinsic factor. Pernicious anaemia is now virtually the only cause of severe vitamin B12 deficiency in the UK. With widespread health screening, it is diagnosed & treated after finding of macrocytic red cells in routine blood counts and long before a neuropathy/anaemia has developed. Vitamin B12 neuropathy now extremely rare in the UK. • Interpretation of the plasma folate level as a measure of folate status in B12 deficiency is also compromised. Vitamin B12 deficiency causes an accumulation of plasma folate (methylfolate) because of the block it causes in further metabolism of methylfolate inside cells. This block greater the more severe the vitamin B12 deficiency. Thus higher plasma folate levels can be result of more severe vitamin B12 deficiency rather than an indication of folate status. This explains why in studies quoted by Selhub & Rosenberg (2016) higher plasma folate levels may be associated with more severe biochemical and cognitive features of vitamin B12 deficiency. In these subjects with high plasma folate levels it is the severe vitamin B12 deficiency that causes these folate levels to be raised. • No evidence for any haematological response even in vitamin B12 deficient subjects, at levels of unmetabolised folic acid in plasma that result from fortification at the concentrations (140-220ug/100g/flour or grain) used worldwide. No evidence for 'masking' B12 deficiency at these intake levels. No data which justify imposing upper limit of folic acid intake of 1mg/d taken in different meals throughout day.	Professor A V Hoffbrand	SACN was not asked to reassess the appropriateness of the UL/GL which was set by other expert committees with that remit. Agreed to include fuller explanation of the UL/GL in the report. Report does not make assumptions about causality where this is unclear. Detailed consideration of unmetabolised folic acid in report.

Comments	Org/Individual	Action agreed by SACN
Relevant literature well reviewed in Report. Appears to be no evidence that cognitive impairment occurs at daily doses of folic acid used in RCTs in subjects with normal/subnormal plasma B12. Doses in trials are substantially above those used for fortification. Interpretation of the plasma folate level as measure of folate status in vitamin B12 deficiency is compromised. Vitamin B12 deficiency causes an accumulation of plasma folate (methylfolate) because of the block the deficiency causes in further metabolism of methylfolate inside cells. This block is greater the more severe the vitamin B12 deficiency. Thus higher plasma folate levels can be the result of more severe vitamin B12 deficiency rather than an indication of folate status. This explains why in studies quoted by Selhub & Rosenberg (2016) higher plasma folate levels may be associated with more severe biochemical & cognitive features of vitamin B12 deficiency. In these subjects with high plasma folate levels it is the severe vitamin B12 deficiency that causes the folate levels to be raised.	Professor A V Hoffbrand	References were not provided to support these comments.
CANCER		
Evidence evaluated by SACN on the impact of folate on all forms of cancer found that whilst there is some evidence of increased risk, this is genotype specific. Conversely, there is consistent evidence to show a protective effect of an intake of 400µg/d folic acid against the development of NTDs across the entire population (other than those individuals who have a genetic predisposition and require higher intakes).	PAGB	Consideration of genotype in relation to folic acid and cancer risk is more complex than stated here and is fully explained in report. Much of the genetic evidence was considered in the context of an approach termed *mendelian randomisation* and intake was not assessed in many of these studies. The genetic evidence was used primarily to infer nutritional effects and the validity of this approach was considered in detail.
The literature well reviewed in draft report shows no overall increase in the incidence of cancer or of any specific cancer in those taking folic acid daily at levels up to 50 times the amount recommended for fortification (Vollset et al, 2013; Qin et al 2013). Although the report points out that these data are based on only a few years of folic acid ingestion, patients with sickle cell anaemia usually take for life, folic acid at a single dose of 5mg/d or even 5mg three times/day from childhood aimed at preventing folate deficiency. They therefore have unmetabolised folic acid circulating in high concentrations life-long. No reports of an overall increased incidence in sickle cell anaemia, cancer or any cancer subtype or of untoward effect of this folic acid therapy. Others may also take such large doses of folic acid for many years or for life. These include those with other chronic haemolytic anaemias and those on chronic renal dialysis. Again there are no reports of any untoward effects and no reports of an increased incidence of any type of cancer associated with folic acid in these large doses.	Professor A V Hoffbrand	Considerations regarding cancer risk more complex than implied in this statement and are discussed in detail in report. In relation to patients taking folic acid for anaemias, noted the difficulties of finding sufficient numbers to assess the outcomes considered by SACN and the potential for genetic confounding. References were not provided to support these comments.
UNMETABOLISEDFOLIC ACID		
Over 70 countries fortify their diet with folic acid. In N America fortification carried out since 1998. Thus after many billions of subject years, there is no evidence (as reviewed in report) that fortification has been associated in any country with increased incidence/progression of cancer of any type.	Professor A V Hoffbrand	Observation noted. Trend data from the USA & Canada, covering the period before and after fortification, was considered extensively in the SACN 2006 report and 2009 update.

Comments	Org/Individual	Action agreed by SACN
A problem with assay of unmetabolised folic acid (UMFA) was identified by NDNS contractor and final figures have not been published. However early indications are that serum free folic acid concentrations in the UK are low which in turn implies UMFA is unlikely to present any significant risk in the UK.	PAGB	Considerations more complex than implied here and covered in considerable depth in report.
Para 106 states "*It has been suggested that UMFA…. may be produced endogenously from natural folates (Bailey et al. 2010)*." This suggestion is not in the cited publication and cannot find in any published literature. Statement should not be made without proper citation.	Professor A D Smith	Noted. Agreed to check reference and correct text as appropriate.
Para 109 describes 2 studies in relation to health outcomes. Morris et al (2010) important because found cognitive impairment associated with high folate status in those with poor B12 status was not significantly associated with serum 5-MTHF but with high levels of UMFA. Result consistent with hypothesis that high circulating UMFA can inactivate B12 and so exacerbates B12-deficiency. Authors concluded: "*Our findings for cognitive test performance in the subjects with low vitamin B-12 status may be consistent with the idea that folic acid harms the nervous system via a mechanism that involves circulating unmetabolized folic acid*". Potential public health implications of these findings in the elderly may be significant (Smith et al, 2008). In the USA, 33-67% take supplements containing folic acid. The approximate prevalence of low B12 status & high folate status is 4%,so about 1.8 million American elderly may be at risk of cognitive impairment due to exposure to folic acid.	Professor A D Smith	The cited result from Morris (2010) is described in the report and was considered in drawing conclusions from the totality of the evidence. Exposures to high folic acid intakes from different sources are considered in the modelling.
A study not mentioned in report was the finding in American women that impairment of natural killer (NK) cell cytotoxicity occurred at high serum folate levels and was related to concentration of UMFA but not to concentration of 5-MeTHF (Troen et al. 2006). As authors pointed out, results are a 'cause for concern'. So far, only 1 animal study has also shown harmful effect of folic acid consumption on NK cell function (Sawaengsri et al. 2016).	Professor A D Smith	Study not included because it had already been considered in 2006 Report. SACN's remit was to consider evidence since the 2006 report.
Raising concerns over possible harmful effect of UMFA in the blood is unwarranted. Any possible harm is speculative. Millions of people have been taking folic acid supplements leading to UMFA in the blood without any indication of harm.	Professors Wald, Morris, Law/RCOG	SACN considered the potential adverse effects of UMFA on basis of safety concerns raised by others and concluded *'the evidence is still insufficient to assess whether the presence of UMFA in the systemic circulation has any long term adverse effects on health'.*
OTHER		
Might be worth adding comment on the increased risk of NTDs in obesity and the current increased recommended intake for this group.	Dr M R Sweeney	Was not within remit to assess the RNI or intakes required to protect against NTDs in specific population subgroups.
Should be noted that the Food Safety Authority of Ireland (FSAI) report, *Update Report on Folic Acid and the Prevention of Birth Defects in Ireland*[5] (2016) was incomplete as it did not make reference to the most recent and relevant research conducted in Ireland by Kelly et al (2016)[6]: **"***Folic acid levels in some food staples in Ireland are on the decline: implications for passive folic acid intakes***"**	Dr M R Sweeney	Folic acid levels in foods in the UK are fully considered in modelling exercise.
I have been following and contributing to the folate field for many years as well as providing diagnostic services specializing in one carbon metabolism for large hospitals in central London. Despite frequently seeing low serum folate concentrations in my daily practice in the laboratory, I am opposed to mandatory folic acid supplementation in the UK. Some of my concerns have been recently included in a review published in EJCN (attached). I believe that a balanced diet should provide a sufficient daily intake of the vitamin for most people, and I fully support dietary advice and supplementation programmes targeting vulnerable groups e.g. women planning pregnancy. However, I do not consider it ethical to supplement the whole population with synthetic compounds without their consent.	Dr A Sobczyńska-Malefora	Opinion noted.

[5] https://www.fsai.ie/news_centre/press_releases/folic_acid_report_04052016.html
[6] https://academic.oup.com/jpubhealth/article/38/2/265/1752731/Folic-acid-levels-in-some-food-staples-in-Ireland

Table 3: Comments relating to risk management (for information; risk management is outside SACN's remit)

Comment	Individual/Org
The health risks that nearly everyone takes with OTC drugs (e.g. paracetamol) must surely be greater than any hypothetical risk from folic acid fortification. Could this be useful comparison? Found papers quantifying risks from cough mixtures, paracetamol & NSAIDs. Is there a better comparator such as health risks from artificial food additives? If could compare risks to general health & survival from paracetamol with risk of prostate cancer from fortification, this might help to put it into perspective.	John Nichols
Despite several decades of recommendations for supplementation the prevalence of NTDs has not decreased[7]. Any approach in resolving occurrence of NTDs should be holistic & multifactorial & unless action taken to implement policy on this issue, incidence of avoidable NTDs in UK will continue.	PAGB
The report can unfortunately be interpreted as implying that unless there is clear evidence of the absence of harm, there is no basis to adopt policies with clear evidence of benefit. This would be a mistake; it would mean that very few useful public health measures would be introduced.	Professors Wald, Morris, Law

[7] http://www.bmj.com/content/351/bmj.h5949

References

Bailey RL, McDowell MA, Dodd KW *et al.* Total folate and folic acid intakes from foods and dietary supplements of US children aged 1-13y. *Am J Clin Nutr*. 2010: 92:353-58.

Durga J, van Boxtel MP, Schouten EG *et al.* Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *Lancet*. 2007; 369:208-16.

Faux NG, Ellis KA, Porter L *et al.* Homocysteine, vitamin B12, and folic acid levels in Alzheimer's disease, mild cognitive impairment, and healthy elderly: baseline characteristics in subjects of the Australian Imaging Biomarker Lifestyle study. *J Alzheimers Dis*. 2011; 27:909-22.

Hoffbrand AV and Jackson BF. Correction of the DNA synthesis defect in vitamin B12 deficiency by tetrahydrofolate: evidence in favour of the methyl-folate trap hypothesis as the cause of megaloblastic anaemia in vitamin B12 deficiency. *Br J Haematol.* 1993; 83(4):643-7.

Miller JW, Garrod MG, Allen LH *et al.* Metabolic evidence of vitamin B12 deficiency, including high homocysteine and methylmalonic acid and low holotranscobalamin, is more pronounced in older adults with elevated plasma folate. *Am J Clin Nutr*. 2009; 90:1586-92.

Mills JL, VonKohirin I, Conley MR. Low vitamin B12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr*. 2003; 77:1474-2477

Moore E, Ames D, Mander A *et al.* Among vitamin B12 deficient older people, high folate levels are associated with worse cognitive function: combined data from three cohorts. *J Alzheimer's Dis.* 2014; 39:661-668.

Morris MC, Evans DA, Bienias JL *et al.* Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons. *Arch Neurol*. 2005; 62:641-5.

Morris MS, Jacques PF, Rosenberg IH *et al.* Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. *Am J Clin Nutr*. 2007; 85: 193-200.

Morris MS, Jacques PF, Rosenberg IH, Selhunb J. Circulating unmetabolized folic acid and 5-methyltetrahydrofolate in relation to anemia, macrocytosis, and cognitive test performance in American seniors. *Am J Clin Nutr.* 2010; 91:1733–44.

Morris MS, Selhub J, Jacques PF. Vitamin B-12 and folate status in relation to decline in scores on the Mini-Mental State Examination in the Framingham Heart Study. *J Am Geriatr Soc*. 2012; 60:1457-64.

Morris JK, Rankin J, Draper ES *et al.* Prevention of neural tube defects in the UK: a missed opportunity. *Archives of Diseases of Childhood*. 2016; 101:604-607.

Oakley GP. The myth of “masking”. *Teratology* 1994; 66:50.

Philip D, Buch A, Moorthy D *et al.* Dihydrofolate reductase 19-bp deletion polymorphism modifies the association of folate status with memory in a cross-sectional multi-ethnic study of adults. *Am J Clin Nutr*. 2015; 102:1279-88.

Qi YP, Do AN, Hamner HC *et al.* The prevalence of low serum vitamin B-12 status in the absence of anemia or macrocytosis did not increase among older U.S. adults after mandatory folic acid fortification. *Journal of Nutrition*. 2014; 144:170-176.

Qin X, Cui Y, Shen L *et al.* Folic acid supplementation and cancer risk: A meta-analysis of randomized controlled trials. *International Journal of Cancer*. 2013; 133:1033-1041.

Reynolds EH. The neurology of folic acid deficiency. In: Biller J, Ferro JM (Eds). Handbook of Clinical Neurology, Neurological Aspects of Systemic Disease, Part II. Vol 120 (3rd series) 2014; pp.927-943.

Reynolds EH. What is the safe upper intake level of folic acid for the nervous system? Implications for folic acid fortification policies. *Europ J Clin Nutr*. 2016; 70:537-540.

Savage DG, Lindenbaum J. Neurological Complications of Acquired Cobalamin Deficiency: Clinical Aspects. Bailliere's Clinical Haematology. Vol 8. Bailliere Tindall 1995; pp 657-678.

Schwartz SO, Caplan SR, Armstrong BE. The long-term evaluation of folic acid in the treatment of pernicious anaemia. *J Lab Clin Med*. 1950; 35:894-898.

Sawaengsri H, Wang J, Reginaldo C *et al*. 2016. High folic acid intake reduces natural killer cell cytotoxicity in aged mice. *J Nutr Biochem*. 2016; 30:102-7.

Selhub J, Morris MS, Jacques PF. In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. *PNAS*. 2007; 104:19995-20000.

Selhub J, Morris MS, Jacques PF *et al*. Folate-vitamin B12 interaction in relation to cognitive impairment, anaemia, and biochemical indicators of vitamin B12 deficiency. *Am J Clin Nutr.* 2009; 89 (suppl): 702s-706s.

Selhub J, Rosenberg IH. Excessive folate intake and relation to adverse health outcome. Biochimie. 2016; 126:71-78.

Smith AD, Kim YI, Refsum H. Is folic acid good for everyone? *Am J Clin Nutr*. 2008; 87:517-33.

Smith AD, Refsum H. Homocysteine, B vitamins, and cognitive impairment. *Annu Rev Nutr*. 2016; 36:211-39.

Troen AM, Mitchell B, Sorensen B. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. *J Nutr*. 2006; 136: 189-94.

Vollset SE, Clark R, Lewington S *et al*. Effects of folic acid supplementation on overall and site-specific cancer incidence during randomised trials: meta-analysis of data on 50,000individuals. Lancet. 2013; 381:1029-1036.

Wald NJ, Bower C. Folic acid, pernicious anaemia, and prevention of neural tube defects. *Lancet.* 1994; 3:307.

Waters AL, Mollin DL. Studies in the folic acid activity of human serum. *J Clin Path.* 1961; 14:335.

Will JJ, Mueller JN, Brodine C *et al*. Folic acid and vitamin B12 in pernicious anaemia: studies on patients treated with these substances over a 10-year period. *J Lab Clin Med*. 1959; 53:22-38.

Wyckoff KF, Ganji V. Proportion of individuals with low serum vitamin B-12 concentrations without macrocytosis is higher in the post-folic acid fortification period than in the pre-fortification period. *Am J Clin Nutr*. 2007; 86: 1187-1192.