

## Submission to the New Zealand Food Safety Authority

Regarding the proposal to amend the New Zealand (Mandatory Fortification of Bread with Folic Acid) Food Standard 2007.

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**With reference to NZFSA Public Discussion Paper no. 10/09** dated 22 July, **we wish to support paragraph 5.2: Amendment to the Commencement date.** Our grounds for this opinion are based upon concerns for **Public Health (Paragraph 6.3)** as follows.

1. We believe that the scientific evidence now available is not sufficient to conclude that the Status Quo Option (Paragraph 5.1) – the immediate introduction of mandatory fortification – is without risk to the health of the New Zealand public as a whole. ***More research is needed to establish whether or not certain sections of the population might be harmed by mandatory fortification with folic acid, a synthetic compound not naturally occurring in the human body.***
2. Our views on this question are described in detail in an article we published in the American Journal of Clinical Nutrition in 2008: *'Is folic acid good for everyone?'* [1] After reviewing the evidence, we concluded at that time: "Nations considering fortification should be cautious and stimulate further research to identify the effects, good and bad, caused by high intake of folic acid from fortified food or dietary supplements. Only then can authorities develop the right strategies for the population as a whole." Since this review was written, further evidence has become available that increases our concerns about possible harmful effects and thus the need for more research. This submission will focus on the newer findings.
3. Mandatory fortification is being introduced in order to reduce the number of neural tube defect (NTD) pregnancies. It is important to realise ***how rare NTD pregnancy is in New Zealand.*** The Final Assessment Report of the Australian and New Zealand FSA [2] estimates (page 228) that there are approximately 72 NTD pregnancies per year in New Zealand. The report (Table 5, page 34) estimates that mandatory fortification will prevent 8 (95% C.I. 4-14) NTD pregnancies per year. The total population is about 4.2 million, so ***for every NTD pregnancy prevented by mandatory fortification 525,000 people will be exposed to extra folic acid in their food.*** Thus, mandatory fortification is being introduced to prevent a rare disease but at the same time exposes the whole population to extra folic acid. Our question is: what will happen to the incidence of common conditions known to be influenced by folate, such as cancer, or vitamin B12 deficiency? Can we be sure that extra folic acid will not increase the

number of people with cancer, or with vitamin B12-related cognitive impairment in the elderly, for example? Before discussing these questions, we will first look at the actual intake of folic acid.

4. Mandatory fortification with folic acid has to be seen in the context of *the overall intake of folates by the population*. The level of mandatory fortification proposed is quite low and, by itself, does not cause us any concern if a normal food pattern is adhered to. However, for some time the voluntary fortification of foods with folic acid has been permitted in New Zealand and folic acid containing supplements are freely available in tablet form. What concerns us is that mandatory fortification increases the baseline intake of folic acid so that any additional intake from these other sources may bring levels in the blood above what is considered safe for certain sectors of the population. Evidence of this comes from countries that have already introduced mandatory fortification. Thus, in the USA after mandatory fortification the highest levels of blood folate were found in children aged  $\leq 5$ y, the next highest in children aged 6-11y and the third highest in elderly aged  $\geq 60$ y.[3] It is likely that this uneven distribution of folate levels was a consequence of dietary habits (high consumption of bread, ready-to-eat voluntarily fortified breakfast cereals) and the consumption of supplements containing folic acid. The outcome is that in the USA 43% of children  $< 5$ y are consuming the equivalent of 780  $\mu\text{g}$  of folic acid each day, more than double what is considered the tolerable upper limit for children of that age (200-300  $\mu\text{g}/\text{day}$ ).[4] Likewise, 38% of elderly are consuming the equivalent of 780  $\mu\text{g}/\text{day}$ . We have already expressed our concern that small children at a crucial stage of their development are exposed to such high levels of folic acid. [1]. Below, we will discuss possible implications for the elderly.

***We conclude that to introduce mandatory fortification now (Paragraph 5.1) might lead to exposure of particular sections of the New Zealand population to high intakes of folic acid. We believe that more research is needed to see whether these intakes are harmful before such a decision is taken. In light of this, would the health authorities be willing to inform the population as a whole about the potential risks related to overconsumption of folic acid i.e., in relation to the introduction to fortification, to advise people not to consume too much folic acid provided in foods and supplements?***

5. Poor vitamin B12 status is common amongst the elderly (over 65y) in New Zealand, with 40% having either overt deficiency or marginal status. [5] These authors concluded: "One in eight older New Zealanders has a deficient serum vitamin B12 concentration and may be at risk of neurological complications." It has long been known that intake of folic acid may exacerbate some of the neurological symptoms of B12 deficiency [6] and there is now evidence from the USA that after mandatory folic acid fortification those elderly with high folate levels and low B12 levels show a five-fold increased risk of cognitive impairment and also of anaemia. [7] In the latter study, 4% of the elderly studied had a combination of high folate and low B12 status. There are some 500,000 people  $> 65$ y old in New Zealand so, if this proportion occurs in New Zealand after mandatory fortification, then ***about 20,000 elderly may be at increased risk of both anaemia and cognitive impairment.***

The effect of high folate status seems to be the consequence of impaired B12 function, as shown by metabolic studies, [8] and was not seen before mandatory fortification. This result has been confirmed in another part of the USA, with the additional finding that people with high folate and low B12 had evidence of impaired ability for blood-borne B12 to be taken up into the tissues. [9] These results raise the possibility that the harmful effect is due to folic acid itself, prior to its conversion to blood folates. Folic acid is the oxidised form of folate and is not normally found in humans. There is also preliminary evidence that, after fortification, folic acid may have deleterious effects on the immune system. [10] ***These results raise the question whether folic acid itself has unsuspected toxic effects and whether it is the appropriate form of folate to be used.*** Clearly, further research is needed.

6. Apart from NTDs, there are ***several common diseases that are either dependent on folate or influenced by folate status, notably cancer, rheumatoid arthritis, psoriasis, and malaria.*** We have discussed the possible impact of fortification on these diseases in our review [1] but will now limit our discussion to cancer, with 19,000 new cases each year in New Zealand. Folate is required for cancer cells to grow and divide and one of the earliest effective anti-cancer drugs was methotrexate, which interferes with folate metabolism. On the other hand, many observational studies in populations suggest that a good folate status protects against cancer. These apparently contradictory findings have led to the idea that folate has a dual effect in cancer, preventing the initiation of cancer but promoting its growth once the cells have become cancerous. [1] Precancerous cells and subclinical cancers are common, notably in the prostate and in the colon, where some 21% of those between 55 and 64y carry polyps. [11] There has been much recent debate about whether the levels of folate involved in mandatory fortification might tip the balance and, in some people, facilitate the growth of cancer. There are three lines of evidence: animal studies (not discussed here: see Kim [12]); population studies; and clinical trials. Recent pertinent reports published since our review will be discussed briefly.

Two studies have been published on cancer incidence in countries after mandatory fortification with folic acid. In the USA and Canada there was an approximately 3% increase in reported colorectal cancer that was almost contemporaneous with the introduction of fortification [13] and in Chile there was an even larger increase in hospital discharges for colon cancer after fortification. [14] These reports have been controversial and are much debated, but it has to be pointed out that they are similar in approach to those reports that describe decreases in the incidence of NTD pregnancies after fortification. If we don't believe in this approach for estimating the effect of fortification, we cannot favour one result (reduction in NTD) over the other result (increase in colorectal cancer).

Three important clinical studies have been reported, in which folic acid was administered either to see if it protected against colorectal cancer or if it reduced the risk of a secondary cardiovascular event.

- (a) The trial: "Folic acid for the prevention of colorectal adenomas: a randomized clinical trial" reported that over a 6-year period of treatment, 1mg folic acid daily was associated with higher risks of having 3 or more adenomas and of non-colorectal cancers, mainly prostate cancer. [15, 16] The association was

not found in the first phase of the trial, lasting 3 years, suggesting that it might be important in such trials to have a long period of exposure.

- (b) Two cardiovascular trials (NORVIT and WENBIT) in Norway have been combined to give a total of 6,837 ischemic heart disease patients and the incidence of cancer followed for 78 months by linkage to the national cancer registry. Both cancer incidence and cancer mortality were higher for the group receiving a combination of folic acid (0.8mg/d) and B12 (0.4 mg/d) than receiving no such treatment: overall, the hazard ratio for cancer incidence was 1.21 [95% C.I. 1.03-1.41; P=0.02] and that for cancer mortality was 1.39 [1.07-1.81; P=0.02]. There was no effect of treatment on cardiovascular disease. The association with increased cancer was largely driven by an increase in lung cancer and was mainly found in those who smoked. [17]
- (c) A meta-analysis based on The B-vitamin Treatment Trialists' Collaboration (set up as a prospective meta-analysis of results from all B-vitamin trials in order to provide more reliable assessments of the effects of B vitamins on CVD and cancer risk) showed no statistically significant effect of folic acid supplementation on cancer risk, but the current data still raise concerns because the overall pattern goes in the direction of increased risk, and the meta-analysis was only powered to detect an overall increase of >10% in cancer and also may be too small to detect risk increases in subgroups.

The latter two results were reported at a conference in June 2009

([www.homocysteine2009.org](http://www.homocysteine2009.org)) and are still subject to peer review. However, the results of the first two studies raise an important point: ***the harmful effects of folic acid may be restricted to subsets of the population with particular characteristics***, such as those who smoke, certain age groups, those having a particular genetic make-up, or those with certain types of cancer. We pointed this out in our review [1] but two other examples have since been reported. An association between plasma folate and breast cancer risk was found only in premenopausal women whose tumours expressed either oestrogen or progesterone receptors. [18] In the Malmö study there was an association between the intake of folate and breast cancer, but the relationship depended upon which combination of two polymorphisms of the enzyme methylenetetrahydrofolate reductase (MTHFR) that the women had. [19] Women who had one combination of polymorphisms showed an increased risk of cancer, while those with the other combination showed a decreased risk. It was notable that the highest risk was found in women with the first combination of alleles who reported taking supplements containing folic acid.

We conclude ***that there is significant evidence to raise concern that the consumption of folic acid could be associated with an increased risk of cancer and that this association may be confined to particular subsets of the population***. Many outstanding research questions are raised by these reports, which is one of the main reasons why we favour Option 5.2. It is noteworthy that many other scientists in this field also have a sense of concern: thus a leading expert, Cornelia Ulrich wrote "Countries that are currently considering mandatory fortification with folic acid (such as Australia and several European countries) may be best advised to defer decisions until more is known about the potential cancer-promoting effects of added folic acid." [20] The European Food Safety Authority (EFSA) held a meeting in January 2009 attended by experts on folic acid from around the world to discuss this issue. The New Zealand authorities are strongly advised to await the publication of the

report of this meeting before taking any decision regarding mandatory fortification.

## 7. Conclusions.

- (a) Although an effect of folic acid fortification on NTDs is likely, ***the fact that only eight NTD cases per year may be prevented compared to the large number of people exposed in the whole population (> 4 million), makes it exceedingly important to document in advance that there are no adverse events related to such exposure.*** For example, a very small increase, say 1%, in cancer incidence would mean 190 additional cases per year; can the likelihood of this be excluded on present evidence?
- (b) Many scientists share our view that ***we do not at present have adequate evidence to prove or disprove whether or not mandatory folic acid fortification will have harmful effects in the context of current voluntary fortification and supplement use.*** We hope that the New Zealand government will give a lead in recognising that more research is needed and will sponsor some of this research so that New Zealanders can look forward to a healthy future.
- (c) For these reasons we strongly support Option 5.2, Amendment to the Commencement date.***

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