

Folic acid fortification for the reduction of neural tube defects

1. Purpose of the paper

- 1.1. In the absence of UK Government action, the then Scottish Minister for Public Health, Ms Watt, wrote to the Chair of Food Standards Scotland (FSS) in March 2016 for formal advice on how Scotland could fortify flour with folic acid, in a way which is evidence based, straightforward and with minimal cost burden on industry. This paper outlines to the Board the work undertaken in relation to this request.
- 1.2. The Board is asked to:
 1. **Consider** and **agree** updated advice to the Minister for Public Health as outlined in Section 10.
 2. **Agree** that the Chair will write to the Minister for Public Health accordingly.

2. Strategic Aims

- 2.1 The work discussed in this paper supports FSS Strategic Outcome 3 – Consumers Have Healthier Diets.

3. Summary

- The introduction of folic acid fortification of flour would reduce the numbers of NTD affected pregnancies, including spina bifida, in the UK. This is a long-standing, unresolved issue going back to 2006. Based on its updated 2017 risk assessment, the Scientific Advisory Committee for Nutrition (SACN) continues to recommend fortification of flour with folic acid. SACN also reiterates its previous advice that fortification should be accompanied by action to reduce intakes from voluntarily fortified foods.
- New dietary modelling confirms that there are options for the fortification of flour which, when combined with limits on voluntary fortification, would reduce the numbers of NTD affected pregnancies by 8-25% without any increase in the numbers exceeding the Tolerable Upper Intake level or Guidance Level (UL/GL) for folic acid.
- The bread and flour sector operates within a fully integrated UK market model and engagement with industry stakeholders has indicated that fortification on a Scotland only basis would not be straightforward and would incur significant complications and additional cost burden. In

addition, it is unlikely that the necessary reductions in voluntary fortification of other products could be achieved on a Scotland only basis, again due to the UK wide nature of the supply chain.

- To address the requirement to limit voluntary fortification, any intervention model needs to be comprehensive and multi-faceted to ensure that public health is protected as well as improved.
- As this type of policy intervention would result in benefits across the whole of the UK, this issue was previously considered on a UK-wide basis. We recommend that FSS advice to Ministers is that a Scotland only solution is not possible within the context of the original Ministerial request, i.e. that it be done in a way which is evidence based, straightforward and with minimal cost burden on industry .

4. Background

- 4.1. The introduction of folic acid fortification of flour is a long-standing, unresolved issue going back to 2006. Fortification of flour, together with limits on voluntary fortification, as previously recommended by SACN in 2006¹ and 2009², would reduce the numbers of Neural Tube Defect (NTD) affected pregnancies in Scotland and the UK as a whole. There are currently around 1043 NTD cases in the UK per year; many of which could be prevented with the introduction of fortification. For further information on folic acid and NTD risk, see Annex A.
- 4.2. There is no doubt that this is a public health issue. Data show that 75% of women between 16 and 49 years in the UK and 81% in Scotland currently have blood folate levels below the World Health Organisation (WHO) recommendation for the prevention of NTDs³ and Scottish Ministers are long term advocates of fortification of flour with folic acid to reduce NTDs, with a stated preference for a UK-wide solution in recognition that this is a UK wide issue.

¹ <https://www.gov.uk/government/publications/sacn-folate-and-disease-prevention-report>

² There was a further review of new evidence by the Scientific Advisory Committee on Nutrition (SACN) following concern from the Chief Medical Officers (CMOs) about an association between high intakes of folic acid and increased risk of colorectal cancer, SACN concluded in 2009, that there was no reason to change its previous advice to the FSA.

³ Bates B, Prentice A, Bates C, Page P, Steer T, Cox L, Nicholson S & Swan G. (2015) National Diet and Nutrition Survey Rolling Programme (NDNS RP) Supplementary report: blood folate results for the UK as a whole, Scotland, Northern Ireland (years 1 to 4 combined) and Wales (years 2 to 5 combined). London.

- 4.3. In 2014, the Food Standards Agency (FSA) advised Scottish Ministers that it was within their competence to introduce mandatory fortification of flour on a Scotland only basis. However, there is no legal power within the devolved administrations or UK Government to impose legal restrictions on businesses who are voluntarily fortifying foods with folic acid in accordance with the existing EU rules. Therefore the addition of folic acid to flour can be a legal requirement, however the accompanying restrictions on foods that are currently voluntarily fortified or restrictions on folic acid containing supplements, could only be achieved through voluntary agreement.
- 4.4. As there was (and still is) a risk that the food industry might not be prepared voluntarily to reduce the levels of folic acid in the products which are already fortified, the Board advised that this risk might be mitigated if a uniform approach to fortification could be secured across the UK. The FSA recommended that Scottish Ministers enter into discussions with other administrations across the UK, in an attempt to secure agreement to a consistent UK approach.⁴
- 4.5. In response to the Minister's request in March 2016, FSS undertook a number of strands of work. The results, presented in this paper include:
- information on the updated folic acid risk assessment by SACN;
 - results of new dietary modelling, on folic acid intakes, potential fortification scenarios and estimated NTD risk reductions; and
 - evaluation of initial industry engagement regarding practical implication and likely business impact of folic acid fortification.

5. 2017 Folic acid risk assessment by SACN

Background

- 5.1. As it is more than ten years since the main SACN risk assessment of folic acid was undertaken, FSS asked SACN whether:
- its previous assessment remained valid and sufficient to enable a decision on folic acid fortification to be made; and
 - its recommendation in 2006 and 2009 that "mandatory fortification should only be introduced in the UK if accompanied by action to reduce folic acid intakes from voluntarily fortified foods" still applied.

⁴ <https://www.food.gov.uk/sites/default/files/multimedia/pdfs/board/board-papers2014/fsa-140306.pdf>

In April 2016, SACN agreed to consider new evidence published since 2005 relating to potential adverse effects of folic acid.

- 5.2. Following SACN's previous advice in 2006/9, the FSA held meetings with sectors of the food industry on potential controls on voluntary fortification, noting that Unilever had reduced the folic acid content of spreads in response to SACN's advice.^{5,6} In September 2015, SACN noted its advice had led to action, prompting reductions in the levels of folic acid fortification in some commercial food products. However, the combination of not implementing fortification of flour in the UK alongside reductions in voluntary fortification is likely to have increased the risk of low folic acid intakes and folate status in the population.^{7,8} This cannot be a desirable policy or public health outcome.
- 5.3. Although the sufficiency of blood folate status was beyond the scope of this SACN folic acid review, in its letter to UK Health Ministers in October 2015 SACN noted that low folate status in the UK remains a concern.⁹ In other words, the UK Government has not enabled any action to address low folate levels in the population generally and particularly for women of child-bearing age.

Results

- 5.4. On the basis of its updated review of the evidence and risk assessment, published 12th July 2017,¹⁰ SACN continues to recommend fortification of flour with folic acid, reiterating its advice of 2006 and 2009, including maintaining the Tolerable Upper Intake Level (UL) or Guidance Level (GL) for folic acid. For further information on the UL/GL see Annex B.
- 5.5. SACN reiterates that fortification should be accompanied by measures to monitor folic acid intakes and blood folate concentrations of the population.

⁵http://webarchive.nationalarchives.gov.uk/20120403145508/http://www.food.gov.uk/aboutus/how_we_work/ourboard/boardmeetings/boardmeetings2008/board080312/boardmins12mar08

⁶ See Board paper: <http://webarchive.nationalarchives.gov.uk/20130221093809/http://www.food.gov.uk/about-us/how-we-work/our-board/board-meetings/boardmeetings2008/board080312/boardagenda080312>

⁷ <https://app.box.com/s/p66vloezimv7je6s0j9l962z3gizr381/1/4509873782/42609000313/1>

⁸ <https://www.food.gov.uk/sites/default/files/multimedia/pdfs/board/board-papers2014/fsa-140306.pdf>

⁹ Available at <https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition>

¹⁰ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/626231/SACN_Update_on_folic_acid.pdf

6. FSS Stochastic modelling to estimate the potential impact of fortification of flour with folic acid in the UK

Background

- 6.1. Wheat flour (including white and brown flour) is an established effective vehicle for fortification and is consumed regularly and in sufficient quantities by most people in the population regardless of their income and their folate intakes. It is therefore the preferred choice for folic acid fortification. The exclusion of wholemeal flour from fortification allows consumers the option of choosing non fortified products.
- 6.2. The previous dietary modelling undertaken by SACN in 2006¹ and FSA in 2008¹¹ included data up to 20 years old, therefore FSS commissioned new work based on current UK population intakes to model folic acid fortification scenarios and provide estimates of NTD risk reduction.
- 6.3. The work, jointly funded by FSS, the FSA in Northern Ireland (FSANI), the Welsh Government and the Chief Medical Officers (CMO) in Scotland, was carried out by Biomathematics and Statistics Scotland (BioSS). The report was published on the FSS website today, 16th August 2017.¹²
- 6.4. The FSS modelling included different levels of flour fortification. In addition, limits on the current levels of folic acid in voluntarily fortified foods (breakfast cereals and spreads) were modelled which would still allow companies to claim that the product was a 'source of folate (an important marketing feature for businesses). A limit on supplements was also set taking into account the Reference Nutrient Intake (RNI) of the general population¹³ and government advice that women of child-bearing age who may become pregnant, should take additional folic acid supplements. It is important that women of childbearing age who may become pregnant continue to take additional folic acid supplements, as this would still be necessary to ensure that the maximum number NTDs are prevented. Supplements will therefore continue to have an important role in preventing NTDs.

¹¹ <http://tna.europarchive.org/20120419000433/http://www.food.gov.uk/multimedia/pdfs/board/info080301.pdf>

¹² FSS Stochastic modelling to estimate the potential impact of fortification of flour with folic acid in the UK.

<http://www.foodstandards.gov.scot/publications-and-research/stochastic-modelling-to-estimate-the-potential-impact-of-fortification-of-flour-with-folic-acid-in-the-uk>

¹³ Department of Health. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report on health and social subjects 41. London: HMSO, 1991. The reference nutrient intake (RNI) for folate for adults is 200 µg/d.

Results

- 6.5. At baseline, the average population intake of total folate in the UK was 276 ug, with 79 ug of folic acid coming from voluntary sources, including supplements. Nearly 30% of the population had intakes below the RNI for folate (200 ug for adults, which is the minimum amount required to ensure that nearly everyone's needs are met). The proportion of the population exceeding the UL/GL was 0.4%. For all adults and most children, exceeding the UL/GL was due to folic acid from supplements. See Annex B.
- 6.6. Since 2006 the public health position has become worse. Overall, population intakes of folic acid were lower than the modelling in 2006. This confirms the concern expressed by SACN, about current intakes from voluntary sources reducing, and concern raised in recent report by the Scientific Committee of the Food Safety Authority of Ireland (FSAI).¹⁴ FSAI noted the reduction in voluntary folic acid fortification and suggested that this may have reduced folic acid intakes and worsened the folate status of the Irish population. As the UK is in a similar position to Ireland, it is reasonable to assume the same consequences.
- 6.7. The modelling, identified a number of beneficial fortification scenarios which met the following criteria set by FSS:
- reduce NTDs;
 - ensure no decrease in average folate intakes below the status quo;
 - ensure no increase in numbers exceeding the UL/GL; and
 - ensure folic acid reaches women of child bearing age, particularly those with the lowest current intakes.
- 6.8. To achieve these criteria it was confirmed that it was necessary to limit the levels of folic acid in voluntarily fortified foods and limit levels in supplements.
- 6.9. Example scenarios presented in the table below achieve reductions in NTD risk ranging between 8-25%, similar to the preferred scenarios in previous modelling carried out in 2006 (11-18%)³ and 2008 (10-17%).⁹
- 6.10. There was more benefit in terms of NTD risk reduction from fortification of all wheat flour rather than bread flour alone.
- 6.11. There was also more benefit in terms of NTD risk reduction in scenarios when higher levels of folic acid fortification were combined with limits on the content of

¹⁴ https://www.fsai.ie/resources_publications.html

supplements. More information on the influence of supplements is provided in Annex B.

- 6.12. The increase in the mean population intake of folic acid in all the scenarios presented ranged from 38-101 µg/day. The previous modeling in 2006 and 2008 both proposed increases of about 80 ug/day. This is equivalent to the folic acid content of just over two fortified breakfast wheat biscuits which normally provide around 62 ug folic acid.
- 6.13. Further information on the scenarios modelled is available in the FSS report.¹² In addition, an excel tool has been developed which provides a means of testing additional levels of flour fortification and limits on voluntary fortification.

Table 1 providing example fortification scenarios that meet the FSS required criteria

Scenario	Level of Folic acid fortification in flour*	Predicted whole population intakes of folic acid above the current status quo (ug/day)	% UK NTD affected pregnancies prevented**
BREAD FLOUR (NDNS definition***)			
Limiting**** folic acid in breakfast cereals, spreads and supplements	450 ug	43	121-177 (10-15%)
Limiting folic acid in breakfast cereals and spreads only	350 ug	38	90-133 (8-11%)
Limiting folic acid in supplements only	450 ug	78	170-246 (14-21%)
ALL FLOUR			
Limiting folic acid in breakfast cereals, spreads and supplements	350 ug	85	186-270 (16-23%)
Limiting folic acid in breakfast cereals and spreads only	200 ug	43	103-154 (9-13%)
Limiting folic acid in supplements only	300 ug	101	205-297 (17-25%)

*ug of folic acid per 100g of flour.

**in UK per year (range using 2 different methods and assuming that 30% of women were taking folic acid supplements per conceptually).

***from the National Diet and Nutrition Survey, includes white, brown, granary, wheatgerm bread, buns, rolls, bagels, muffins, pitta bread etc. Full details provided in the report.

****limits on voluntary sources were 15% RNI (Reference Nutrient Intake: the amount set to meet the requirements of 97.5% of the population) for breakfast cereals and spreads (30 ug/100g) and 200 ug for supplements (600 ug for women 14-49 years). When the analysis was repeated with the limit set per portion (15g) for spreads, only marginal differences in folic acid intakes were apparent due to the relatively small contribution of spreads.

7. Industry Engagement

Background

- 7.1. The fortification of flour is not a new concept to industry as any non-wholemeal wheat flour milled in the UK is already required to have calcium carbonate, iron, thiamine and nicotinic acid added, and this has been shown to be an established, effective vehicle for mandatory fortification. Therefore any additional burden associated with adding folic acid in the same way on a UK basis should be minimised.
- 7.2. Mandatory fortification, as recommended by SACN in 2006 and 2009, where the amount of folic acid added to flour would be controlled and legally defined, was considered by SACN to be the most effective mechanism to ensure the necessary redistribution of folic acid intakes towards those with the lowest current intakes, thus helping to prevent NTDs. Coupled with mandatory fortification, limits on voluntary fortification are required to prevent sub-groups of the population consuming intakes above the UL.
- 7.3. By contrast, uncontrolled and entirely voluntary fortification of flour may either be insufficient to elicit benefit or alternatively it may cause excess consumption of folic acid by some consumers. Both scenarios therefore constitute a public health risk. It has also been shown to be largely ineffective in addressing the NTD problem in countries, such as the Republic of Ireland.¹⁵
- 7.4. The Minister for Public Health asked FSS to ensure that any implementation of fortification of flour with folic acid in Scotland would be straightforward for industry with the cost burden kept low.
- 7.5. FSS undertook a series of face to face meetings with key affected stakeholders to explore this, including a site visit to one of the main Scottish flour mills (ADM Milling (Leith), to look at practical application issues. FSS also carried out informal consultation to request specific information on costs and burdens associated with potential implementation mechanisms.
- 7.6. The meetings involved representatives of the bakers and millers sectors, the Food and Drink Federation of Scotland (FDF Scotland) and the Scottish Retail Consortium (SRC). Preliminary discussions also took place with the British Retail Consortium (BRC) with respect to current practices involving voluntarily

¹⁵ https://www.fsai.ie/news_centre/press_releases/folic_acid_report_04052016.html

fortifying products. As well as helping to provide significant evidence of the practical issues associated with fortification, these meetings were used to provide up to date market and sales information to support the modelling work.

Results

- 7.7. Following these meetings, the Federation of Bakers and the National Association of British and Irish Millers Limited (NABIM) also provided written responses emphasising that the bread and flour sector operates within a fully integrated UK market model. They explained that flour milled in Scotland is distributed to all parts of the UK and the Scottish baking industry is reliant on mills throughout the UK and Ireland for the flour it uses in manufacturing. The bakery products they produce are also distributed across the whole of the UK. Estimated costs for the Scottish milling industry include capital costs of £3 million and on-going costs of approximately £800k a year. The potential for significant loss of trade in flour containing products to the rest of the UK was also highlighted, with up to £100 million of Scottish exports 'at risk'. This indicates that there is no straightforward, cost-efficient Scotland only solution. A Scottish solution would be both costly and complex, with significant implications for both the current UK and international markets. The cost of fortification in Scotland will impact Scottish millers, Scottish bakers, and businesses in other parts of the UK. In addition, it was considered that fortifying flour milled in Scotland only, would be insufficient to meet the objectives of fortification.
- 7.8. It was suggested that the cost of fortification would include: the folic acid itself, re-labelling, additional audit and verification for both industry and enforcers. A Scotland only solution was considered much more costly as, in addition to these costs, new infrastructure for segregation of product lines for different UK markets would be required, along with related labelling, enforcement and verification costs.
- 7.9. Concerns were expressed about the potential for an adverse customer (consumers and retailers) reaction due to an emerging consumer preference in both the UK and EU member states for 'clean label' products.¹⁶ However, this of course has to be counterbalanced against the sectors of the industry who are clearly pro-actively marketing the health benefits of fortification in their products.

¹⁶ Consumer expectations of 'clean label' include: absence of chemical additives, simple ingredients lists, minimal processing etc.

- There was also concern that a Scotland only approach would be likely to confuse consumers. Other UK administrations not taking similar action might be seen as implying that there are concerns over the safety of the policy.
- 7.10. Industry stakeholders also highlighted potential legal issues associated with a Scotland only approach. For example, legal challenge from UK manufacturers if they were forced to comply with Scottish marketing rules, or challenge associated with the EU notification process for any Scottish national measures.
- 7.11. With respect to the need to reduce folic acid intakes from voluntarily fortified foods, there is no legal power, at the moment, within Scottish Ministers' (or UK Government) competence to impose legal restrictions on businesses who voluntarily fortify foods with folic acid in accordance with the existing EU rules. It would, therefore, be necessary to reach a voluntary agreement with industry.
- 7.12. Earlier FSA discussions with food retailers and manufacturers were generally positive about restrictions on voluntary sources on a UK basis. Indeed, there was a reduction in voluntary fortification of spreads in expectation of mandatory fortification. Recent FSS discussions with the BRC have remained positive on this point so long as current marketing arrangements can be accommodated in any new model. It should also be noted that any such voluntary changes would also incur initial set up costs related to reformulation and re-labelling.
- 7.13. Original FSA discussions indicated that the supplements industry was not supportive of supplement capping, so their current position would require to be established. However, our proposals are related to sensible reduction of high dose supplements to protect people from consuming too much. We still support the use of supplements as a key mechanism for increasing folate intake, particularly for women of childbearing age. Although those in the population who take folic acid containing supplements are not the target for a fortification policy, they may still benefit from the additional folic acid intake.

8. Discussion of potential policy solutions

- 8.1. An entirely voluntary scheme with no associated regulatory framework has been discounted for the reasons set out earlier in the paper (see paragraph 7.3).

Mandatory Fortification of Bread or Flour with folic acid in Scotland alone with no market intervention elsewhere within the UK

- 8.2. Whilst the updated advice from SACN and the modelling work undertaken by FSS has confirmed the public health benefit of introducing mandatory fortification of flour, this could only be effected with agreement from industry to reduce the amounts of folic acid currently voluntarily added to foods and some supplements. Such an agreement is unlikely to be achieved in the context of a Scotland only intervention model.
- 8.3. The Minister asked that any implementation in Scotland be straightforward and with a low cost burden for industry. Our industry engagement found that this is not possible within the context of a Scottish only intervention model. There are significant industry concerns about the practical challenges and costs of fortification of flour on a Scotland only basis and of limiting current voluntary sources of fortification due to the strong interdependency of the food supply chain across the UK in this particular sector.
- 8.4. To evaluate fortification, in addition to the need to collect data on population intakes and blood folate status, more robust data on rates of pregnancy affected NTDs would be required. There would be cost and resource implications of taking this forward, which would be disproportionately higher if developed on a Scotland only basis.
- 8.5. The Minister asked for advice on how Scotland could fortify flour with folic acid, in a way which is evidence based, straightforward and with minimal cost burden on industry. However, the evidence indicates that a straightforward solution to implementing fortification of flour on a Scotland only basis, with minimal cost burden, is not possible.

9. Conclusions

- 9.1. On the basis of updated evidence, SACN has again recommended that fortification should go ahead and be accompanied by action to reduce intakes from voluntarily fortified foods.
- 9.2. Our dietary modelling provides a number of beneficial scenarios for fortification with sensible limits on voluntary fortification, applicable on a UK basis, to inform an implementation plan for the fortification of flour with folic acid.

- 9.3. The milling and baking industry has indicated that fortification on a Scotland only basis would not be straightforward and would incur a significant cost burden.
- 9.4. There are potential difficulties associated with setting voluntary limits for breakfast cereals, spreads and supplements on a Scotland only basis, as these products have a UK-wide distribution pattern.
- 9.5. Therefore, a straightforward solution to implementing fortification of flour on a Scotland only basis with minimal cost burden on industry, is not possible.

10. Recommendations

- 10.1. Given the previous reductions in voluntary fortification of the folic acid, in expectation of mandatory fortification, coupled with current evidence of low intakes and low blood folate levels in women of childbearing age, it is considered important that a solution can be identified to take forward policy to reduce the risk of NTDs in the population. However, in the context of the Ministerial request, regrettably fortification of flour on a Scotland only basis is not possible. This supports previous recommendations for fortification of flour with folic acid which were made on a UK wide basis.
- 10.2. Given the conclusion in paragraph 10.1, the Board is invited to discuss and agree its updated advice to Scottish Ministers along the following lines:
1. Updated advice from SACN and FSS is that regulatory intervention around the fortification of bread or flour to improve NTDs remains appropriate and can be implemented safely with support from industry on applying controlled restrictions on products currently voluntarily fortified;
 2. Engagement with industry has failed to identify a straightforward and low cost solution which can be applied on a Scotland only basis.
- 10.3. The Board is asked to:
1. **Consider** and **agree** updated advice to the Minister for Public Health as outlined in Section 10.
 2. **Agree** that the Chair will write to the Minister for Public Health accordingly.

[END]

Anne Milne, Bill Adamson, Heather Peace, Sam McKeown

7th August 2017

Annex A

Folate, folic acid and the prevention of NTDs

1. The term folate describes a family of B-group vitamins. The reference nutrient intake (RNI) for adults is 200 µg/d.¹⁷ Folic acid is a synthetic form of folate. It is widely used for food fortification and in supplements because it is more stable in foods than natural folates and is better absorbed.
2. There is conclusive evidence that taking additional folic acid before conception and up to the 12th week of pregnancy can reduce the population risk of neural-tube defects (NTDs), including spina bifida and anencephaly.¹⁸
3. All women who could become pregnant are therefore advised to take supplements. In Scotland, all pregnant women are eligible to receive free Healthy Start vitamins throughout their pregnancy including 400 µg of folic acid/day. A higher dose (5 mg/d) is recommended for some women, including those with a previous pregnancy affected by NTD¹⁹ or with diabetes.²⁰ However, maximum protection comes from consumption of folic acid pre-conception.
4. In addition to folic acid supplementation prior to pregnancy, fortification of food with folic acid is necessary to reduce the risk of an NTD affected pregnancy, as most women, particularly younger women and those from more deprived areas, do not follow the advice on supplements.²¹ In addition, it is estimated that only 55% of pregnancies in the UK are planned, and supplements are unlikely to be consumed by the 45% of women whose pregnancies are unplanned.²²
5. Current data show that 75% of women between 16 and 49 years in the UK and 81% in Scotland currently have blood folate levels below the World Health Organisation (WHO) recommendation for the prevention of NTDs.²³ The data

¹⁷ Department of Health. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report on health and social subjects 41. London: HMSO, 1991

¹⁸ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/626231/SACN_Update_on_folic_acid.pdf

¹⁹ Food and Nutrition Board, 1998

²⁰ Diabetes UK recommends that all women with diabetes, who are planning a pregnancy, should take a daily folic acid dose of 5 mg. https://www.diabetes.org.uk/Guide-to-diabetes/Living_with_diabetes/Pregnancy/

²¹ Bestwick JP, Huttly WJ, Morris JK & Wald NJ (2014) Prevention of neural tube defects: a cross-sectional study of the uptake of folic acid supplementation in nearly half a million women. PLoS One 9, e89354.

²² Wellings K, Jones KG, Mercer CH, Tanton C, Clifton S, Datta J, Copas AJ, Erens B, Gibson LJ, et al. (2013) The prevalence of unplanned pregnancy and associated factors in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). Lancet 382, 1807-1816.

²³ Bates B, Prentice A, Bates C, Page P, Steer T, Cox L, Nicholson S & Swan G. (2015) National Diet and Nutrition Survey Rolling Programme (NDNS RP) Supplementary report: blood folate results for the UK as a whole, Scotland, Northern Ireland (years 1 to 4 combined) and Wales (years 2 to 5 combined). London.

suggest that there are around 1043 NTD cases in the UK per year.²⁴ Data from Scotland suggests that 158 infants were born in Scotland with an NTD between 2007 and 2011 and that there were 125 terminations between 2010 and 2014 in Scotland with a diagnosis of NTD. Due to different methods of data collection, information on the numbers of NTD affected pregnancies in Scotland may be underestimated.

6. Mandatory fortification of wheat flour and other cereals with folic acid is undertaken in a number of other countries and there is clear evidence of a reduction in Neural Tube Defects (NTDs) as a result.²⁵ For example in the USA a reduction of 28% was recorded between the pre-fortification period (1995–1996) and post-fortification period (1999–2000).²⁶ Researchers have estimated that a similar policy in the UK would have prevented 1,798 pregnancies with NTD in England and Wales, 152 in Scotland and 64 in Northern Ireland over a 14-year period up to 2012.²⁷ Canada, South Africa, Costa Rica, Chile, Argentina, and Brazil also have reported declines in NTDs following mandatory fortification of between 19% and 55%.²⁸ To date no European countries have introduced mandatory fortification.
7. A study in 2011 reviewed studies on the impact of NTDs on health, treatment costs and society.²⁹ The review was only able to include a few studies that evaluated the economic burden of the disease and the economic impact of prevention with folic acid. These studies reported findings from a limited number of countries (mainly the USA) and focused on spina bifida over other NTDs. The lifetime direct medical cost for patients with NTDs was significant, with the majority of cost being for inpatient care, for treatment at initial diagnosis in childhood, and for comorbidities in adult life. The lifetime indirect cost for patients with spina bifida was even greater due to increased morbidity and premature

²⁴ as provided in EUROCAT (European Surveillance of Congenital Anomalies) Excluding genetic cases

²⁵ Atta CA, Fiest KM, Frolkis AD, Jette N, Priingsheim T, St Germaine-Smith C, Rajapakse T, Kaplan GG & Metcalfe A (2016) Global Birth Prevalence of Spina Bifida by Folic Acid Fortification Status: A Systematic Review and Meta-Analysis. *Am J Public Health* 106, e24-34.

²⁶ Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ, Ethen M, Frohnert B & Kirby RS (2015) Updated estimates of neural tube defects prevented by mandatory folic acid fortification - United States, 1995-2011. *MMWR Morb Mortal Wkly Rep* 64, 1-5.

²⁷ Morris J, Rankin J, Draper E, et al. Prevention of neural tube defects in the UK: a missed opportunity. *Archives of Disease in Childhood* 2016;101:604-607.

²⁸ Crider, K.S.; Bailey, L.B.; Berry, R.J. Folic Acid Food Fortification—Its History, Effect, Concerns, and Future Directions. *Nutrients* 2011, 3, 370-384.

²⁹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3197907/>

mortality. Caregiver time costs were also significant. The review concluded that the benefits of prevention of NTDs with folic acid, including mandatory and voluntary fortification in all countries assessed (with the exception of mandatory fortification in New Zealand), far outweighed the cost.

Annex B

The Tolerable Upper Intake Level or Guidance Level of Folic Acid and the dietary modelling results

1. In the USA a Tolerable Upper Intake Level (UL) of 1 mg/d of folic acid (1000 µg/d) was set for adults by the Food and Nutrition Board of the Institute of Medicine. The potential hazards of high intakes were reviewed including neurological impairment in individuals with B₁₂ deficiency, general toxicity, reproduction and development and carcinogenicity.³⁰ The most serious potential adverse effect of excessive intakes was considered to be progression of neurological symptoms in individuals with vitamin B₁₂ deficiency and this was the critical end point to set the UL. The UL represents the highest level that is likely to pose no risk of adverse health effects for almost all individuals in the general population.
2. In Europe the European Scientific Committee on Food (SCF) also set a UL for folic acid of 1mg/day in 2000 taking account of a similar range of safety concerns. ULs for children in the USA and Europe were extrapolated from the UL for adults on the basis of relative body weight.³¹
3. The Guidance Level (GL) in the UK, for folic acid of 1mg was set by the Expert Group on Vitamins and Minerals in 2003³², based on the risk of progression of neurological symptoms in vitamin B₁₂ deficient patients.
4. The NDNS data suggests that currently 0.42% of the UK population exceed the UL/GL for folic acid intake (equivalent to around 264,000 people). As part of the dietary modelling, we looked at those participants in the UK NDNS who were consuming folic acid above the UL/GL and the reasons why. Findings confirmed that supplement use was the main reason that people, particularly adults, exceeded the UL/GL.
5. The dietary modelling showed that the most effective mechanism for maximising the reduction in NTDs, without increasing the numbers above the UL/GL, was to

³⁰ In the USA and Europe, a UL of 1 mg/d of folic acid was set for adults. ULs for children were extrapolated from the UL for adults on the basis of relative body weight. In the UK, the Expert Group on Vitamins and Minerals set a GL of 1 mg/day of folic acid for adults. GLs were not set for children as there were no data reporting adverse effects in children.

³¹ ULs for children, Europe: 4-6y, 300 µg/d; 7-10y, 400 µg/d; 11-14y, 600 µg/d; 15-17y, 800 µg/d. ULs for children, USA: 1-3y, 300 µg/d; 4-8y, 400 µg/d; 9-13y, 600 µg/d; 14-18y, 800 µg/d.

³² <https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf>

limit supplements. For example with only breakfast cereals and spreads limited,³³ a maximum of 200 ug folic acid/100g flour could be added, reducing NTDs by up to 13%. By limiting supplements alone³⁴, a maximum of 300 ug/100g of folic acid could be added, reducing NTDs by as much as 25%.

6. Although only 9% of participants in the NDNS³⁵ reported taking supplements containing folic acid, the contribution of supplements to the overall mean intake of folic acid in the population was larger than for fortified breakfast cereals or spreads. However, it would be prudent to place limits on both voluntarily fortified foods and supplements as the amount of folic acid added could increase in future.
7. SACN have advised that mandatory fortification of flour should only be introduced if it is accompanied by controls on voluntary fortification and guidance on supplement use. In addition, SACN have advised that people aged over 50y and those with a previous history of colorectal adenomas due to a link with developing cancer, should not consume supplements containing folic acid above the reference nutrient intake for folate of 200 µg/d.³⁶

³³ Limits on voluntary food sources were 15% RNI (Reference Nutrient Intake: the amount set to meet the requirements of 97.5% of the population) for breakfast cereals and spreads (equivalent to E0 ug/100g)
³⁴ at 200 ug/day (600 ug/day for women of child-bearing age)

³⁵ The dietary modelling was based on UK data from the National Diet and Nutrition Survey (NDNS) including years 1 to 6 (2008/9 to 2013/14) of the rolling programme with intake data from over 9000 participants.

³⁶ SACN. (2009) Folic acid and colorectal cancer risk: Review of recommendation for mandatory folic acid fortification.