**The urgent need for folic acid fortification of flour and grains: Response to the 2019 UK Government’s public consultation**

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**Introduction**

In June 2019 The UK Government took a step forward towards making a decision on the mandatory fortification of flour with folic acid (vitamin B9) in the prevention of neural tube defects. It issued an open public consultation on the proposal in the form of a set of questions. The questions covered a range of issues including efficacy, safety, feasibility and cost. This review sets out the nine main questions and our answers. The aim is to present the rationale for mandatory fortification, what products should be fortified and the mean daily folic acid intake increase fortification should achieve across the population.

**Do you agree or disagree with the proposal for mandatory fortification of non-wholemeal wheat flour in the UK with folic acid to help prevent neural tube defects?**

Answer: The evidence strongly supports agreeing with the proposal. In 1991 the report of the MRC Vitamin Study,[1] a randomised trial, showed that most cases of neural tube defects (NTDs) can be prevented by increasing folic acid intake immediately prior to pregnancy and in the early stages of pregnancy. Other studies have confirmed these results and over 80 countries have introduced mandatory fortification of flour and/or grains with folic acid. There has been no indication of any adverse effect in any of these countries, including the United States and Canada, where fortification started in 1998. The Centres for Disease Control and Prevention have recently estimated that in the USA, fortification has saved 1,300 children each year from death or a lifetime of handicap – a total of more than 27, 000 since 1998 when fortification was introduced in the US.[2]

In 2015 it was estimated that over 2000 children would have been saved each year from death or a lifetime handicap if folic acid fortification had been implemented in the UK at the same time as it was in the USA.[3]

Women have been advised to take folic acid supplements before pregnancy and in early pregnancy . This is the current policy in the UK. In practice about two-thirds of women do not do so [4]. Data from the National Diet and Nutrition Survey show that, despite widespread promotion of the policy of voluntary supplementation, folate intakes of women who could become pregnant have declined [5] and periconceptional folic acid supplement use has also declined. This failure to take folic acid is particularly high in less advantaged groups in society.[4,5] Flour is already fortified with two minerals and two other B vitamins, and there is no rational reason not to add folic acid at an adequate level designed to prevent most cases of this serious and sometimes devastating disorder.

While there has been speculation about possible adverse effects of high levels of folate intake, no claim has survived detailed scientific scrutiny. Raising folate levels through the fortification of a staple food that is eaten by all members of society is an important and safe public health measure that requires urgent action. In the UK alone, one affected pregnancy for every working day in the year could be prevented with folic acid fortification [3]. In the absence of fortification many of these affected pregnancies will be diagnosed antenatally leading to a therapeutic abortion. Babies born with particularly severe neural tube defects usually die soon after birth and many of those who survive are destined for a life with severe handicap. The economic arguments for preventing such disorders are obvious, but the humanitarian arguments are paramount. Fortification will prevent both affected live births and medically induced abortions and stillbirths. It will prevent the tragedy of lost babies and the impact of infant mortality and lifetime handicap on children, their families, and society as a whole. In the absence of evidence for any harm to the rest of the population, the moral arguments for the public health intervention of fortification are undeniable.

Folic acid fortification should be set at a level that delivers, on average, 0.4mg folic acid per day, through fortification of all flour and grains, including wholemeal, corn flour and rice. There is no scientifically valid basis for any toxic effects at folic acid intake levels exceeding 1mg per day. As explained below there is no need for the government to impose restrictions in the intake of folic acid.

**Which products do you think mandatory fortification with folic acid should apply to?**

* just non-wholemeal wheat flour in the UK (the most commonly used type)
* just non-wholemeal wheat flour used to make bread in the UK
* all flour in the UK, including wholemeal and other grains
* all flour in the UK and other non-wheat products such as ‘gluten free’
* there are no products that should have mandatory fortification with folic acid

Answer: The clear preference is for the fourth option “All flour including wholemeal in the UK and other non-wheat products such as ‘gluten free’” which should include grains such as rice. It is important to bring the benefits of fortification to all sections of the population, whatever their personal or cultural preferences for cereal products and their dietary restrictions. Limiting fortification to one type of cereal product would inevitably lead to the criticism that this policy discriminates against certain groups, especially minority groups, who have nutritional habits different from the mainstream. Fortification should include other grains, especially corn and rice. Wholemeal flour should be included as well as non-wholemeal flour. This is important, because many people consume wholemeal flour believing that it is healthier. It would be perverse public policy if wholemeal flour were not fortified because it would give an inconsistent message supporting wholemeal bread for the fibre and white bread for the folic acid fortification. It is important to acknowledge that the purpose of fortification is not just to replace folic acid removed in the white-flour milling process, but to use flour as a vehicle to deliver a vitamin to prevent NTDs. Currently, wholemeal flour is not fortified with any vitamins or minerals and adding folic acid to wholemeal flour might involve amending the Bread and Flour regulations. But, if that is necessary, it is important that it should be done.

**Are there any alternative ways of helping reduce the number of neural tube defects that you may prefer, other than our proposal for mandatory fortification of flour with folic acid?**

Answer: There is no alternative way to maximise the population wide benefits of increased folate intake. Encouraging women who may become pregnant to take folic acid supplements immediately before pregnancy has been largely unsuccessful; only a third or less of women do so.[4,5] Mandatory fortification is the only proven method for providing a population wide ‘safety net’ of folate intake that is important for women whose pregnancies were not intended or expected. Voluntary fortification of some food products, as now happens in the UK, is helpful, but its impact is arbitrary and limited, given that it depends on commercial decisions and social differences in food preference. Given the evidence that the benefits of folate increase with the level of folate intake[6] a complementary approach is needed, that combines the safety net of fortification with the added benefit of taking folic acid supplements. Public education about the benefits of fortification and of the value of voluntary supplementation is important. Teaching in schools about the role of folic acid in preventing NTDS should be part of the curriculum.

**Are there any particular groups or individuals that might be negatively affected by mandatory fortification of flour with folic acid, or miss out on the benefits?**

Answer: No. Everyone stands to benefit and there is no evidence that high levels of folic acid intake are harmful. Recent publications have shown that limiting folic acid intake to 1mg or less per day is without scientific or medical justification. This widely cited ‘upper limit’ had its origins in a 1998 report from the US Institute of Medicine (IOM, subsequently renamed the National Academy of Medicine) [7], which considered whether there was a basis for defining an adverse effect level for excessive folate intake. The IOM found no evidence of harm from folic acid or food folate in respect of toxicology, reproductive, and developmental health or cancer.

The well-known observation that folic acid can relieve the anaemia of vitamin B12 deficiency (described over 50 years ago as ‘masking’ of B12 deficiency by folic acid) is still sometimes cited as a basis for concern about excess exposure to folate and even as a potential end-point for the assessment of an adverse effect level. However, delay in the correct diagnosis of B12 deficiency, which might have occurred many decades ago, is not an indication of folate toxicity but simply inappropriate diagnosis and treatment.[8] Nowadays, the ready availability of specific serum B12 assays makes differential diagnosis of the causes of anaemia routine.

Significantly, even 20 years ago, the IOM did not consider ‘masking’ to be a problem and certainly not an appropriate end-point for the establishment of an adverse effect level for folic acid or folate. They focused instead on the possibility that high doses of folic acid might exacerbate neuropathy due to vitamin B12 deficiency (in cases where inappropriate diagnosis had led to patients being wrongly ‘treated’ with high doses of folic acid). The IOM reviewed 23 studies, mainly from the 1950s, 11 of which were single-case studies, and found more examples of progression to neuropathy in patients treated with doses of folic acid higher than 5mg/day. They proposed that dose as the lowest-observed-adverse-effect level (LOAEL) for folic acid. Following the arbitrary convention, 20% of this proposed LOAEL was taken as a conservative “upper level” for intake of folic acid by the general population, and this 1mg/day figure has been widely cited and adopted.

A paper published last year [9] demonstrated that the IOM’s analysis was both logically and statistically flawed. Surprisingly, the IOM study compared only the absolute number of cases of neuropathy in patients treated with doses of folic acid lower and higher than 5mg/day, without taking account of the total numbers in each group. A comparison of percentage incidence shows absolutely no evidence for an effect of folic acid dose. Robust support for this conclusion is given in a recent paper from Dr Berry of the Birth Defects Division of the US Centers for Disease Control and Prevention (CDC).[10]

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) did not dismiss concern about ‘masking’ (https://cot.food.gov.uk/sites/default/files/cotfolatepositionpaper.pdf), the COT judgement on this is incorrect and was made before publication of the recent confirmation of the conclusion by Dr Berry that there is no need to set an upper folic acid limit and good reason not to do so from the US CDC. A rebuttal of their conclusion is available from the authors. The notion that folic acid ‘masks’ or even exacerbates the effects of B12 deficiency should be abandoned [9] and acknowledged only for its historical interest, as concluded by the US Public Health Service.[10].

**Are there any businesses that might be negatively affected by mandatory fortification of flour with folic acid, or miss out on the benefits?**

Answer: No. If, as suggested, folic acid fortification is treated as an additional intervention to provide a ‘safety-net’ for those who do not take peri-conceptional folic acid supplements, no business group will be disadvantaged. Manufacturers of folic acid supplements will still be able to market their products. Women who intend to, or might, become pregnant, should still be encouraged to take supplements because the beneficial effect in preventing neural tube defects increases with dose.[6]

Mandatory fortification of all grain products removes any economic discrimination between different millers or grain merchants as well as enhancing the nutritional value of all flours and grains.

The cost of fortification is very small and, on the basis of statements already made, is likely to be borne by industry, given that all the relevant manufacturers are equally affected by the small additional cost. This is, of course, not the case with voluntary fortification, which puts companies that fortify at a marginal disadvantage.

The grain and milling industry has supported mandatory fortification and stands ready to implement a policy of fortification with folic acid. Since there is already a requirement for two other B vitamins (niacin and thiamine) to be added to flour, it would be simple for folic acid to be added as well. It should be noted, however, that the imposition of a 1mg daily upper limit on folic acid intake would create a problem because some industries, for example, breakfast cereal manufacturers, voluntarily fortify some of their products with folic acid and other vitamins, and they make this a feature of their marketing. They are likely to be reluctant to stop this and they might be disadvantaged by having to supply the same products both with and without added folic acid, for different countries. Therefore, abandoning the 1mg upper limit is not only justified on medical and scientific grounds, it also supports food manufacturers.

**If the fortification of flour with folic acid is made mandatory, do you agree or disagree that there should be limits on voluntary fortification of other food products and/or supplements with folic acid?**

Answer: Strongly disagree. There is no need for such limits. Other countries that have introduced folic acid fortification have not imposed such limits.

The basis for introducing such limits arose from acceptance of the 1mg upper limit, but as indicated above this was based on a flawed statistical analysis [9]. Fortification will prevent more neural tube defects and reduce the incidence of folate deficiency in the general population (see below) but will, of course, inevitably shift the distribution of folate intake upwards and therefore increase the proportion of the population whose total daily intake exceeds 1mg, particularly people taking folic acid supplements [11]. However, as argued above, there is no evidence that increasing folic acid intake poses any medical problem. The 1mg upper limit is not only unnecessary but is harmful in that it will needlessly limit the extent of folic acid fortification and hence limit the preventive potential of fortification.

No disease or disorder has been linked to high folate or folic acid intake. Among the hundreds of millions of people living in countries that have introduced fortification, there is no evidence of any associated rise in the incidence of any medical condition. It is worth pointing out that folic acid supplements and mixed vitamin pills containing folic acid are widely available and used in north America. So, a significant fraction of the 350 million people in the United States and Canada will have exceeded an intake of 1mg/day during the past 21 years. Yet no associated adverse effects have been established. Like other B vitamins, folic acid is water-soluble and is readily excreted in urine. It is important that harm is not done by unnecessarily limiting the benefit of a safe intervention.

**What are your views on the cost/benefit of mandatory fortification?**

Answer: Folic acid fortification is highly cost beneficial. The cost of fortification is minimal and far less than the cost of lifetime care of people with spina bifida. Fortification of flour with folic acid is a highly effective public health measure from both a medical and humanitarian perspective. On the basis of the financial savings, it will also benefit the NHS, Social Services and the families involved.

Food Standards Scotland (FSS) have modelled the effect of fortifying flour to achieve an extra mean folic acid intake of 0.06 – 0.1mg/day and estimated an NTD reduction of between 8- 25%. The lower estimate is more likely to be correct. The level of fortification to achieve such a small increase in average folic acid intake is much too low by any standards, but was was introduced to avoid fortification increasing the fraction of the population exceeding the historical and unwarranted 1mg/day upper limit after allowing for the intake of folic acid from supplements, breakfast cereals and other foods and drinks that are voluntarily fortified.[11] The 1mg/day upper limit constraint in the model should be removed and revised modelling performed to achieve a significant health benefit – the brake on fortification can be released. The public health objective is not simply whether mandatory fortification be introduced, but also, an equally important consideration is to set the fortification level sufficiently high to achieve a significant benefit. The original MRC Vitamin Study [1] demonstrated that about 80% of cases can be prevented with adequate intake of folic acid. A 42% reduction in birth prevalence has been achieved in Chile, where fortification provides 0.4mg/day of folic acid.[12]

The findings of the MRC Vitamin Study,[1] nearly 30 years ago, have led to the saving of thousands of lives each year in countries that have introduced folic acid fortification. It would be a huge disappointment if fortification in the UK were to achieve the lowest rate of benefit of any country with fortification, when the poor predictions result entirely from unjustified efforts to maintain the discredited 1mg/day limit.

There is no reason why fortification should not be designed to achieve an approximate 40% reduction, as in Chile.[12] Women consuming fortified flour and grain with a 0.4mg per day increase in folic acid who also take 0.4mg supplements can expect about a 60% reduction in NTD risk.[10] The risk in the proposals for consultation is that the fortification policy proposed would under-achieve and would not realise the full public health potential.

**Do you think there are any other benefits, costs or wider impacts of this policy proposal that have not been mentioned yet?**

Answer: Yes. First, it will promote confidence in the Government taking positive steps to promote health and to prevent disability and terminations of pregnancy.

Second, folic acid fortification will bring a wider benefit to the population through reduction of folate deficiency, which is itself a cause of anaemia. In the UK, some 6% of over 60s are folate deficient (serum folate below 5nmol/L (2.2ng/ml)) [13]. The prevalence of folate deficiency in the general population has decreased in countries that have introduced fortification. In the USA, folate deficiency anaemia has been nearly completely eliminated following mandatory folic acid fortification of cereals [13].

Third, folic acid reduces homocysteine levels [14], which has been shown to reduce the incidence of strokes.[15,16].

**What are the practical issues for businesses that need to be thought about for mandatory fortification with folic acid?**

Answer: Modelling should be undertaken to determine a fortification level applied to all flour and grains to achieve a mean of 0.4mg/day increase in folic acid intake. In the proposals there is a suggestion that voluntary folic acid should be restricted. This would produce an unnecessarily confusing message to the public and to industry – that increasing folic acid intake through fortification should be welcomed, but that other sources of folate are somehow dangerous. Adherence to an unjustified limit of 1mg/day would restrict fortification to a level that would provide only a small benefit and would require restrictions and controls on the availability of other sources of folate, including other fortified foods, supplement pills and conceivably even dietary sources. This complexity and confusion, which is likely to be resisted by food manufacturers, is entirely unnecessary because there is no reason to set an upper limit. There is therefore no need to stop industry from fortifying other prepared foods with folic acid, nor to discourage dietary intake of folate.

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