Mandatory fortification of flour with folic acid

A brief update March 2014

A. David Smith and Helga Refsum, Universities of Oxford and Oslo

For earlier more detailed reports see:

Is folic acid good for everyone?
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An update on folic acid fortification: benefits and risks 2012
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Executive Summary

1. The New Zealand government does not know what the annual incidence of neural tube defect (NTD) pregnancies is in the country, because no data on NTDs in pregnancy terminations have been collected since 2003. The folate status of women of childbearing age is as good as that currently in the USA, which fortified in 1998. It is therefore difficult to justify introduction of mandatory folic acid fortification since the baseline NTD rate is unknown and it is likely that the maximum effect of folate has already been reached.
2. The debate over folic acid and cancer has not been settled by a meta-analysis of trials published in *The Lancet* in March 2013. This meta-analysis of folic acid trials in >50,000 people found that there was a 6% higher rate of cancer in those treated with folic acid, but that this increase was not quite significant, with a Rate Ratio of 1.06 and Confidence Intervals of 0.99-1.13. The conclusion from the meta-analysis is probably flawed because the analysis is underpowered to detect a significant 6% difference, and because it did not consider important sub-groups of people who might be more, or less, susceptible to the harmful effects of folic acid.
3. There is increasing evidence that maternal consumption of folic acid can have epigenetic effects in human offspring, which modify the functioning of certain genes in the child and so could influence the child's risk of later adverse health, such as increase the risk of diabetes. This is a critical matter for future research because such effects are irreversible.
4. Important new evidence has appeared in USA and in Australia showing that high folate status in the elderly can interact with low vitamin B12 status and lead to a faster rate of cognitive decline. About 4% of the elderly population might be at such a risk after fortification; in New Zealand that means more than 20,000 people.
5. We believe that there are sufficient concerns about possible harm to significant numbers in the population and that these concerns outweigh the benefit of the possible small reduction in NTD pregnancies by fortification. ***Overall, these concerns have increased since our last report and we advise the government to hold back on mandatory fortification***. Instead, we suggest that New Zealand takes an international lead in this matter and attempts to answer the certain specific challenges before they conclude that fortification will benefit the entire country. These challenges are listed in the main report.

The prevalence of neural tube defect (NTD) pregnancies in New Zealand

A country that proposes to take a major public health action that exposes the entire population to increased intake of folic acid in order to reduce the incidence of NTD pregnancies must take this step with the knowledge of the current incidence of NTD pregnancies. As we pointed out in our 2012 report (pages 10-12), this information has not been available for NZ since 2003 because no data has been collected after that year on the prevalence of NTDs in pregnancy terminations. The only available data is of live and stillbirth NTDs. With the extensive use of prenatal screening, the majority of NTD pregnancies are terminated and so the current statistics are of little or no value.

We repeat what we wrote in the last report (pages 13-15): the current folate status of women of reproductive age in NZ is so high that little if any change in NTD incidence can be expected if folic acid fortification is introduced. This is because there is a 'floor effect' in that folate-susceptible NTDs have by now largely been prevented, and so the residual NTDs in NZ must have other causes (see page 13, 2012 report)[a]. All estimates of the effect of fortification on the future incidence of NTD pregnancies are thus subject to high uncertainty, and we do not believe that these estimates should form the basis of a change in public health policy.

The cancer question: will fortification increase the incidence of cancer?

Since our report in 2012 there have been a few studies on this important question.

1. *The Vollset meta-analysis*[1]. This report updates the 2010 meta-analysis that we commented on in our 2012 review. It is a meta-analysis of randomised clinical trials (predominantly in cardiovascular disease) on a total of more than 50,000 people in which folic acid was administered (usually together with other B vitamins) in doses averaging 2 mg per day. The paper has been widely cited and has led to statements like "…the publication in March this year of the paper by Vollset et al in the *Lancet* puts the concerns [about cancer] to rest." [Lord Rooker, House of Lords, 6 November 2013 (*Hansard* vol 749 No 66, page 285)].

This paper can easily be misunderstood. The editorial in *The Lancet* that accompanied the article warned about this, emphasizing "*the fragility of the results of this meta-analysis and the need for cautious interpretation*."[2]. Indeed, Vollset et al. concluded *"Folic acid supplementation does not substantially increase or decrease incidence of site-specific cancer during the first 5 years of treatment.*" [Underlined by us]. What the report showed (Figures 1- 3 and Table 2) was that in the placebo group (24,822 people) there were 1,809 cancers while in the folic acid group (24,799 people) there were 1,904 cancers. *This difference corresponds to a 6% higher cancer incidence in the folic acid treated group*. However, this difference did not quite reach statistical significance, with a Rate Ratio of 1.06 and 95% confidence intervals of 0.99-1.13 (for a significant result the lower confidence interval must be greater than 1.00). What the authors did not do was to estimate how many subjects they would have needed in the meta-analysis to obtain a significant difference for a 6% higher rate. Without this kind of estimate (called a power estimate), it cannot be

[a] It is notable that low vitamin B12 status is a risk for NTDs and that 23% of NZ women aged 19-30 are considered to have an inadequate intake of B12 (see Table 4.19 in ref. 25).

concluded that there was no effect of folic acid treatment on cancer risk. We have estimated that a total of around 70,000 subjects would be needed to determine if the apparent 6% increase is true or false. A 6% increase may seem unimportant, but it would mean an extra 1,270 cases of cancer a year in NZ. This possible increase in cancer must be compared to the potential benefit in preventing NTD pregnancies.

The authors' expression that folic acid "*does not substantially increase"* cancer incidence is thus correct, since they did *not* conclude that there was *no* increased risk. Basically, we consider that their study was inconclusive since it was underpowered, in particular, if the intention is to weigh benefit in terms of NTDs vs. potential harms in relation to cancer events.

A second problem with the Vollset meta-analysis is that it did not examine several sub-groups in the population that might be more susceptible to the harmful effects of folic acid. We gave a list of possible sub-groups in our 2012 report (Table 4, pages 43-44). The best studied of these sub-groups are people with the 677TT genotype of the gene for methylenetetrahydrofolate reductase (MTHFR). As described in the latter report, two studies have shown how this genotype interacts with folate in the risk of cancer. The first is the population study of women in Malmö, Sweden which found that although a good folate status is protective against breast cancer in the overall population, the sub-group of women with the TT genotype showed a significantly increased risk of breast cancer the higher their blood folate level[3]. Sweden does not have folic acid fortification and the plasma folate levels associated with increased risk (17 nmol/L) are well within the levels in women in NZ. The prevalence of the TT genotype in NZ is about 10%, so according to the Malmö study, up to 200,000 NZ women might be at an increased life-time risk of breast cancer if exposed to high folate intake. The second study is the intervention trial of folic acid in Norway, where a marked increased risk of dying from cancer was found for those with the TT genotype who were treated with folic acid[4]. In view of these reports, it is unfortunate that the meta-analysis of Vollset et al. did not even consider the need to look at certain sub-groups. In our view, this omission further reduces the value of their report.

The importance of sub-groups is further emphasized results from the Netherlands (submitted for publication) of a 2-y randomised trial of daily 0.4 mg folic acid in older people (>65 y) with high homocysteine (>12 µmol/L). The trial showed a significant increase in cancer events in the folic acid group, which was much greater in the oldest sub-group. The possible reason for a stronger effect in this study than in the Vollset meta-analysis may be related to the group that was studied, i.e., it was older, it was in a population not exposed to mandatory folic acid fortification, and in contrast to the Vollset study, the participants did not routinely receive daily aspirin (see below).

Another sub-group should be considered in relation to the Vollset report: people who regularly take aspirin. In relation to cardiovascular disease, folic acid has been shown to interact with aspirin[5,6], which appears to prevent its beneficial effect. It is well established that aspirin protects against cancer[7], and the majority of subjects included in the meta-analysis by Vollset et al. are likely to be taking aspirin since they have had a cardiovascular event (49,621 were in CVD trials and 2,652 in cancer trials). In a trial of aspirin and folic acid in relation to colorectal adenomas[8], there was a trend for those not taking aspirin to show an increased risk of advanced adenomas (their Figure 2) compared with those taking aspirin. This interaction was not statistically significant, possibly because of the small numbers involved. But if it is true that folic acid only increases cancer in those not taking aspirin, then Vollset's conclusion may be flawed.

2. *Colorectal cancer in USA after fortification: the Women's Health Initiative Observational cohort*[9]. This large observational study on 88,045 postmenopausal women that included the period when folic acid fortification became mandatory, found that intake of vitamins B2 and B6 reduced the risk of developing colorectal cancer. On the other hand, folate intake was associated with an increased risk between 3 and 9 years after fortification. In each of the two periods 3 – 6 years and 6 – 9 years after fortification, there was a dose-related increased risk of colorectal cancer. For the period 6 – 9 years after fortification, the Hazard Ratio for those consuming >340 micrograms folate per day from food was more than 3 times greater than those consuming <189 micrograms. The risk was not significant <3 and >9 years after fortification. This important study is consistent with earlier reports of a temporary increase in colorectal cancer in the USA following fortification derived from national cancer statistics (discussed on pages 37-8 in our 2012 review). While there has been a lot of debate about the results from national registers, this carefully executed observational study is more difficult to question.

3. *Retinoblastoma in children of mothers taking folic acid*[10]. As we discussed in our two previous reports, folic acid is a synthetic substance and has to be reduced by the enzyme dihydrofolate reductase (DHFR) before it can enter normal metabolism. This preliminary report suggests that women who take folic acid before conception and who have a double mutation on the gene for DHFR appear to have a greater chance of having a child with a rare cancer, retinoblastoma. The mutation in the gene leads to higher blood levels of unmetabolized folic acid[11] and so it can be speculated that raised blood levels of folic acid may be related to the induction of the retinoblastoma. This study needs confirmation and ideally risk ratios should have been reported, but it is important because it highlights a potential problem for a large sub-group of the population (about 20%) who have this double mutation in DHFR: if they consume folic acid, they will be exposed to higher levels of circulating folic acid, with possible harmful effects (see below, under Folate-B12 interactions).

Possible epigenetic effects on children whose mothers are exposed to folic acid

We discussed these in our 2012 report (pages 32-34). The question is whether maternal folic acid intake can affect (probably via its role in DNA methylation) the functioning of certain genes in the child and so influence the child's risk of later adverse health. Since 2012 there have been additional relevant reports. These reports are only observational and so should be interpreted with caution. The striking result from India that high maternal folate status was associated with increased risk of obesity and insulin resistance in children at 6 years of age has now been confirmed in another cohort, where it was found that high maternal folate was linked to a small but significant increased risk of insulin resistance when the children were 9 or 13 years old[12]. In the latter study, the mothers had been prescribed folic acid throughout pregnancy and their median plasma folate level was 35 nmol/L, a value that we believe will be exceeded if NZ introduces mandatory fortification (see page 49, 2012 report). These correlations are of concern and urgently need replication in randomised trials.

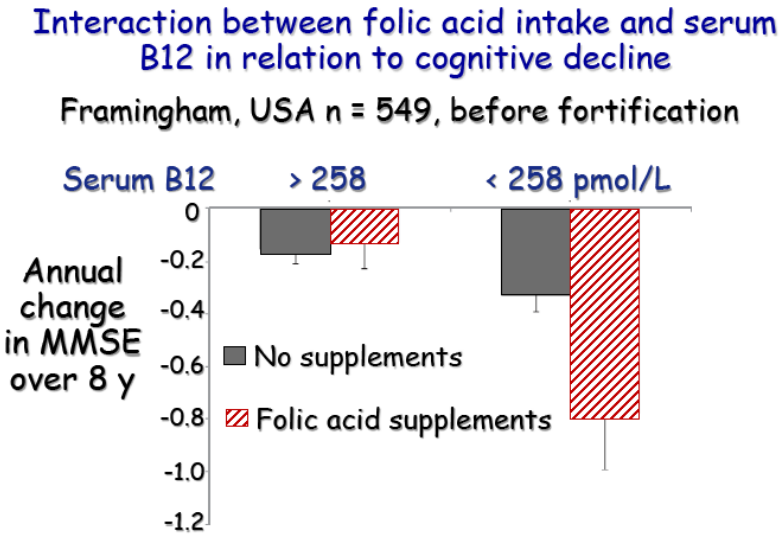
Because folate is critically involved in methylation reactions and methylation of DNA is believed be involved in genomic imprinting, several studies have examined the methylation

status of imprinted genes in children born from mothers who were exposed to folic acid in pregnancy. This is important because modifications of the imprint status in humans have been associated with development of diabetes, obesity, cancer and cognitive impairment. Two recent studies found that taking folic acid in pregnancy led to differential methylation of several imprinted genes, with some genes showing increased methylation and some, paradoxically, decreased methylation[13,14]. These studies are consistent with the basic hypothesis, i.e., that folic acid in the mother can influence key genes in the child. Hence, an important question for future research is the identification of long-term effects of such modifications. We quote a statement by leading experts in this field: *"…in the face of the implementation of folic acid fortification in a number of countries and the ongoing debate about this strategy in others, failure to address the nature and extent of the effects of prenatal folic acid exposure on the offspring may have negative implications for future public health."*[15]

Folate – vitamin B12 interactions

1. *High folate and low B12 in the mother.* As we described in our earlier reports, the children of Indian mothers who had high blood folate levels and low B12 levels during pregnancy, were at increased risk at age 6 of obesity and insulin resistance[16]. The folate levels in Indian mothers are often high because doctors prescribe folic acid during pregnancy. In South India, it has been reported that high folic acid intake and low B12 intake during pregnancy in the mother is associated with small-for-gestational age babies[17]. Such babies often do not develop well and have later adverse health as adults. The folic acid intakes were high in this population and it remains to be established what blood values of folate might be associated with this adverse outcome.

2. *High folate and low B12 status in the elderly and cognitive impairment.* Ever since the idea of folic acid fortification was first discussed, there have been concerns about the so-called 'masking' of B12 deficiency. It has turned out that this is of more concern than previously anticipated, because several reports suggest that elderly people with low B12 status and high folate status are at risk of developing cognitive impairment. The first studies were discussed in our 2012 report (pages 27-8). These early studies were cross-sectional and so subject to some uncertainty. However, a prospective study has now been published[18]. In this study, a cohort of subjects aged 75 at baseline was studied for 8 years, with cognitive assessments (Mini-mental state examination, MMSE) every 2 years. The rate of cognitive decline was greater in those with baseline low B12 (< 258 pmol/L) than those above this cut-off (black bars in Figure). When plasma folate was entered into the equation, there was a highly significant interaction (P<0.001) between high folate (> 22 nmol/L) and B12 status, such that the cognitive decline was much greater in those with low B12 and high folate than those with normal B12 and high folate. Furthermore, in response to questionnaires, it was found that those who took supplements containing folic acid also showed a greater cognitive decline if they had low B12 status (red columns in Figure).



It is noteworthy that the plasma folate levels associated with accelerated cognitive decline in those with low B12 status are well within the range found today in NZ. The question is, therefore, could it be the folic acid consumed from supplements that causes the cognitive effects? A cross-sectional study strongly supports this idea[19]. In this study on the elderly it was found that the concentration of circulating unmetabolized folic acid was associated with cognitive impairment in those with low B12 status, whereas the concentration of the natural folate species, methyltetrahydrofolate, was not related to impairment. This important result suggests that folic acid has properties that are different from that of natural folates, which could have wider implications.

Two additional reports from the USA have produced evidence of an unexpected effect of folic acid: in those with low B12 status, high folate is associated with a functional impairment of B12-dependent enzymes[20,21] and with a lower level of circulating holotranscobalamin, the functional form of B12 in the blood[21]. These changes were only found in studies done after the introduction of mandatory fortification[20]. The conclusion is that low B12 is associated with more pronounced metabolic evidence of B12 deficiency when folate is elevated than when folate is not elevated, and that this effect is probably related to folic acid intake.

A recent report from Australia confirms these findings[22]. In this study, three different cohorts of elderly subjects with memory problems were combined and the relationship between blood levels of folate, B12 and cognition (MMSE) were determined. The blood samples were taken long after the introduction of voluntary folic acid fortification and some after the introduction of mandatory fortification in 2009. As expected, those subjects with low B12 status (<250 pmol/L) and normal folate showed a greater odds of cognitive impairment than those with normal B12 status. However, as in the USA studies, those with low B12 and high folate status showed an even greater odds of cognitive impairment. It is a big effect: in the group with normal folate and normal B12, 21% were cognitively impaired, in the group with high folate and normal B12, 34% were cognitively impaired, whereas in the group with both high folate and low B12 almost half (49%) showed cognitive impairment. Thus, there is a greater than doubling of the risk of cognitive impairment for elderly who have high folate coupled with low B12. In this selected Australian cohort of elderly with memory problems, the

proportion who were at greatest risk of cognitive impairment (i.e. having high folate and low B12) was 2.9%, which is similar to the 4% of the overall American elderly population that have high folate and low B12[23].

In another country that has introduced mandatory fortification with folic acid, Chile, the proportion of elderly (>65y) who have both high folate and low B12 status was very similar, at 4.1% [24].

It is important to ask, *what is the proportion of elderly people in NZ who have the combination of low B12 status and high folate status*? While there is reasonably good data on folate levels in NZ, there is no comprehensive report on B12 levels. The 2008/2009 Adult Nutrition Survey[25] only reports B12 intake, not blood levels. The report considered that in those over 71 y-old, 3.8% of men and 27% of women had inadequate B12 intake (Table 4.19). The folate levels in the report were from blood samples taken before the introduction of voluntary folic acid fortification and so do not reflect the current status. In those over 71, the mean serum folate in men was 31.6 nmol/L and in women was 39.7. It is very likely that the current levels in the elderly will be higher since, as shown by a survey of women of child-bearing age[26], folate levels have increased in NZ since voluntary fortification.

There are two earlier reports on the vitamin B12 levels in blood samples from NZ elderly. In 103 women it was found that 13% had levels below150 pmol/L, while as many as 50% had values below 200 pmol/L[27]. (Note that in the Australian study cited above a cut-off value of 250 pmol/L was used.) A larger survey of nearly 500 elderly of both sexes in NZ[28] found that 12% had levels below 148 pmol/L and 40% had levels below 221 pmol/L. It is well known that vegetarians, and especially vegans, have a low B12 status[29] and in a small survey this was also the case in NZ[30]. Although the proportion of vegetarians in NZ is low (about 2%) they are a sub-group that might be at particular risk due to an imbalance between folate and B12.

This data for NZ, although incomplete, is of concern: we consider it likely that a significant proportion of the elderly in NZ might have low B12 status and high folate status and so be at increased risk of cognitive impairment. The number of NZ citizens over 65 y-old is now more than 610,000; if we extrapolate from USA where, after fortification, 4% of elderly had high folate and low B12 status, then about 24,000 elderly in NZ may be at increased risk of cognitive impairment due to this vitamin imbalance if mandatory fortification is introduced.

Conclusion

We believe that there are sufficient concerns about possible harm to significant numbers in the population and that these concerns outweigh the benefit of the possible small reduction in NTD pregnancies by fortification. ***Overall, these concerns have increased since our last report and we advise the government to hold back on mandatory fortification***. Instead, we suggest that New Zealand takes an international lead in this matter and attempts to answer the following challenges before they conclude that fortification will benefit the entire country.

Challenges for the immediate future

1. Establish for NZ the annual number of NTDs that occur (including terminations), and then estimate the number of NTDs that may be prevented by mandatory fortification (our analysis on pages 15-16 of the 2012 report suggests between 0 and 6 per year).

2. Determine the blood folate and B12 status in a representative section of the NZ population, but especially in relevant sub-groups that will be at risk
    a. women of fertile age, including those that are vegetarians
    b. the older population
3. Decide the increase in risk of cancer that is acceptable, including sub-groups of cancer, e.g., is 2%, 5%, or 10% acceptable? List actual numbers that may suffer harm.
4. Decide the increase in risk of cognitive impairment in the elderly that is acceptable and/or consider supplying free B12 supplements to all elderly, especially vegetarians.
5. Have a critical debate about whether the numbers that may suffer harm from cancer, cognitive impairment, and the potential long-term effects related to epigenetic changes can be defended in view of the number of NTDs that can possibly be prevented.
6. Consider alternative strategies to folic acid fortification for prevention of NTDs that directly target the group that will benefit, i.e., women during their menstrual life time:
    a. Providing a folate and perhaps B12 supplement (± iron) in feminine hygiene products
    b. Providing free folate and perhaps B12 supplements to all female students, starting at 15 y of age, until they have completed secondary schooling (19 y), to make them aware of the importance of these B vitamins.[b]
    c. Consider the more expensive, but safer, alternative 5-methyltetrahydrofolate rather than folic acid.

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[b] It might be noted here that in Swedish children aged 15, higher intake of folate was related to better academic performance[31].

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Conflict of interest statements can be found in our 2012 report.

david.smith@pharm.ox.ac.uk helga.refsum@medisin.uio.no