Comments on FSANZ Draft Assessment Report: Proposal P295 Consideration of Mandatory Fortification with Folic Acid 31 July 2006

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Congratulations to all at FSANZ for the brilliant work done in preparing the detailed assessment report and accompanying documents, especially the success of the fast track process, in order to enable the implement mandatory folic acid fortification without any further delay. Every single child conceived in Australia and New Zealand is precious, not just to the family, but to the nation as whole. Every single child has the right to be born, and to be born without Neural Tube Defects (NTD), and mandatory fortification leads to reduction of termination of pregnancy due to NTD, and that as many children as possible are born without NTD.

It is appropriate that FSANZ has chosen mandatory fortification as the preferred option because extension of voluntary fortification, without implementation of mandatory, would amount to leaving the management of a public health issue entirely in the hands of the food industry. Mandatory fortification ensures that the benefit of fortification is available to all socioeconomic groups, and to those who do not change their dietary habits in response to public education campaigns.

Other benefits of folic acid to be highlighted in public awareness campaigns

Although the case for mandatory fortification is based on reduction of NTD, it is necessary to highlight other benefits of increased folic acid intakes for the general population, in public awareness campaigns [1,2].

Level of fortification

The level of fortification could be fixed without concern at 280 mcg/100 gm of bread making flour, because of the 30% loss during the baking process and 150 gm of bread made from 100 gm of flour, 100 gm of bread provides approximately 131 mcg of folic acid.

Extension of fortification to include other staple food

Mandatory fortification could be extended, at a later stage, to include staple foods consumed by ethnic groups, which eat little or no bread. In the US, corn grits, cornmeal, farina, rice and macaroni products were fortified as well.

Innovative participation of food industry to fill gaps left by mandatory fortification

The food industry has the opportunity to step into the gaps left by mandatory fortification, and be innovative in providing more folic acid to the target population, thus enhancing the effect of the public health initiative.

Education on prevention of NTD to be part of school curriculum on sex education

The most effective way to ensure that the target population is aware of the role of folic acid in the prevention of NTD is to include it in the school curriculum on sex education. With time, it could then become everyday knowledge, like use of contraceptives to prevent unwanted pregnancy.

Risk Management – exceeding UL

Even though no adverse effects of mandatory fortification has been observed for a decade, in those consuming above the recommended UL levels, in countries like the US, with fortification level 140 mcg/100gm, and the lowest level at which toxicity has been observed is 5 mg/day, it is still advisable to limit consumption of synthetic folic acid above the recommended UL, eg 1 mg/day in the elderly. One mg of synthetic folic acid per day, in addition to a healthy diet, would adequately meet the higher level of the vitamin required for genomic stability, as determined by Fenech [2]. Consumption of folic acid in excess of UL as per current recommendation, in growing children should not however be cause for concern. The German Federal Institute of Risk Assessment recommends limiting the level of folic acid in voluntarily fortified foods consumed by groups likely to exceed UL, as a strategy to manage the risk (personal communication: Dr A Weissenborn and Dr I Lukassowitz) [3].

Risk Management – multiple births

To resolve the concern of multiple births, Boxmeer and colleagues suggest: 'If the problem of multiple pregnancy in IVF is to be properly addressed, opinion leaders need to emphasise that the solution lies in transferring a single embryo, and not in manipulating nutritional supplements. Moreover, generating a "fear of folate" could have detrimental effects on fertility treatment outcomes [5].

Risk Management – drug interaction

FSANZ P295 report points out that drug interaction at doses below 1 mg/day of folic acid is unlikely.

- Clinicians should be aware of folic acid – drug interactions and manage their patients accordingly.
- Any potential risk could be avoided by careful monitoring of treatment using such drugs, by a vigilant clinician.
- It is well known that phenytoin and folic acid has a bidirectional interaction – phenytoin causes folic acid deficiency, and 1 mg of folic acid is routinely given as supplement. Folic acid in turn lowers serum phenytoin.
- In the rare event that seizures should occur with the routine dose, it is possible for the clinician to manage it by raising the level of phenytoin to control it [personal communication: Professor O Toenz].

Risk Management – increased risk of some cancers

At the present time, the fear of increased risk of some cancers is still at the level of hypothesis. Extrapolation of conclusions from animal studies to humans should be interpreted with caution because the aetiology of cancer in a human being is multifactorial [personal communication: Dr M Fenech].

- However, monitoring for any increased incidence of cancer, and steps to ensure that the long term consumption of synthetic folic acid does not exceed 1 mg/day, by reducing the level of folic acid in voluntarily fortified foods, goes a long way in keeping the perceived risk to a minimum.

Risk of masking of B12 deficiency in the elderly

FSANZ Proposal 295 draft assessment report considers masking of B12 deficiency in the elderly possible when intake of folic acid exceeds 1 mg/day. The report prepared by University of Newcastle for FSANZ by Professor Capra et al [6], assessing the risk of masking vitamin B12, concludes that there is no evidence that at intake levels of 1mg of dietary folate equivalents, that masking of B12 will occur.

Macrocytic, megaloblastic anaemia is a common haematological sign to both folic acid and B12 deficiencies. The concept of masking of B12 deficiency, due to folic acid intake higher than 1 mg/day is based on the following assumptions:

- B12 deficiency is always accompanied by megaloblastic anaemia, which is then corrected at folic acid intake above 1 mg/day.
- Megaloblastic anaemia is the only sign to diagnose B12 deficiency.

But:

- *B12 deficiency does not necessarily manifest itself as megaloblastic anaemia.*
- *Megaloblastic anaemia, not B12 deficiency, may be masked, not only in a folic acid replete individual, but also in patients who have concomitant conditions that lead to microcytic anaemia, for eg iron deficiency anaemia, thalassemia, anaemia of chronic disease, haemoglobinopathies.*
- *Folic acid deficiency does not manifest the specific neuropsychiatric symptoms and signs associated with B12 deficiency.*
- *The tests specific to B12 – levels of methylmalonic acid(MMA) and holotranscobalamin II (holoTC II) - are independent of folic acid levels.*

In my response to SACN draft report 'Folate and Disease Prevention'
23 November 2005, posted under Sydney West Area Health Service, Australia
(http://www.sacn.gov.uk/pdfs/health_service_australia.pdf), I pointed out that even if masking of megaloblastic anaemia did occur due to higher levels of folic acid, it was possible to diagnose vitamin B12 deficiency.

Conclusion:

1. When symptoms, signs and tests specific to B12 are used for diagnosis of B12 deficiency, the level of folic acid becomes irrelevant.
2. The term 'masking of B12 deficiency by folic acid' is obsolete. It would be applicable only if B12 deficiency was always marked by megaloblastic anaemia

and it was not just a specific and conclusive sign of B12 deficiency, but also the only one.

Unmasking B12 deficiency

The *guiding maxim* in diagnosing B12 deficiency: *The eye does not see what the mind does not know.*

1. One does not see B12 deficiency if one is not aware that the prevalence is high in the elderly, vegans, and alcoholics and hence does not look for it.
2. There is as yet no gold standard for estimation of B12 deficiency.
3. If one looks for confirmation of B12 deficiency in macrocytic, megaloblastic anaemia, one does not find it, because the haematological sign is absent in many cases.
4. Pernicious anaemia, due to atrophic gastritis type A, with lack of intrinsic factor is present only in a minority of cases. Mild B12 deficiency due to atrophic gastritis type B, with hypochlorhydria/achlorhydria, without lack of intrinsic factor - food cobalamin malabsorption syndrome - is relatively common in the elderly which is easily reversed with low level supplementation.
5. After determining the presence of B12 deficiency, it is necessary to determine the cause of it if necessary and manage it, as all B12 deficiency may not be due to a simple nutritional deficiency. For example, infection with Helicobacter pylori, causing non-atrophic/ leading to atrophic gastritis and B12 deficiency, needs to be treated with antibiotics.
6. Since B12 deficiency takes several years to develop, it is advisable to start occasional screening of patients over the age of 40, along with education about B12 and folic acid deficiency in the elderly.
7. Over the age of 50, folic acid and B12 estimation should become a regular part of investigation.

History: Age, dietary habits – vegans, chronic alcohol consumption, poverty/poor dietary habit induced insufficient intake of B12 containing food, foodfads -, depression, amnesia in the elderly, surgery, eg gastrectomy, drugs, eg long-term use of antacids, metformin, omeprazole etc., neuropsychiatric symptoms, which may be vague, anaemia related manifestation etc.

Physical examination: related to neuropsychiatric signs, eg peripheral neuropathy etc.

Investigation:

Screen for diagnosis, confirm diagnosis, check for possible causes, test for serum anti-intrinsic factor antibodies [7].

1. Peripheral blood film and count – may or not show raised MCV, macrocytosis, hypersegmented neutrophils…
2. Screening: seum and/or RBC folate,serum B12, homocysteine (tHcy).
3. If there is no folic acid deficiency and serum B12 >300 pmol/L, and tHcy <10 micromol/L, then it can be assumed that there is no deficiency.
4. If serum <300 pmol/L and tHcy >10 micromol/L, then further investigation is warranted.

5. Determine holotranscobalamin II (holoTC) level and methylmalonic acid (MMA) for functional B12 deficiency. HoloTC II is the most sensitive, followed by MMA. Both are unreliable when there is kidney impairment [8].High levels of holoTC I and III maybe indicative of liver disease.
6. Test for serum anti-intrinsic factor antibodies. Results not always reliable.
7. If low level oral substitution improves serum levels of B12, then it can be assumed that there is no lack of intrinsic factor.
8. If lack of IF is suspected, proceed with high level >500 mcg, preferably 1 mg.

Golden rule to follow in treatment of B12 deficiency – when in doubt, administer B12, first low dose, and then high dose, if there is no response. B12 is inexpensive and completely safe even at high doses. However high doses meant for lack of IF should be administered only after low dose has been found to be ineffective.

Case for co-fortification with vitamin B12

The successful case for mandatory folic acid fortification was made in 1996. Australia and New Zealand have the opportunity to take advantage of the results of mandatory fortification in other countries which have shown that B12 deficiency in the elderly in the emerging public health issue in a folic acid fortified fortification.

There is a high incidence of mild B12 deficiency in the elderly [9]. Respondents to the SACN draft report 'Folate and Disease Prevention' 23 November 2005, in addition to me who advocated co-fortification with B12 included, Professor J David Spence, Professor Sir John Grimely Evans, Dr Robert Clarke, Professor Godfrey Oakley, Dr Anthony Wright, Dr Paul Finglas and Eddie Vos [10].

- Co-fortification enhances the effect of folic acid fortification, as B12 deficiency leads to 'methyltrap'.
- B12 leads to further reduction in homocysteine by 7%.
- B12 co-fortification would reverse the mild B12 deficiency in the elderly.
- Other vulnerable groups for B12 deficiency – vegans and alcoholics would be helped.
- B12 is inexpensive and completely safe, hence the decision to co-fortify can be made with relative ease.
- The concern about B12 masking in the elderly would no longer be an issue.

Recommended level for B12 co-fortification: 10 mcg/100 gm flour.

Public education about B12 deficiency in the elderly should be started, targeting those above 40 years of age.

Folic acid and B12 estimation should be made routine.

Laboratory diagnostic companies should be encouraged to offer cost-effective B12 kits. Abbot laboratories has already introduced an automated estimation for holoTC II which is cost-effective. Other companies should be encouraged to do the same.

References

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