Ministry for Primary Industries
Manatū Ahu Matua

Scientific evaluation of comments on submissions received on the future of folic acid fortification in New Zealand

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1 Executive summary

Ministry for Primary Industries (MPI) has undertaken consultation on the future of the Standard on fortifying bread with folic acid in New Zealand. As part of this process, the Science and Risk Assessment Directorate of MPI has undertaken an evaluation of selected scientific issues raised in submissions.

1.1 NEURAL TUBE DEFECT PREVALENCE AND POTENTIAL IMPACT OF FORTIFICATION

Data on neural tube defects (NTDs) are collated by the New Zealand Birth Defects Registry (NZBDR). Data on NTDs occurring in births beyond 20 weeks' gestation (either live births and stillbirths) are available only until 2009; the prevalence of NTDs for the years 2005-2009 was 5.3 NTD-affected births per 10,000 live or stillbirths. Robust data on NTD-affected pregnancies ending in termination before 20 weeks' gestation are not available, but can be estimated based on data collated by birth defect registries in Australia. Using these estimates suggests that the prevalence of NTD-affected pregnancies for the period 2005-2009 may have been 12.9 per 10,000 live or stillbirths.

A stochastic model was used to estimate the changes in serum folate and NTD prevalence that might occur as a result of mandatory fortification of sliced bread at a level of 80-180 µg per 100 g bread. Mean serum folate levels were predicted to increase by 26% in women of childbearing age, reducing the rate of NTD-affected pregnancies to 10.2 per 10,000 (mean reduction of 17 NTD-affected pregnancies from 2005-2009 rates; 95% confidence interval 14-20).

1.2 CANCER RISK

The effect of folic acid on cancer incidence has been addressed in a systematic review conducted by MPI. The review assessed all pertinent studies published between 2007 and February 2012, and updated in this document. In general, the results report that folic acid has no significant effect on overall cancer incidence. In 2009 colorectal cancer and prostate cancer were specifically identified as potentially affected by folic acid. Since 2009 new data have shown that the risk of prostate cancer is much less than originally thought. The evidence does not suggest that there is an increased or decreased risk of colorectal cancer in the general population or in the recurrence of colorectal adenomas but remains inconclusive with regards to the risk of advanced adenomas in high risk individuals consuming high dose folic acid containing supplements. There is also some evidence of a protective effect for breast cancer. It is noteworthy that all these trials used supplements with concentrations of folic acid that would have caused higher daily folic acid intakes than would occur with fortified bread.

1.3 VITAMIN B_{12} MASKING AND COGNITIVE IMPAIRMENT

Masking of B_{12} deficiency and cognitive decline in the elderly have been raised as possible negative effects of folic acid fortification. Masking of vitamin B_{12} deficiency is considered negligible in current medical practice in NZ as diagnostic testing of B_{12} insufficiency is routine practice in the elderly. One study has reported poorer cognitive function among elderly with concurrent vitamin B_{12} deficiency and elevated blood folate; this was a cross-sectional study so cannot provide causal inference, findings from this study have not been replicated elsewhere and may be due to the small size and unusual characteristics of the population group with this combination of B_{12} and folate levels. Data pooled from multiple prospective studies designed to control for confounding have not supported suggestions that folic acid supplementation has either a positive or negative effect on cognition in the elderly.

1.4 ASTHMA

Several studies reported in 2008 and 2009 raised the possibility that folic acid supplement usage by mothers during their pregnancies increased the risk of asthma symptoms among their resulting children. More recent data collected with more robust study designs have not supported these suggestions.

1.5 STROKE

Some submissions raised the prospect that folic acid fortification of the food supply may reduce the risk of stroke. A recent study that has combined data from several randomized-controlled trials provides support for this suggestion.

1.6 CHILDHOOD CANCERS

Two longitudinal observational studies in populations with folic acid-fortified food supplies have suggested that reductions have occurred in the incidence of some childhood cancers following introduction of fortification. These studies have not included contemporary control groups so must be interpreted with caution, however they provide some reassurance that universal flour fortification at least does not heighten the risk of paediatric cancer.

2 NTD rates and potential impact of fortification

Data on the incidence of NTD-affected pregnancies are available from the New Zealand Birth Defects Registry (NZBDR) and presented in the Voluntary folic acid fortification monitoring and evaluation report (MPI 2012). The most recent data available on the NTD rate of live and still births in NZ is 2009. From 2001-2008 the average rate of live births and fetal deaths with a NTD was 5.4 per 10000 births. Taking into account the 2009 data on NTDs, the average rate for the period 2005-2009 has decreased to 5.3 per 10000 births.

It is important to also consider the rate of NTD-affected pregnancies that result in a termination to determine the overall rate in NZ. However, complete data on terminations is not available in New Zealand. It was assumed that NZ had similar NTD-affected pregnancies outcome proportions (live birth, fetal death, termination of pregnancy) as Australia. Therefore the proportion of terminations of all NTD affected pregnancies from a complete dataset from three Australian States (AIHW 2011) was considered appropriate to apply to estimate NZ terminations. Advice from the co-ordinator of the NZBDR confirmed that this was a reasonable assumption (personal communication, B. Borman). Taking into account an estimate of NTD-affected pregnancies resulting in terminations of pregnancy; the average incidence rate of NTD affected pregnancies for the period 2005-2009 is 12.9 per 10000 births. This is approximately 80 NTD affected pregnancies (33 live births and fetal deaths, 47 terminations) (Table 1).

Table 1: Neural tube defect affected pregnancies in New Zealand between 2005-2009

Year	Live births	Foetal deaths* (stillbirths)	Termin-ations‡	Total live and stillbirths	Total live births and stillbirths		Total live births, stillbirths and terminations‡	
	Number	*Number*	*Number*	*Number*	*Number*	*Rate*†	*Number*	*Rate*†
2005	22	19	59‡	58105	41	7.1	100‡	17.2
2006	20	18	55‡	59563	38	6.4	93‡	15.6
2007	15	15	43‡	64503	30	4.7	73‡	11.3
2008	23	11	49‡	64850	34	5.2	83‡	12.8
2009	13	9	32‡	62907	22	3.5	54‡	8.6
2005 - 2009	93	72	238‡	309928	165	5.3	403‡	12.9

Notes:

* Defined as foetal deaths of 20 weeks' or more gestation, or 400g or more birth weight

† Prevalence rates are per 10000 live births and foetal deaths

‡ Estimated number of terminations calculated based on the NTD outcome proportion published in the AIHW 2009 report "Mandatory folic acid and iodine fortification in Australia and New Zealand: Baseline report for monitoring."

Source: New Zealand Birth Defects Registry. Data extracted on 13 February 2012 by Associate Professor Barry Borman, Centre for Public Health Research (Massey University, Wellington, NZ). Data presented at Folic Acid Working Group meeting 16 February 2012.

2.1 FINDINGS FROM MODELING

A stochastic model has been used to predict the changes in serum folate and NTD prevalence that might occur following introduction of mandatory fortification of bread with folic acid. A full account of the methods and results from this modeling study can be found in the MPI report Modelling health benefits of mandatory folic acid fortification. Summary outcomes are as follows.

Based on the results of the modeling study mandatory fortification of sliced bread under the 2007 *New Zealand Mandatory Fortification of Bread with Folic Acid Food Standard* would

result in an average (95% CI) increase in folic acid intake in women of childbearing age of 79.6 (24.9, 213.8) µg per day if fortified between 80 – 180 µg per 100 g of sliced bread. Under mandatory fortification, mean serum folate levels would increase by 26% in women of childbearing age. The increase in serum folate in the population corresponded to a mean reduction (95% CI) of 17 (14, 20) NTD affected pregnancies from 2005-2009 rates. It is estimated that mandatory fortification of sliced bread could reduce the rate of NTD affected pregnancies to 10.2 per 10,000.

Folic acid fortification at 80 – 180 µg per 100 g of 50% of bread consumed by women of childbearing age would result in a mean (95% CI) reduction of five (3, 8) NTD-affected pregnancies per year. This corresponds to a total of 75 NTD affected pregnancies and an average rate of 12.1 NTD affected pregnancies per 10,000. This is a reduction from the 2005-09 baseline NTD incident rate of 12.9 per 10,000 NTD affected pregnancies per year. Whereas, if 50% of the bread consumed by the target population is fortified at 200 µg per 100 g of bread, it is estimated to have mean (95% CI) reduction of 11 (9, 13) NTD-affected pregnancies. This equates to a reduction in the rate of NTD-affected pregnancies to 11.1 per 10,000 births a year.

It is likely that the 2010-2012 incident rate of NTD affected pregnancies has decreased from the 2005-09 rate modelled in this report, but it is uncertain by how much. MPI has been informed that 12.5% of the sliced bread volume for sale in NZ is fortified with folic acid. Analytical data has found that the median (interquartile range) of folic acid detected in bread during this time period was 144 (41, 189) µg per 100 g of bread.(8) Using this model it was estimated that if 12.5% of the bread consumed by the target group was fortified between 80-180 µg per 100 g of bread then between zero and two NTD-affected pregnancies could have been prevented.

3 Total cancer incidence

Some submissions referred to the hypothesis that folate/folic acid might have a dual role in the development of cancer. The hypothesis proposes that folate deficiency promotes transformation of normal cells into pre-neoplastic cells and supplementation to achieve normal folate status would protect against this. Further, the hypothesis proposes that high folate status from supra-physiological doses of folic acid may enhance the development and progression of pre-existing pre-neoplastic cells (Kim, 2004). One implication of this hypothesis is that a population with widespread low/deficient status would be at particular risk if intakes of high doses of folic acid occurred quickly, assuming that the hypothesis is correct. The author of this hypothesis stated in this paper in 2004 that long-term follow-up studies were required to test the hypothesis. Since this time the results of numerous long-term follow-up studies have been published.

MPI previously committed to assessing this hypothesis with the most up-to date evidence in the systematic review published in the 'Voluntary folic acid fortification monitoring and evaluation report' (MPI 2012). This has been updated to take into account new evidence published since Feb 2012. Many submissions highlight specific individual RCTs as evidence of risk; however there is variation between trials. MPI has reviewed all literature in the area and takes all RCTs and meta-analyses into account in assessing risk. It is important that the totality of evidence is reviewed when conducting risk assessments.

In general, the results of RCTs and meta-analyses of the RCTs report that folic acid has no significant effect on overall cancer incidence. Results from the eight large RCTs published since 2006 have generally reported either no effect in the incidence of cancer with folic acid supplementation (Logan, 2008; SEARCH 2010; Zhang 2012; Hankey 2012), with only one study reporting a slight significant increase in incidence on non-colorectal cancer with folic acid supplementation (Cole, 2007).

The most thorough analysis of the randomised trials that has been conducted to date is that of the B-Vitamin Treatment Trialists' Collaboration (Clarke, 2010). The group conducted an individual participant data meta-analysis which included seven large RCTs, involving a total of 35603 individuals. Trials were limited to supplementation of B vitamins for the prevention of vascular disease, and were double blinded RCTs, recruiting a minimum of 1000 participants for a minimum of one year follow-up. The results of this meta-analysis found there to be no significant differences in the incidence of cancer overall (RR 1.05, 95% CI: 0.98-1.13; $p = 0.14$) or in any pre-specified sub-groups including fortified and non fortified populations.

More recently the Norwegian Knowledge Centre for the Health Services released a report in which they examined all trials using folic acid and reporting cancer outcomes, irrespective of size or purpose. This report was published in full (Pike, 2011) and in summary form (Wien, 2012). The full version is in Norwegian, but the forest plots were produced with RevMan in English, Wien summarises their methods and is published in English in a peer reviewed online scientific journal. The results of this meta-analysis (RR 1.07; 95% CI: 1.00, 1.14) (Pike, 2011; Wien, 2012) were very similar to those found in the individual participant data meta-analysis of the B Vitamin Trialists' Collaboration (2010) (RR 1.05; 95% CI: 0.98, 1.13) (Clarke, 2010).

Neither meta-analysis has included the results of the recently published VITATOPS trial. This trial of more than 8000 people was conducted in 20 countries, including New Zealand

(Hankey et al, 2012). In the VITATOPs trial a non-significant decrease in the incidence of total cancer in the folic acid supplemented group was found (RR 0.86; 95% CI: 0.66, 1.14). MPI has added the data from the VITATOPS trial to the graphs produced by the Norwegian Knowledge Centre for the Health Services (Pike, 2011). The incidence of total cancer, colorectal, breast, lung and prostate cancers was lower in the group that received folic acid than the control group. Consequently, adding these data to the meta-analyses produced by others would decrease the overall estimate previously reported (Table 2, Figure 1). Figure 1 below shows that there is no increase or decrease in overall cancer across the human trials. Adding the newer data from the VITATOPs study would lower the relative risk of 1.07. The totality of evidence does not indicate that folic acid affects overall cancer incidence. The quantity of folic acid used in these studies ranged from 0.4mg to 5mg, with the most frequent doses being 2-2.5mg which is about 20 times higher than the amounts of folic acid which would be obtained from bread under mandatory fortification.

Table 2: Results of the relative risk of total and sub-type cancer incidence in two meta-analyses and the latest results from the VITATOPs study - a large multi-country RCT

	Summary RR (95% CI) reported in			Impact of Vitatops result on meta-analysis
	B vitamin trialists' meta-analysis (Clarke, 2010)	Wein et al meta-analysis(2012)	VITATOPS (Hankey 2012)	
Total death	1.02 (0.97-1.08)	-	0.97 (0.87-1.07)	decrease
Total cancer incidence	1.05 (0.98-1.08)	1.07 (1.00-1.04)	0.86 (0.66-1.14)	decrease
Colorectal cancer incidence	-	1.00 (0.83-1.21)	0.98 (0.44-2.18)	decrease
Breast cancer incidence	-	0.86 (0.64-1.14)	0.58 (0.21-1.62)	decrease
Lung cancer incidence	-	1.11 (0.92-1.33)	0.92 (0.48-1.80)	decrease
Prostate cancer incidence	-	1.24 (1.03-1.49)	0.63 (0.28-1.44)	decrease

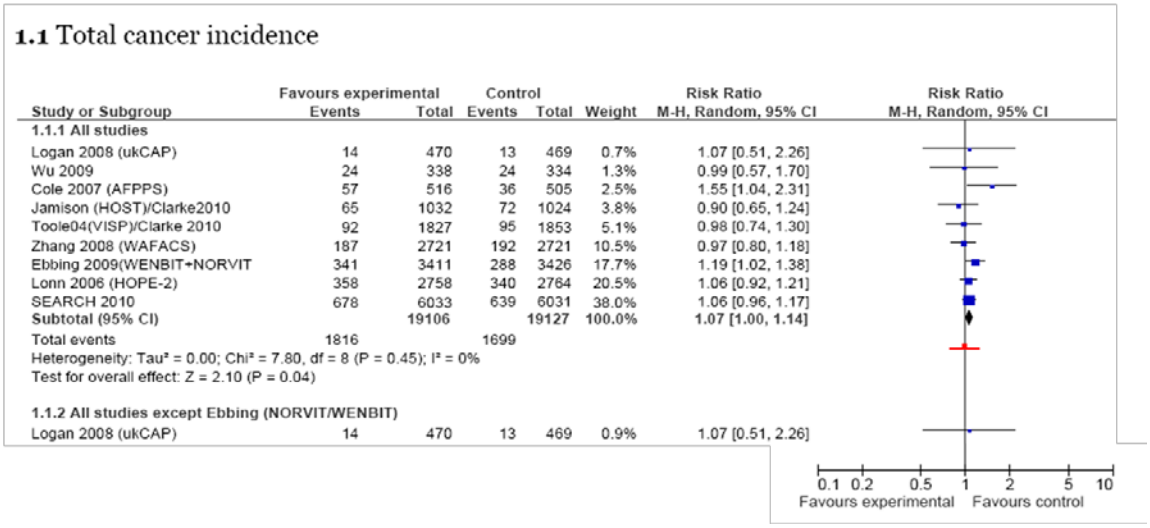
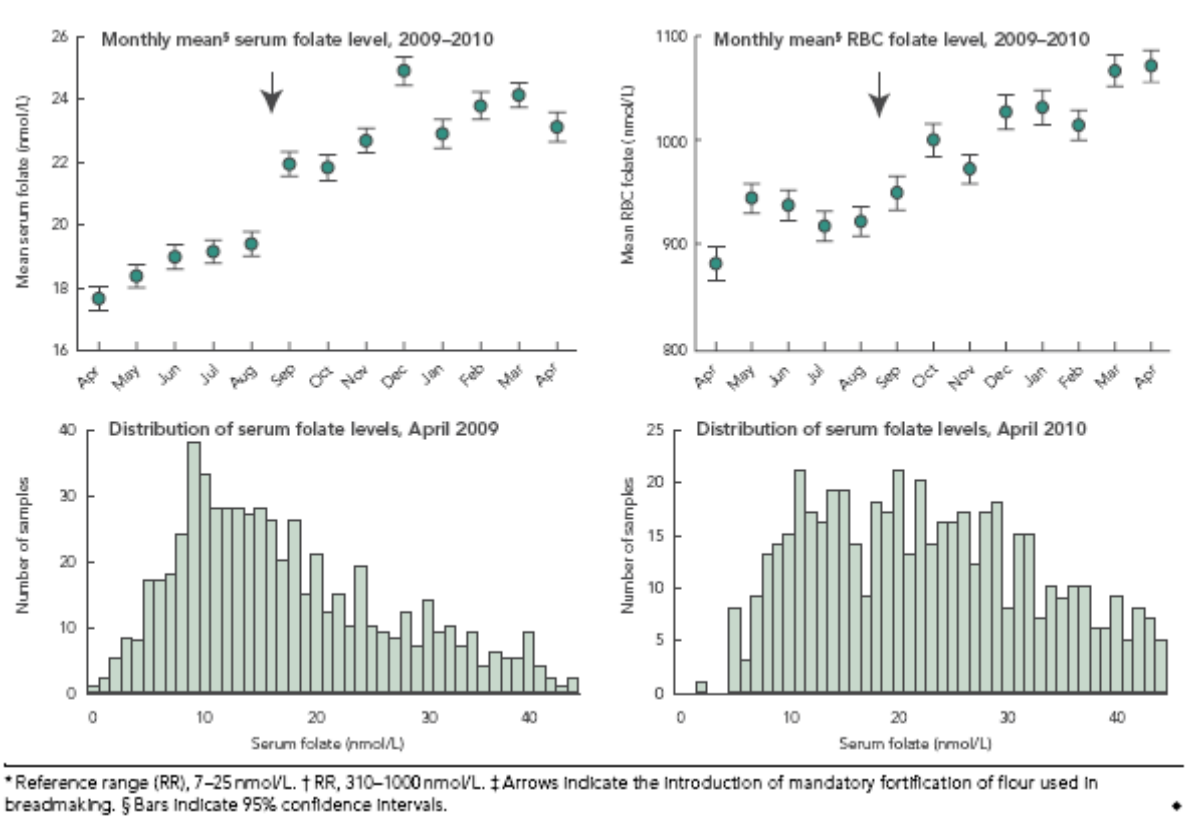


Figure 1: Forest plot of total cancer incidence from **the** Norwegian Knowledge Centre for the Health Services (Pike, 2011; Wien, 2012) with the results from Hankey et al (2012) added in red

Some submissions have hypothesised that there may be an increased risk of total cancer incidence in people with a TT polymorphism for the gene for MTHFR. This is a common

polymorphism of the gene for the enzyme that uses folate to metabolise homocysteine. Individuals with the TT genotype have a less efficient MTHFR enzyme and consequently are not able to metabolise homocysteine, resulting in higher homocysteine levels. Recently a study genotyping a nationally representative prospective cohort of the US adult population prior to the introduction of mandatory fortification has been published (Yang 2012). The association between the MTHFR genotypes and all cause mortality was assessed in 6000 US adults followed up for between 12 – 15 years. Findings from this cohort were that there was no association between MTHFR variants and all-cause mortality, cancer mortality, CVD mortality or stroke mortality. Furthermore, there is evidence that there may be publication bias in studies assessing MTHFR variants and health outcomes (Clarke 2012). In a recent meta-analysis there was found to be a significant effect found only in published studies assessing the association between TT genotype and CVD mortality, compared to a null effect in unpublished studies (Clarke 2012) thus the hypothesis that TT genotypes have different health outcomes is much weaker than previously thought.

One submitter proposed that the studies reported in Ebbing et al (2009) which used doses of 0.8 mg/day (shown in Figure 1) were especially important as they showed that serum folate values above 60 nmol/L were related to increased mortality. The submitter proposed that it was likely that more than 10% of the New Zealand population would achieve this level of serum folate if folic acid fortification were introduced. Figure 2 shows serum folate values reported from a pathology laboratory in Australia during the period in the period leading up to the enforcement date for mandatory folic acid fortification in Australia. The lower values would reflect the situation under voluntary fortification in Australia and similar values would be expected in New Zealand for the time period owing to the common food regulations and trans-Tasman trade. There is a clear jump in September 2009 in line with the enforcement date of mandatory folic acid fortification in September 2009. The lower right-hand figure shows that few samples exceeded values of 40nmol/L after mandatory fortification in Australia.



*Reference range (RR), 7–25 nmol/L. † RR, 310–1000 nmol/L. ‡ Arrows indicate the introduction of mandatory fortification of flour used in breadmaking. § Bars indicate 95% confidence intervals.

Figure 2: Trends in serum folate* levels for samples analysed in one Australian diagnostic pathology laboratory before and after the enforcement date for mandatory folic acid fortification of wheat flour for bread making in September 2009 (Brown et al, 2011)

4 Colorectal cancer

The totality of evidence published to date does not indicate that there is an increased risk of colorectal cancer with folic acid intake in the general population. All RCTs published from 2007 onward report a non-significant reduced risk of colorectal cancer incidence with folic acid (Cole, 2007; Logan, 2008; Search 2010; Zhang, 2008; Wu, 2009) only one RCT was published before 2007 and reported a non-significant increase in colorectal cancer incidence (Bønaa, 2006). One RCT has been published since the MPI systematic review was conducted (Hankey, 2012). After a median follow-up duration of 3.4 years no significant difference in the incidence of colorectal cancer between the intervention and control group was found (Hazard ratio: 0.98 (95% CI: 0.41, 2.33).

Of the meta-analyses published, those assessing the results of RCTs have found no significant effect of folic acid supplementation on colorectal cancer incidence (Ebbing, 2009; Clarke 2010; Carroll 2010; Figuerido 2011; Wein 2012). Investigators who have performed meta and pooled analyses of cohort studies with up to 20 years of follow-up duration report a reduced risk of colorectal cancer with either higher dietary folate intakes or total folate including folic acid supplements (Wein, 2012; Pike, 2011; Kennedy, 2010; Kim 2010).

Some submitters have expressed concern that folic acid fortification may increase the risk of colorectal cancer based on the article by Mason (2007). Mason (2007) had proposed that time trend data from the US and Canada indicated that colorectal cancer increased when fortification was introduced. Their graph showed an upturn within one year of introducing mandatory fortification in addition to the pre-existing voluntary fortification. If this were a true reflection of the latency period of colorectal cancer following an increase in folic acid consumption, then the randomised controlled trials conducted would have been able to find the effect as their follow-up durations ranged between 3 and 8 years. Furthermore, the recent evidence from a cohort study conducted in the US of half a million participants that after 8.5 years of post-fortification follow-up those in the highest quintile of intake had no increased risk in colorectal cancer incidence, in fact a protective effect was found (Gibson 2011).

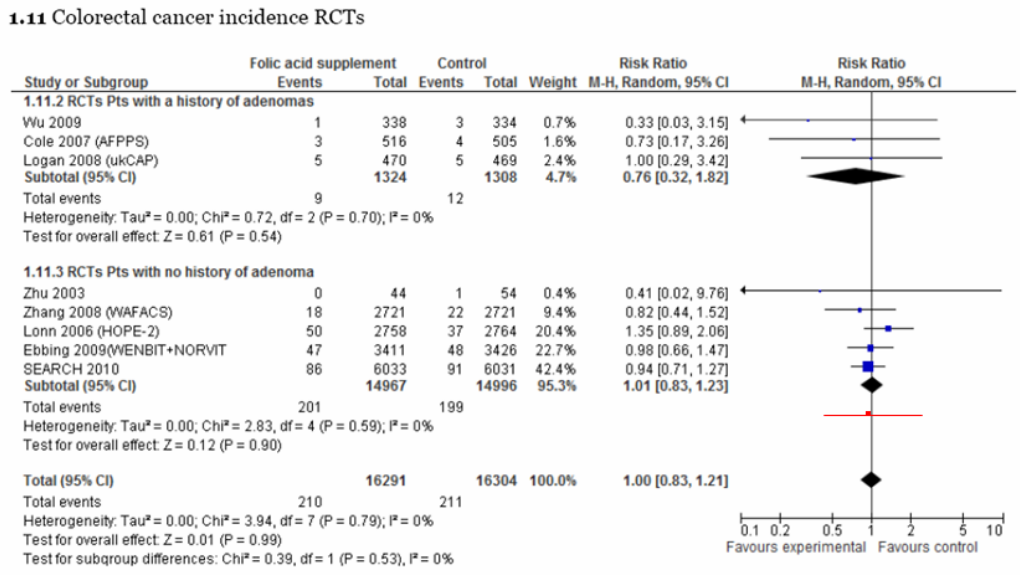


Figure 3: Forest plot of colorectal cancer incidence from **the** Norwegian Knowledge Centre for the Health Services (Pike, 2011; Wien, 2012) with the results from Hankey et al (2012) added in red

5 Recurrence of colorectal adenomas

Referring to the systematic review conducted by MPI, the evidence to date suggests that folic acid supplementation has a null effect on the recurrence of colorectal adenomas. However, it remains uncertain as to whether supplementation beyond three years increases the risk of advanced adenomas. MPI agrees with the position statement of the Cancer society (NZ) which recommends "that people with existing bowel adenomas and those with an increased risk of developing bowel adenomas should avoid taking nutritional supplements that contain high dose (greater than 1mg (1000μg) per day) folic acid." (Cancer Society 2010). The amount of folic acid that is likely to be consumed through fortification is much lower, even in high consumers in the population. In the initial dietary assessment conducted by FSANZ it was estimated that under mandatory fortification in New Zealand folic acid intake would increase by approximately 0.2 mg at the 95th percentile of the population aged 15 years and above, resulting in a total intake of folic acid of approximately 0.4 mg per day. This is well below the amounts that were consumed in the folic acid supplementation trials.

To summarise, the totality of evidence does not suggest that there is an increased risk of colorectal cancer in the general population or in the recurrence of colorectal adenomas. However, the evidence remains inconclusive with regards to the risk of advanced adenomas in high risk individuals when consuming daily supplements of greater than 1 mg of folic acid per day. As previously mentioned, the amount of folic acid that would be consumed under fortification of bread is much less than has been consumed in the supplementation trials.

6 Prostate cancer

Concerns that folic acid supplementation may increase the risk of prostate cancer arose after the publication of the Aspirin Folate Polyp Prevention Study (AFPPS) in which the increase in cancer incidence was primarily attributed to the increase in prostate cancer in the treatment group (Cole 2007). Secondary analysis of the trial revealed that the treatment group were 2.58 times more likely to develop prostate cancer than the placebo (95% CI: 1.14, 5.86; $p = 0.02$) (Figueirido 2009). However, the authors noted that the results may in fact be due to chance due to the small number of cases over the follow-up period (33 cases) (Figueiredo 2009). Since 2009, the results of several larger trials have been published and have shown that the risk of prostate cancer is much lower (Wu, 2009; SEARCH 2010; Ebbing 2009; Hankey, 2012). Of these trials, one has reported a small non-significant decrease in risk (Wu, 2009), one a 42% non-significant decrease in risk (Hankey, 2012) and two papers have reported a non-significant increase of around 20% in the treatment groups. (SEARCH 2010; Ebbing 2009) A meta-analysis of these trials, published prior to the VITATOPS trial (Hankey, 2012) reports a borderline significant effect of folic acid supplementation on prostate cancer incidence (RR 1.24; 95%CI: 1.03, 1.49) (Pike, 2011; Wien, 2012). Inclusion of the results from the recently published VITATOPs trial (Hankey, 2012) which found a substantial reduction in risk, although non-significant, would reduce the relative risk of 1.24 reported in the meta-analysis published by the Norwegian Knowledge Centre for the Health Services (Pike, 2011; Wien, 2012).

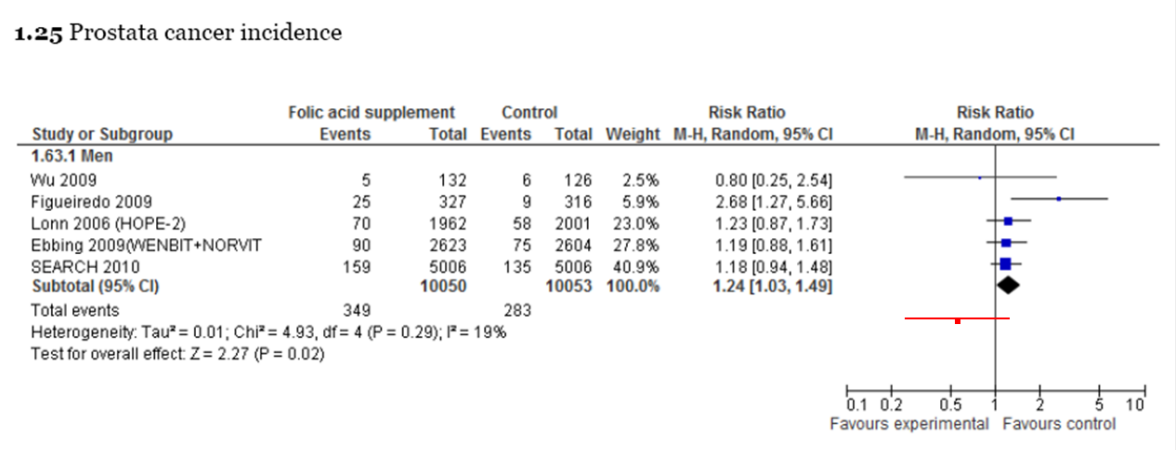


Figure 4: Forest plot of prostate cancer incidence from **the** Norwegian Knowledge Centre for the Health Services (Pike, 2011; Wien, 2012) with results from Hankey et al (2012) added in red

To summarise, the results of several larger trials have demonstrated that the risk of prostate cancer is much lower than previously thought. The meta-analysis including data published until 2011 is suggestive of a small increase in risk, of borderline significance. However, inclusion of the latest trial (Hankey et al, 2012) which found a substantial reduction in risk of prostate cancer will to reduce this risk further. The collaborative individual participant data meta-analysis by the B-Vitamin Treatment Trialists' Collaboration is due to be published shortly and will provide more robust evidence as to the effect, if any, of folic acid supplementation on risk of prostate cancer.

Furthermore, prostate cancer is generally not life-threatening or disabling, although a small proportion of cancers are aggressive. The NZ National Health Committee stated:

> "Post-mortem studies show that histological evidence of prostate cancer is very common and increases with age. Prevalence rates from any form of prostate cancer greatly overstate the prevalence of localised prostate cancer that has the potential to progress to overt disease.
>
> The majority of cases of prostate cancers are very slow-growing and not life-threatening, only a small minority of cases progress rapidly with invasion of surrounding tissues and distant metastases. Unfortunately, it is not possible to accurately determine which tumours are slow-growing and which are aggressive.
>
> Age has no significant prognostic effect on the rate of progression of prostate cancer. In particular, aggressive tumours are not more common in younger men compared with older men."

A Health Technology Assessment report from the UK National Health Service has a similar view:

> "The natural history of prostate cancer is poorly understood. It is primarily a disease of older men, with the median age at onset of clinically apparent disease around 72 years, and median age at death of 79 years.(Neale & Donovan, 2000; Meikle& Smith, 1990). Post-mortem studies make it clear that the vast majority of prostate cancers never develop into clinically apparent disease. At autopsy, small tumour foci are found in 30–40% of 60-year-old men in most countries. It has been estimated that the life-time risk ofa 50-year-old man with a 25-year life expectancy of having microscopic cancer is 42%, of having clinically evident cancer is 9.5%, and of dying of prostate cancer is 2.9%. It is a well-known (and true) aphorism that "more men die with prostate cancer than of it."

The severity of prostate cancer ranges from non-fatal, asymptomatic slow-growing tumours, which probably require no treatment, to aggressive fast-growing tumours that metastasise quickly, often before symptoms are noticed. We do not yet know what factors are important in the progression of micro-focal tumors into symptomatic forms of the disease." (Donovan et al, 2003)

7 Breast cancer

Since 2006 three RCTs have been published which have assessed the effect of folic acid supplementation on the incidence of breast cancer in women (Zhang, 2008; Wu, 2009; Hankey, 2012). All these RCTs have reported a non significant protective effect of folic acid on breast cancer incidence, ranging from a decrease of 11 to 47%. A meta-analysis conducted by the Norwegian Knowledge Centre for the Health Services (Pike, 2011; Wien, 2012) found a reduction in risk of breast cancer incidence with folic acid supplementation of 15% (95% CI 0.65, 1.14).The evidence to date does not indicate that there is an increased risk of breast cancer incidence, and may be a protective effect if any, with intake of folic acid.

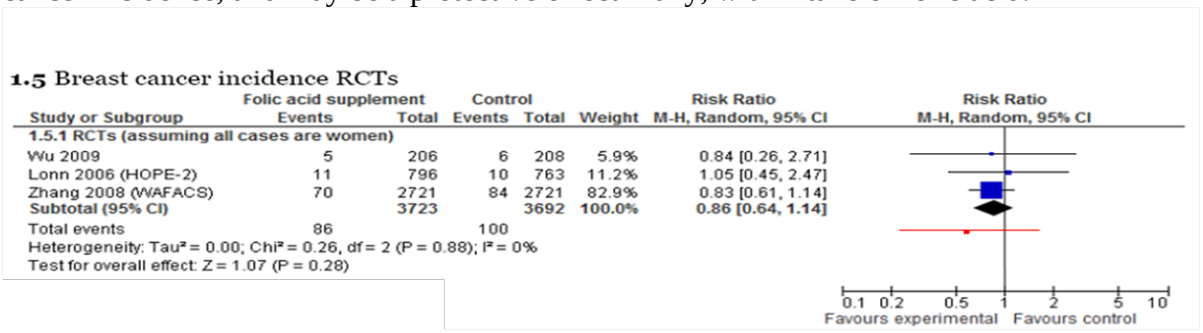


Figure 5: Forest plot of breast cancer incidence from the Norwegian Knowledge Centre for the Health Services (Pike, 2011; Wien, 2012) with the results from Hankey et al (2012) added in red

8 B_{12} masking and cognitive decline in the elderly

8.1 B_{12} MASKING IN THE ELDERLY

Submitters were concerned that adding folic acid to food would mean that doctors would not be able to detect vitamin B_{12} deficiency in the elderly. This would be an important effect because vitamin B_{12} deficiency can cause cognitive impairment, and is more frequent in the elderly due to reduced production of intrinsic factor, necessary for vitamin B_{12} absorption across the gut.

Formerly, a first-line diagnostic method to detect B_{12} deficiency was to test for macrocytosis (large red blood cells) in the blood. Vitamin B_{12} is important for normal development of red blood cells, and an inadequate concentration of the vitamin can be signalled by the presence of large, poorly-functioning red blood cells. However, adequate folate status can normalise red blood cell size even in the absence of adequate levels of vitamin B_{12}, creating the risk that neurological impairment may develop without macrocytosis providing a warning sign for doctors. This is often referred to as "masking" B_{12} deficiency.

This theoretical risk is considered negligible in current medical practice. Laboratory methods that directly test for the level of vitamin B_{12} in the blood are now widely available. Diagnostic testing for vitamin B_{12} insufficiency, largely ordered by primary medical practitioners and specialist medical physicians (particularly geriatricians), includes tests for vitamin B_{12} as a first-line test, in parallel with and not consequent on tests for macrocytosis. The threshold for ordering vitamin B_{12} tests has fallen to the point that tests for levels are routinely arranged purely as a general health check in elderly persons, without a requirement for presence of signs or symptoms suggestive of vitamin B_{12} deficiency. In fact, some commentators have advocated guidelines to restrict the volume of tests performed for vitamin B_{12} levels but note that patients with clinical evidence of cognitive or neurological impairment would still be appropriate for testing under these guidelines (McHugh et al, 2012). Folate status does not itself alter affect vitamin B_{12} levels, so alteration of blood folate levels does not potentiate or exacerbate vitamin B_{12} deficiency.

8.2 COGNITIVE FUNCTION

Submitters referred to the analyses by Morris et al (2007) who reported an interaction between high serum folate, low B_{12} status and cognitive impairment, based on a population-level study conducted in the United States. While of interest, for several reasons this study alone cannot be considered to demonstrate that elevation of serum folate may be injurious to cognitive function among elderly people with low levels of vitamin B_{12}. Firstly, this study was a cross-sectional study, i.e., the levels of folate, vitamin B_{12}, and cognitive functioning were measured at approximately the same point in time. While this study suggests an association between these variables, the direction of association cannot be determined: in other words, the study cannot provide any basis for suggesting whether the cognitive effects occurred before, after or simultaneously with the changes to the vitamin status levels that were subsequently measured.

Secondly, the study by Morris et al (2007) measures the association between folate and vitamin B_{12} status and cognitive function using an odds ratio. Odds ratios only estimate the relative risk if the prevalence of the condition (in this case, impaired cognitive function) is low, for example less than about 1%. In the population studied by Morris et al, the prevalence of the cognitive impairment was very high: 18% in the reference group and 45% in the high

folate/low B_{12} group, and in this context the odds ratio would have been an overestimation of the relative risk, therefore inflating the apparent degree of risk in the data.

A letter published by Berry et al (2007) provides further comment on the Morris et al (2007) paper. The subgroup in the Morris et al paper that had high serum folate and low B_{12} accounted for only 1.1% (42/3706) of the overall sample; 3.2% (42/1302) of those who had cognitive evaluation. Drawing inferences from findings in a relatively small subgroup may be problematic. In addition, Berry et al observe that the United States subpopulation of the elderly with high folate levels were almost exclusively taking folic acid supplements, and commonly-consumed supplements available at the time of data collection for this study were most often combined multivitamin preparations that included vitamin B_{12}. The presence of vitamin B_{12} deficiency in this population taking vitamin B12 supplements is difficult to explain, and Berry et al suggest that this may be an indication of inability to absorb vitamin B_{12}, and that this may itself explain the cognitive impairment.

Two studies performed in other jurisdictions have failed to demonstrate an interaction effect between folate and vitamin B_{12}, however these studies have features that differ from the Morris study. Mills et al (2011) performed a cross-sectional study among university students in Ireland: in this population, markers of vitamin B_{12} function among those with vitamin B_{12} deficiency did not differ between those with or without elevated folate levels. In a cross-sectional study performed by Clarke et al (2008) in the United Kingdom, no association was found between cognitive function and folate levels among elderly persons with vitamin B_{12} deficiency; this study differs from that of Morris et al in that a different measure of cognitive function was used.

Randomised-controlled trials are a stronger design than cross-sectional studies for testing the hypothesis that folic acid affects cognitive function in a longitudinal manner. A number of studies have tested the effect of folic acid with or without other B vitamins in older adults - these studies have included prospective cohort studies and randomised-controlled trials. Three papers published since 2009 have examined the findings from these studies in a collective manner. Wald et al (2010) sought intervention trials published between 1950 and 2009 that involved participants aged at least 45 years of age, without cognitive impairment at commencement, and that compared folic acid against placebo. Nine studies met inclusion criteria (including a New Zealand-based trial), consisting of 2835 participants in total. The summary standardised mean difference in cognitive function between the study groups was 0.01 (95% confidence interval: -0.08, 0.10), ie no material effect was demonstrated. Four of the nine studies suggested poorer outcomes in supplemented group compared with placebo, but none of these results were statistically significant.

Dangour et al (2010) conducted a systematic review of studies examining the association of B-vitamin and/or fatty acid consumption with deterioration in cognitive function. 160 studies (91 cohort and 69 intervention) were identified; of these 33 were included in the systematic analysis, including both cohort studies and intervention trials. The authors concluded that some observational cohort studies indicated that higher dietary intake or elevated serum levels of folate and fish/fatty acids and low levels of serum homocysteine were associated with increased risk of incident Alzheimer's disease and dementia, while other studies reported no association. The results of intervention studies examining the effects of folic acid or fatty acid supplementation on cognitive function are inconsistent. In summary, the available evidence is insufficient to draw definitive conclusions.

Ford et al (2012) performed both a systematic review and meta-analysis of randomised-controlled clinical trials of the effect of B-vitamin supplementation on cognitive function in

older adults. Nineteen trials were included. The amount of folic acid used in trials using folic acid ranged from 0.4-15mg/day and the studies lasted between 60 days and 5.4 years. The authors report that in combination these trials demonstrated no effect of these on cognitive function in adults either with pre-existing mild cognitive impairment or with no pre-existing cognitive impairment, irrespective of the study duration, study size or whether participants came from countries with low folate intake.

These systematic reviews and meta-analyses were designed to explore the hypothesis that supplementation with B-vitamins, including folic acid, improves cognitive function or slows cognitive deterioration. The studies found no proof for this hypothesis; simultaneously, the studies did not identify any concern that B-vitamin supplementation has the reverse effect, i.e., worsening cognitive function or speeding cognitive deterioration.

To summarise, available evidence does not indicate that folic acid fortification interacts with vitamin B_{12} deficiency to increase the risk of cognitive impairment in elderly people. An association has been suggested on the basis of results from a cross-sectional study, but findings from this study have not been replicated in similar studies. Several recent papers that have aggregated the results of clinical trials of the effect of folic acid supplementation on cognitive function have not shown any basis for claims that folic acid supplements either benefits or jeopardises cognitive function.

9 Asthma

Three studies published between 2008 and 2009 suggested that children born to women taking folic acid supplementation in pregnancy may have an increased risk for developing asthma, defined by parental report of an asthma diagnosis made by a doctor (Grenell, 2008; Whitrow, 2009), or by parentally-reported asthma symptoms (Haberg, 2009). While raising concern, there are three main reasons why these studies could not be considered conclusive. Firstly, in each study the statistical significance of the findings was borderline. Secondly, the diagnosis of asthma had been made based on parental report and not on confirmatory testing. Each study was an observational cohort study, potentially subject to confounding if 'health conscious' mothers were more likely to have taken supplements and also more likely to report asthma symptoms (Sharland, 2011); as asthma diagnoses were not objectively confirmed, this residual confounding may have affected findings. Thirdly, the studies gave inconsistent results in the timing of supplement usage associated with asthma outcomes: two studies found that supplement usage was associated with asthma in children if supplements were taken in late pregnancy but not if supplements were taken in early pregnancy (Grenell , 2008; Whitrow, 2009), whereas the reverse was shown in the remaining study (Haberg, 2009), which detected an association with supplement usage in early pregnancy but not with supplement usage in late pregnancy.

Further to these concerns regarding the study methods and strength of findings, it is pertinent that each of these studies largely concentrated on folic acid supplement usage, which provides greater intake of folic acid than would occur through fortification of the food supply. Two of the studies reporting significant associations between asthma and folic acid supplement usage did not attempt to measure the dose of folic acid consumed (Grenell, 2008; Haberg, 2009). The one study (Whitrow, 2009) that determined the folic acid supplement dose used reported a significant association with asthma symptoms at a dose of 1mg/day; greater than the folic acid intake that would be expected with fortification.

Subsequent to these reports, findings from four studies published between 2011 and 2012 have cast doubt on concerns that folic acid supplement usage in pregnancy may increase risk of asthma in children (Miyake, 2011; Bekkers, 2011; Magdelijns, 2011; Martinussen, 2012). Each of these studies have followed a similar basic design approach to the earlier studies, but some had additional features that provide strength to their findings: two of the studies measured asthma outcomes empirically using respiratory function testing (Bekkers, 2011; Magdelijns 2011), and in one of these studies (Magdelijns, 2011) information about folic acid intake was validated by measurement of red blood cell folate levels – this is the first study to incorporate these assessments. None of these four recent studies demonstrated any significant association between consumption of folic acid supplements in pregnancy and asthma diagnoses or symptomatology in children. Two of the studies attempted to measure dietary folate consumption (Miyake, 2011;Whitrow, 2009): neither of these demonstrated an association with between asthma and dietary folate intake.

To summarise, initial concerns regarding increased risk of asthma among children born to mothers who consumed folic acid supplements in pregnancy have not been supported by recently-reported studies, several of which have used more robust study designs than had been used in the earlier studies.

10 Stroke

Some submissions raised the prospect that folic acid fortification of the food supply may reduce the risk of stroke. This is of particular interest, as stroke carries high mortality, and in survivors can lead to reduced life expectancy and considerable disability. Folic acid fortification leads to reduction in plasma homocysteine levels (Clarke et al, 2010), and it is thought that this may affect risk of stroke.

Findings from trials on the association between folic acid supplementation and the risk of stroke have not been definitive. Clarke et al (2010) performed a meta-analysis of 8 randomised-controlled trials of folic acid supplementation that compared rates of stroke between intervention and control groups. No significant change in the risk of stroke was seen in the meta-analysis (relative risk 0.96, 95% confidence interval 0.87-1.06). A more recent meta-analysis conducted by Huo et al (2012) examined fifteen trials that randomised participants to either receive folic acid supplementation (with or without other B vitamins) or not, and then followed participants for at least six months and recorded stroke as an outcome. Five trials were in populations with a folic acid-fortified food supply, and the remaining 10 were in populations without folic acid fortification. Daily folic acid supplement doses ranged from 0.5mg to 40mg. Analysis of all 15 trials indicated a reduction in risk of stroke of borderline statistical significance (relative risk = 0.92, 95% confidence interval: 0.86-1.0, p=0.038); no significant reduction in risk was seen in the analysis of the five trials conducted in folic-acid fortified populations (1.03, 0.88-1.21, p=0.69), but significant risk reduction was seen in the 10 trials in unfortified populations (0.89; 0.82–0.97, p=0.01). However this tests each of the relative risks separately against the null effect (RR=1) without testing for the interaction variable (population fortification), so the comparison between populations with and without fortification is at present difficult to interpret. Furthermore, in all but three trials the majority of participants were male, and in all trials participants had pre-existing illnesses, including ischaemic heart disease, prior stroke, end-stage renal failure, or diabetes.

In summary, some recent evidence suggests that folic acid supplement usage may reduce the risk of stroke, This finding has not been shown in previous studies.

11 Childhood cancers

The submitters cite a study from Canada in support of a suggestion that introduction of mandatory folic acid fortification can reduce rates of a childhood cancer called Wilms' tumour. The study compares the incidence of Wilms' tumour in Ontario (Canada) before and after the introduction of mandatory fortification of flour in Canada in 1997. Among children aged 0 to 4 years, the incidence rate of Wilms' tumor declined from 1.94 to 1.43 per 100 000 (incidence rate ratio 0.74, 95% confidence interval, 0.57-0.95). No significant change was seen in other childhood cancers.

The submitters also cite a similarly-conducted study that used data from the United States. This study (Linabery et al, 2012) reported findings from surveillance systems that appeared to demonstrate a significant reduction in three childhood cancers (Wilms tumor, primitive neuroectodermal tumors and ependymomas), also by comparison with pre-fortification rates. Although both these studies appear well-conducted study, in the absence of contemporary control groups to which the incidence among those exposed to folic acid fortification can be compared does mean that the findings may be due to other secular trends, such as changes in diagnosis or reporting, although the authors are careful to suggest these are not likely explanations. Grupp et al state that their data may provide some reassurance that universal flour fortification does not heighten the risk of paediatric cancer, which appears a reasonable claim in the absence of other conflicting findings.

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