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PSNZ Submission: The Future of Folic Acid Fortification in New Zealand July 2012

Part 2: Critical Analysis of the Paper:

"An update on folic acid fortification: benefits and risks 2012" A David Smith and Helga Refsum,
Prepared for the New Zealand Baking Industry Research Trust and New Zealand Food and Grocery Council February 2012

This submission has been prepared by Andrew Marshall, Paediatrician, Wellington Hospital, and PSNZ representative on the Folic Acid Working Group, Ministry of Primary Industry, and has been endorsed by PSNZ membership through an e-mail based consultation process.

Summary:

This analysis is to be read in conjunction with the PSNZ submission, Part 1, on the issue of the future of Folic Acid Fortification of Bread in NZ.

The Smith and Refsum report was commissioned by the two most vigorous opponents of mandatory fortification in New Zealand and written by two academics who are internationally recognized as opponents of folic acid fortification. The Baking Industry and the Food and Grocery Council are the two groups that are directly affected by mandatory fortification, through having to comply with adding folic acid to bread. This has minor economic implications for their industry (discussed in Ministry of Primary Industry consultation documents), and is philosophically opposed by those who do not agree that public health initiatives which benefit the whole community should ever impinge on consumer choice and autonomy.

Those who commissioned the report did so to enable them to attack mandatory fortification in New Zealand and they obtained a suitable return on their investment. This report should not be viewed as an objective, scientific article because it has not been peer-reviewed or published. The authors of the report have been highly selective and biased in the findings they present and the conclusions they draw. Intentional bias in selectively interpreting facts depending on whether the facts fit or do not fit their supposition that folate is harmful is apparent throughout the paper, represents a perversion of the scientific method, and is one of many reasons why their report would not be accepted by any peer-reviewed journal.

The most disturbing and irresponsible content is the calculation of 1000 extra cancers. This is based on a very selective and biased extraction of data, plus a set of assumptions, all of which are highly speculative. The result is a fictional number of 1000 that bears no scrutiny to any scientific analysis. There is no quality evidence to back this claim, and quality evidence which demonstrates a decrease in cancer incidence and death in the USA since mandatory fortification was introduced there.

The Paediatric Society of New Zealand strongly supports mandatory fortification of bread with folic acid. This easy and safe public health initiative offers the likelihood of reducing neural tube defects. The science proving effectiveness of mandatory fortification in reducing NTDs is confirmed in all countries where it has been studied (Berry et al 2010). The safety of such an approach has been more controversial, at least to opponents, although scientific consensus was growing and is now established as summarised in the unbiased Ministry of Primary Industry (MPI) report "The Future of Folic Acid Fortification of Bread in New Zealand**"** MPI Discussion Paper No: 2012/02.

The voluntary regime introduced in 2009, with up to a third of breads being fortified with folic acid, has been partially effective. Blood folate levels in the female child-bearing age population in NZ have risen between 2008/2009 and 2011; more than double the number of women had red blood cell folate levels in the optimum range for preventing neural tube birth defects (from 26% to 59% having RBC folate 906 nmol/L or above) (Bradbury et al 2011) However, a voluntary regime is unlikely to deliver the full benefits seen in countries with a mandatory programme.

Commentary on Smith and Refsum Executive Summary:

1. How big is the problem?

The authors state the prevalence of NTD pregnancies is NZ may have reached **7 per 10000**. The authors use data to 2003 and extrapolate in a way that minimises rates. Therefore, the authors' assertion that the rates have likely reached the 7 per 10000 floor, where folic acid may have no further effect, is unlikely to be correct.

Referring to reliable data from MPI, the estimated annual prevalence is likely to be around **13 per 10000**, using figures 2005-2009, and using estimated proportions for terminations compared to live births from 3 Australian registries (as NZ has not collected the relevant termination data).

International research has consistently shown a 41-46% nationwide decrease in neural tube defects following mandatory fortification as noted by the authors (p11).

Voluntary fortification and increase fortified breakfast cereal consumption will have had some impact in reducing NTD rates. However, given 41% of the female child bearing population in the latest MPI commissioned survey had sub-optimal RBC folate, PSNZ calculations suggest a reduction in the incidence to about half the level achievable by mandatory fortification. Within NZ we have disadvantaged ethic populations such as Maori and Polynesian, who are likely to have poorer nutritional status. Voluntary fortification is least likely to impact these women, as do education campaigns about pre-conceptual folate. Mandatory fortification is likely in these disadvantaged populations to show the greatest benefit, in a similar way Smith and Refsum note that the Newfoundland or northern China populations showed the greatest benefit in overseas studies compared to other parts of Canada and China respectively.

2. What impact would folic acid fortification have on the prevalence of NTD?

The authors state that the general folate status of NZ women of child bearing age is very good, and as such fortification may prevent **0 - 6 NTD pregnancies per year**.

This assertion is incorrect. Referring to Bradbury et al. 2011, the latest research with figures from 2008/2009 show that double the number of women had red blood cell folate levels in the optimum range for preventing neural tube birth defects (NTD) (from 26% to 59 % having RBC folate 906 nmol/L or above). While rates have risen, 41% of women in this survey had inadequate folic acid intake and were in the risk group for NTD.

The scientific consensus, summarised by MPI, is that **around 20-30 NTD pregnancies** could be prevented per year if mandatory folate was introduced.

3. Are the other potential benefits of fortification?
a) Population studies
The authors correctly state that there were significant and important decreases in stroke mortality and stroke incidence. They also state there may be positive effects on cardiac birth defects and on myocardial infarction rates, but the data is much less clear than for stroke, and that causal links cannot be assumed. This is correct.

b) Randomised clinical trials
The authors correctly note that the doses of folic acid used in randomised trials are much in excess of those that could be obtained from food after fortification. They also correctly concede that periconceptual consumption of folic acid prevents around 70% of NTD, and may reduce some cardiac malformations. They note evidence as in population studies of a reduction in stoke, but less clear evidence in reducing myocardial infarction risk. They note evidence for positive effects of B vitamins in the elderly in those with high plasma homocysteine levels.

Applying the USA reduction in stroke death rate to NZ (p19), 12900 fewer strokes in a USA population of 314 million equates to 164 fewer stroke deaths in NZ each year following mandatory fortification.

4. Are there harmful effect of fortification?
The authors note the effect of increased anaemia and cognitive decline in the elderly who have high folate and low Vitamin B12. Professor Skeaff in his reports to MPI has indicated the risk in NZ appears very low, and not a single case has been reported due to awareness by GPs of the potential for pernicious anaemia in rest home residents (Skeaff 2012)

The risk in malaria is not relevant in NZ, and PSNZ notes that mandatory fortification has been introduced in 70 countries including a large proportion of malaria endemic countries with no reported problems.

Theoretical risks are posed about unmetabolised folic acid and natural killer cell cytotoxicity, allergy and diabetes, but the authors note there is no solid evidence to back any of these side effects, and attribute this to studies to assess risk “always being rejected by ethical review boards”. This statement is the author’s opinion but evidence to support this claim is not provided. The concept that studies looking to assess risks of treatments are unable to proceed ethically is incorrect. All studies which assess the efficacy of treatments also analyse for side effects of the treatment. Given that red blood cell folate levels of 906 ng/mL are known to protect women from NTD pregnancies to the same degree as pre-conceptual folic acid tablets, there is no absolute ethical barrier to a study which would randomise women with adequate blood folate levels to either receive or not to receive folic acid supplements pre-conceptually, and measure both benefits and potential risks to the fetus.

5. Folate and cancer

The authors state "a recent meta-analysis on 10 trials (38000 people) in which folic acid (0.4-1mg per day) was administered showed an overall 7 % increased risk of new cancers, with a 24% increase in prostate cancer.

The authors fail to mention in the executive summary, although they do in the text (p40) that the most robust meta-analysis, that of Clarke et al 2010, found in 37465 people that folic acid allocation had **no significant effect** on the rate ratios for overall cancer incidence and or cancer mortality. The authors dismiss this finding by saying that the study was underpowered to detect a 5% incidence of cancer, needing 140000 participants.

The authors base their assertion of risk on the meta-analysis of Wien (38233 people). However, it should be noted that while Clarke was published in a leading peer-reviewed journal (Archives of Internal Medicine), Wien et al was rejected by a journal of equal standing (British Medical Journal) due to methodological flaws and was submitted to BMJOpen, which publishes studies of lower quality.

Wien et al conclude that the cancer risk they identified was of borderline significance – it was not clearly statistically significant as reported by Smith and Refsum. Wien et al make the following points:

> "Our analysis differs from Clarke's by being a systematic review, thus including more studies (five more RCTs and seven observational studies) and by including more diverse populations than the seven B-vitamin trials in populations with cardiovascular disease included in the Clarke's study. In two studies included both in Clarke's meta-analysis and in ours, NORVIT and WENBIT, we included data from the combined analysis with longer follow-up time published in 2009[12]; whereas Clarke *et al* only use cancer data from the original papers[13] [14] with a shorter follow-up. When assessing possible harm, a longer follow-up time is beneficial in order to discover more potential cancer cases, as an augmented cancer risk after folic acid intervention may not be confined to a short post-trial time period.
>
> In our sensitivity analyses of the RCTs, the studies with the largest proportions of smokers showed an increased risk of cancer incidence and cancer mortality associated with folic acid supplements. Smoking is a well-known risk factor for many cancers. Furthermore, unlike folate supplements, folate from diet seems to be protective for cancer development.[7]"

In other words, Wien et al acknowledge the study group was much more tightly controlled in Clarke, and the use in Clarke of individual results from all study participants, rather than pooled date in the systematic review of Wien, makes the Clarke finding more powerful. However, in Wien's favour longer follow-up period were available in a subset of cases shared by both studies. Wien notes that the effects seen were likely to be effects of high-dose supplementation, not folate in the diet (as would be present in fortification of bread).

Overall Wien et al are responsible in their interpretation of their own data, whereas Smith and Refsum have an exaggerated and selective interpretation. Of note, when discussing the *benefits* of folic acid Smith and Refsum state "that causal links cannot be assumed" even when associations are present. However, they believe the reverse is true when assessing *risk* of folate – causation can be attributed. This intentional bias in selectively interpreting facts depending on whether the facts fit or do not fit their supposition that folate is harmful is apparent throughout the paper, and is one of many reasons why their report would not be accepted by any peer-reviewed journal.

6. What is the likely overall balance in public health benefit or harm if fortification is introduced?

6.1 Benefits are understated due to bias, and erroneous calculation of numbers of NTD pregnancies (up to 6 rather than the most reliable consensus estimate of 20-30). The authors do note to their credit a reduction of cardiac birth malformations amounting to 20 births per year.

6.2 Harms are grossly overstated due to very significant bias and selective over-interpretation of data, and the most concerning piece of mis-information is the author's calculation "**up to 1000 extra cases of cancer a year may occur**" (in the 10% of the population with very high folate levels), and 300 extra cases of prostate cancer may occur.

This fact is both deliberately highly inflammatory and completely unsupported. I refer to commentary from RJ Berry, recognized world expert from the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, USA

> "The assertion that fortification might cause 1,000 cases of cancer in New Zealand seems highly exaggerated. New Zealand's population is about 4.3 million. The population of the U.S. is about 314 million, which is over 70-times the population of New Zealand. If their assertion were true then fortification in the U.S. should have increased cases of cancer in the U.S. by over 70,000. In 2012 it is estimated that about 1,639,000 men and women will be diagnosed with cancer. An increase of 70,000 would be about a 4% increase overall. However, no data from the U.S. that suggest that any overall increase has occurred since 1998 when fortification was mandated. The authors of this report did not include any reports from the US cancer registry. The tables below are extracted from Kohler, the latest report, which is attached. In Table 1 the annual percent change in incidence for all sites, colorectal men and prostate have been decreasing from 1998 to 2007. Compared with 1998 -2007 cancer incidence might be decreasing at a faster rate in the period 2003-2007 for all sites and prostate cancer.

Table 1 - Surveillance, Epidemiology, and End Results (SEER) cancer incidence rates		
	Average Annual Percent Change	
Cancer site	1998-2007	2003-2007
All sites, both sexes	-0.8*	-1.0*
Colorectal Men	-3.0*	-3.0*
Prostate	-0.9*	-1.1*
*statistically different from zero (two-sided Z test, P < .05)		

> In Table 2 the annual percent change for deaths for all sites, colorectal men and prostate have been decreasing from 1998 to 2007. Compared with 1998 -2007 cancer mortality might be decreasing at a faster rate in the period 2003-2007 for all sites and colorectal cancer in men.

Table 2 - Surveillance, Epidemiology, and End Results (SEER) cancer death rates		
	Average Annual Percent Change	
Cancer site	1998-2007	2003-2007
All sites, both sexes	-1.4*	-1.6*
Colorectal Men	-2.8*	-3.2*
Prostate	-3.7*	-3.3*
*statistically different from zero (two-sided Z test, P < .05)		

Since 1998, there is no evidence of any increase in cancer incidence or deaths for all sites, colorectal cancer in men and prostate. For some cancers the rate of decline is greater in the later period (2003-2007) than for the whole period (1998-2007). See the full tables in Kohler for details for all cancer sites and sex."

Smith and Refsum ignore robust "real" population data from the USA and elsewhere, as it does not support their theory, and instead base their calculation of 1000 extra cancers on a series of assumptions, all of which are questionable, to create a fictional number:
a) Calculations are based on the 7% rate of cancer in people receiving high dose supplementation from Wien et al. The confidence limit calculation crosses 1.0 which means this result is not statistically significant – it can most positively be described as borderline. It is questionable to base any calculation on a result that has a high likelihood of occurring by chance alone, and even more questionable given more robust data from Clarke et al confirmed no statistically increased risk.
b) An assumption is made that data from high-dose supplementation studies can be extrapolated to low dose population exposure through bread fortification. This assumption is false.
c) An assumption that fortification in NZ will shift 10% of the population into serum folate levels of 60mmol/L, based on USA data. This appears highly unlikely. Yeung at al have demonstrated that very high folate concentrations in blood are associated with taking folic acid supplements, not with consuming foods fortified with folic acid.

d) An assumption that levels of 60mmol/L are correlated with increased cancer risk. This assumption comes from two studies in Norway comprising 6837 patients receiving high dose folic acid and Vitamin B12 (Ebbing et al 2009). In this study serum levels of folate rose on average 6-fold. It is implausible that such a huge increase in folate levels would occur through low-dose supplementation in bread. The only cancer type to show an increase in this Norwegian study was lung cancer. However, this has not been replicated in other studies, lung cancers are not cancers any other studies have identified as being a risk in relation to folate, and Smith and Refsum ignore discussion of lung cancer and focus on cancers in general, which was not supported in this Norwegian study.

In summary, the calculation of 1000 extra cancers is based on a very selective and biased extraction of data, plus a set of assumptions, all of which are highly speculative. The result is a fictional number of 1000 that bears no scrutiny to any scientific analysis.

The real number is zero extra cancers.

In fact a small decrease in total cancers is expected, although as referenced in the MPI documentation, this may be partially offset by a non-significant increase in prostate cancer incidence, but not prostate cancer death. Significantly decreased incidence and mortality from stroke is also likely.

It is highly irresponsible of the authors to make such an elaborately but fundamentally flawed hypothesis and present it as "science" in a forum where it can be misinterpreted as based on fact, and where robust data refutes the assumptions and the conclusion.

It is salient to note, that Professor Smith **withdrew** from his clearly stated calculation of "up to 1000 extra cancers per year" when interviewed on TVNZ Q and A programme 8th July 2012. He stated "I don't want to give a figure that will be quoted against me" and said that the number of extra cancers likely per year would be "several hundred" (www.tvnz.co.nz). It appears Professor Smith would prefer such a claim only to be made to the government directly through an industry submission which seeks to determine government policy, but does not want public recognition of his calculation, due to the likely damage to his professional reputation of making such an irresponsible claim and facing peer review from experts.

Throughout the Smith and Refsum paper assumptions are made based on data from high dose supplement studies, not from low dose fortified dietary intake. Such misuse of the data is not supportable. As Smith and Refsum themselves point out, folate deficiency leads to cancer risk. Normal intake of dietary folates has no effect on cancer. The only possible cancer risk of folic acid is through excess intake. The studies assessing cancer risk are exclusively in populations exposed to high-dose supplementation.

Godfrey P. Oakley, Research Professor of Epidemiology and Director of the Center for Spina Bifida Research, Prevention and Policy, Rollins School of Public Health of Emory University USA notes that

> "Dr. R. J. Berry and his colleagues at CDC have shown that mandatory folic acid fortification provided most Americans about 135 micrograms of folic acid a day. (Yang Q, Cogswell ME, Hamner HC, et al. Folic acid source, usual intake, and folate and vitamin B-12 status in US adults: National Health and Nutrition Examination Survey (NHANES) 2003–2006. *The American Journal of Clinical Nutrition.* 2010;91(1):64-72.) This additional folic acid is less than the recommended daily allowance. Thus, not only does this dose prevent the vast majority of folic acid preventable spina bifida, but also it does so at a dose that is perfectly safe. I have seen the (Smith and Refsum) report sponsored by industry concluding that mandatory folic acid fortification will cause harm in New Zealand. The dose that results from mandatory folic acid fortification -- less than the daily recommended allowance -- means that no rational, unbiased review of the data would conclude that folic acid was harmful to any one. The industry report is biased and simply wrong and should be ignored by policy makers".

Conclusion:

The conclusions in the Smith and Refsum executive summary are erroneous, and the benefits of fortification are deliberately understated. The conclusion that mandatory fortification risks outweigh benefits is the conclusion expected given this report was commissioned by, and written by, opponents of mandatory fortification. However this conclusion is not able to be supported, due to the author's considerable selective bias in extracting and interpreting data, nor by overwhelming consensus scientific opinion pointing to safety and efficacy.

An unbiased summary which accurately represents the true risks and benefits of fortification is found in "The Future of Folic Acid Fortification of Bread in New Zealand**"** MPI Discussion Paper No: 2012/02.

The U. S. Center for Disease Control and Prevention in Atlanta recently declared that mandatory folic acid fortification in the United States was one of the ten most important achievements in public health in the last decade. No child in the world should have a lifetime affected by folic acid-preventable spina bifida. This is especially true in New Zealand, where there are the resources to implement mandatory folic acid fortification.

Professor Sir Nicholas Wald, Professor of Environmental and Preventative Medicine at the Wolfson Institute of Preventative Medicine at Barts & The London, Queen Mary's School of Medicine, notes:

> "To be able to prevent fatal and disabling birth defects is a major public health benefit. To fail to do so when the means of prevention is simple, inexpensive and safe is a failure in public duty. Our elected representatives are charged with the responsibility for public health.
>
> In 1991 it became clear that neural tube defects were due to a lack of the B vitamin folic acid, and that sufficient folic acid immediately before pregnancy can prevent about three-quarters of all neural tube defects. Encouraging women to take folic acid supplements prior to pregnancy has had limited success, because many women are not aware of this and many pregnancies are unexpected. Also voluntary fortification of a staple food such as flour with folic acid has had only limited success because most millers are reluctant to fortify flour with folic acid unless there is a legal requirement to do so. Countries that have introduced mandatory folic acid fortification of flour or other grain products (61 countries have done so) have seen a reduction in the birth rate of neural tube defects without any indication that this has caused harm, public disquiet, or political resistance.
>
> The question of safety is always an issue in any public health measure. This needs to be considered in relation to the harm done by not fortifying and failing to prevent these birth defects. The failure to act when benefit could arise is itself a harm. This harm is real, and quantifiable. It is not uncertain or in any way speculative. Against this there is no evidence that fortification of flour with folic acid will lead to any harm. Each possibility that has been raised, ranging from colon cancer, breast cancer, an increase in the rate of twins, miscarriage and cognitive impairment among the elderly has been found to have no evidential basis. Much is written on possible harms but it is all based on supposition and speculation. At best the expectation of harm from folic acid fortification is nil, and the possibility of any harm remote.
>
> Of all the public health interventions I know of, there are few that are as simple, safe and effective and would prevent so much distress to the individuals affected with the preventable disorder, their families, and the wider community involved in providing the necessary care and support.
>
> Of particular public health importance is that mandatory fortification ensures that the entire population is covered by a safety net without individuals needing to take any special action or even knowing that the community at large has instituted measures to improve health. Such action is surely the mark of a civilized society.
>
> I have no hesitation in recommending that New Zealand should institute mandatory fortification of flour with folic acid for the prevention of neural tube defects."

Sir Nicholas is recognised as the UK authority on mandatory fortification of flour with folic acid and a world leader in promoting the science and research associated with promoting folic acid fortification as a means of preventing NTDs worldwide.

Appendix:
Commentary on subsidiary points:

Considering other information from the Smith and Refsum paper, not covered in the executive summary above, I refer to page numbers for reference:

p9: The authors seek to distinguish folic acid from folate, stating the former should be considered as a drug and the later as a natural vitamin. The argument is spurious as folic acid is converted to folate in the human body, and the health benefits and potential health risks associated with this natural vitamin are considered in research as folate (either serum folate or the more reliable red blood cell folate). However, the point is made to support the industry position as stated in the media in 2009 (www.tvnz.co.nz) that fortification with folic acid amounts to "mass medication". Most consumers buy products with a great many artificial additives and preservatives which are not known to have any beneficial effect on health, unlike folic acid which is known to be beneficial to health.

p10: PSNZ agrees with the authors it is regrettable we do not have termination data from 2003 onwards. In MPI calculations, proportion of NTD terminations to live and stillbirths is estimated from 3 Australian states with robust data collection.

p15: Calculations using the Wald model are no longer considered accurate, and the relationship between mg folic acid ingested and ng/mL increase in serum folate are not linear as the model proposes (Professor Skeaff – personal correspondence). Professor Skeaff can more properly critique the calculations made, however it is clear that the calculated 9% reduction using this method is incorrect. Refer to "The Future of Folic Acid Fortification of Bread in New Zealand**"** MPI Discussion Paper No: 2012/02, for accurate calculations of likely reduction in NTD pregnancies expected with mandatory fortification.

p48-9: Smith and Refsum report concerns that fortification may cause some individuals to have too much folic acid in their serum. He refers to levels Smith has defined as Tolerable Upper Levels (TUL). He references TULs to a letter which he wrote to the American Journal of Clinical Nutrition, which mentions concerns about the lack of knowledge of safe levels in children, but does not mention TUL and does not reference how he came up with his TUL reference ranges. Tolerable Upper Levels for vitamins are published, for instance by the Food and Nutrition Board, Institute of Medicine, National Academies (www.nap.edu) and suggest for children 1-3 years the TUL for folic acid is 300 µg/day and for children 4-8 is 400 µg/day. However the evidence to support these TUL is weak.

p57: In UK, The British Medical Association has endorsed, by a large majority, the call for the governments in Westminster, Edinburgh, Cardiff and Belfast to legislate "to make it a requirement for folic acid supplements to be in flour and flour-based products". The Food Standards Agency and the Scientific Advisory Committee on Nutrition, a group of independent experts that advises ministers, already support the move (telegraph.co.uk).

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"MPI" refers to "The Future of Folic Acid Fortification of Bread in New Zealand" MPI Discussion Paper No: 2012/02

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