Ministry for Primary Industries
Manatū Ahu Matua

Voluntary Folic Acid Fortification

Monitoring and Evaluation Report

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Requests for further copies should be directed to:

Publications Logistics Officer
Ministry for Primary Industries
PO Box 2526
WELLINGTON 6140

Email: brand@mpi.govt.nz
Telephone: 0800 00 83 33
Facsimile: 04-894 0300

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Introducing the Ministry for Primary Industries

The Ministry of Agriculture and Forestry (MAF) has changed its name to reflect the new functions of the organisation following its merger with the New Zealand Food Safety Authority and Ministry of Fisheries.

The new name is the *Ministry for Primary Industries*, Manatū Ahu Matua (MPI). It came into effect on 30 April 2012.

The name was chosen because it covers all of the Ministry's work across the agricultural, horticultural, aquaculture, fisheries, forestry and food sectors, and the protection of our primary industries from biological risk.

It reflects that we continue to be the gateway to government for all of New Zealand's primary industries.

Acknowledgements

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- Analytical Services, Ministry of Health
- Centre for Public Health Research, Massey University
- Life in New Zealand Nutrition and Activity Research Unit, Otago University.

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Abbreviations

AIHW	Australian Institute of Health and Welfare
ANS09	New Zealand Adult Nutrition Survey 2008-09
BIANZ	The Baking Industry Association of New Zealand
BIRT	The Baking Industry Research Trust
CI	Confidence Interval
CAPI	Computer Assisted Personal Interview
DHBs	District Health Boards
EDD	Estimated Delivery Date
FRSC	Food Regulation Standing Committee
IQR	Interquartile range
MAF	Ministry of Agriculture and Forestry
MFD	Manufactured Food Database
MPI	Ministry for Primary Industries
NTD	Neural Tube Defect
NZBDR	New Zealand Birth Defects Registry
SD	Standard deviation
SEM	Standard error of the mean
VAMPS	Vitamins and Minerals in Pregnancy Survey

Symbols

%	percent
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to
µg	microgram
g	gram
L	litre
nmol	nanomole

Introduction

Higher intakes of folic acid in women are associated with a decreased risk of having a neural tube defect (NTD) affected pregnancy. (1) Internationally this has led many Governments to recommend that women take ≥ 400 micrograms per day (µg/d) of folic acid before conception and during the first trimester of pregnancy. Since 1993 the New Zealand Ministry of Health has promoted a health policy recommending women take folic acid supplements during the periconceptional period. Despite this, previous work has suggested that this advice to consume supplemental folic acid has not been followed by a majority of women in the target group. (2)

To help address this nutrient gap, the New Zealand Government issued a New Zealand Food Standard in 2007 requiring the mandatory fortification of bread with folic acid at a level of 80-180 micrograms per 100 grams (µg/100 g) of bread. (3) Alongside existing health promotion and education strategies, including the ongoing promotion of folic acid supplements (Tablets), the Standard was aimed at improving the folate status of women of childbearing age.

The Standard's implementation was subsequently deferred until May 2012 and again to September 2012 with the national focus being on introducing a targeted voluntary bread fortification programme. (4,5) The major bread producers in New Zealand committed to adopting greater voluntary fortification, agreeing to add folic acid at a level of 200 µg/100 g of bread to approximately one third of their range of breads by March 2010. (6)

Monitoring and evaluation approach

The purpose of this report is to summarise technical information and data that will aid decision makers in the pending review of the New Zealand (Mandatory Fortification of Bread with Folic Acid) Food Standard 2007. (3)

While folic acid fortification of bread is the primary risk management strategy of interest to MPI, with a number of concurrent strategies occurring to achieve a reduction in NTD-affected pregnancies, a more multifaceted and detailed approach to monitoring and evaluation is required.

The arrangement of this report is broadly based on a previously agreed Food Regulation Standing Committee (FRSC) monitoring framework for mandatory food fortification. (7) The reports structure also acknowledges the evaluation framework for voluntary folate fortification published by Abraham *et al.* (8) by adding an addition element on consumer knowledge.

The monitoring and evaluation report will as a result summarise information on six main components:

1. folic acid fortified food composition and food industry compliance
2. consumer knowledge of folate and folic acid
3. folic acid intake and folic acid supplement use
4. folate status
5. health benefits
6. adverse health effects.

Table 1. Folic acid fortification monitoring questions.

Framework Component	Monitoring Question
Folic acid fortified food composition and food industry compliance	Are there a variety of folic acid fortified foods that are widely available? Is the food industry adequately complying with the voluntary Food Standard?
Consumer knowledge of folate and folic acid	Do women of childbearing age know why and how to identify folic acid fortified foods?
Folic acid intake and folic acid supplement use	Have folate intakes in women of childbearing age increased? Are women of childbearing age consuming folic acid supplements according to policy guidelines?
Folate status	Has the folate status of women of childbearing age improved?
Health benefits	Has the prevalence of NTDs decreased?
Adverse health effects	Does voluntary folic acid fortification result in adverse health effects for the population?

Source: Adapted from the Australian Institute of Health and Welfare (AIHW) 2011. (7)

The report presents new data for each component of the FRSC monitoring framework wherever possible. It attempts to update the New Zealand baseline information that was previously published by the AIHW as well as presenting new information that is available*. (7)

Finally, due to the nature of some of the data collection procedures and biological endpoints, figures and information for the most recent years were not always available at the time of publication.

* MPI has not tried to reinterpret the information that was summarised by AIHW as New Zealand Government officials were previously consulted in the drafting of the New Zealand sections of that report.

Folic acid fortified food composition and food industry compliance

New Zealand and trans-Tasman food standards permit the addition of folic acid to a variety of foods, including cereal and cereal products, breakfast cereals, cereal flours, pasta, yeast extracts, and fruit juices. (5,9,10) Monitoring the uptake of these permissions into foods is helpful in identifying the food industry's efforts at making a sufficient number and variety of folic acid fortified foods available to consumers. It is also useful at informing dietary folic acid intakes as discussed in later sections.

MANUFACTURED FOOD DATABASE

The Manufactured food database (MFD) is a contracted service between MAF and the Auckland District Health Board. One of the service outputs is the provision of vitamin and mineral label information for a broad variety of fortified foods available in New Zealand.

Methods

The MFD has been compiled from information supplied voluntarily by major brand food manufacturers at the request of the Auckland District Health Board. Foods sold in speciality stores and/or private label (or home brands) foods[†] are not well represented with the MFD. Company information is updated on an annual basis. Major brand food manufacturers are contacted annually in September and requested to review all data currently held on the MFD. This includes noting any changes to existing products, deletions of product lines and data for new products. All data is checked by Auckland District Health Board staff and any anomalies or queries followed up with technical personnel. Products that have not been updated at the end of the data collection period are removed from the MFD. Each year information on folic acid fortified foods is entered into the MFD.

Key Results

A total of 1113 records of individual food products fortified with folic acid were recorded in the MFD over the period 1997-2011. These covered 10 food categories. The earliest records are from 1997, with 18 folic acid fortified products recorded. In the latest year, 2011, there were 161 folic acid fortified products recorded. Non-alcoholic beverages, breakfast cereals, infant cereals and other miscellaneous products are the earliest recorded food categories containing folic acid fortified foods. More recent food categories to adopt folic acid fortification permissions include biscuits, infant formulae, snack foods and milk and milk products (Table 2).

In 2011 products categorised as a breakfast cereal, bread, non-alcoholic beverage or specialist therapeutic product made up 89% of the total number of folic acid fortified foods in the MFD (Table 2). The breakfast cereals category had the highest number of products containing folic acid (n = 86) with a mean folate label value of 280 µg/100 g. There were 26 breads in the MFD that contained folic acid with a mean folate label value of 175 µg/100 g.

The number of products recorded as being fortified with folic acid since 1997 is illustrated in Figure 1 (a). This demonstrates a steady exponential increase each year since 1997. Figure 1 (b-f) illustrate the change in the number of products fortified with folic acid and folate label value across key food categories.

[†] Private label in New Zealand is estimated by local researchers to be about 15-16 per cent. (60)

Compared to the 2008 baseline information reported by AIHW (7) there has been an increase in the number of products fortified with folic acid across several food categories including breads (+19), breakfast cereals (+37), milk and milk products (+1) and snack foods (+2). There were no reported changes in other food categories (Table 3). The increase in the number of products fortified with folic acid does not necessarily reflect an increase in the consumption of folic acid fortified foods. Rather, it suggests that there are a greater number of products available for consumers to choose.

The mean label value of folate in the food categories has remained largely unchanged since baseline with the exception of breakfast cereals (+66 µg/100 g) and breads (-37 µg/100 g) (Table 3). These mean values are influenced somewhat by food products at the extremes of the range. When median values are considered the level of folate in breakfast cereals and breads as reported by label value has remained unchanged (Table 4).

Table 2. Categories of foods containing products fortified with folic acid.

Food Category	First Record	Number of Products (and % of total) in 2011
Beverages, non-alcoholic	1997	22 (14%)
Biscuits	2004	3 (2%)
Breads, rolls, muffins, crumpets	2000	26 (16%)
Breakfast cereals	1997	86 (53%)
Infant cereals	1999	2 (1%)
Infant formulae	2005	2 (1%)
Milk and milk products	2008	4 (2%)
Snack foods	2005	3 (2%)
Specialist therapeutic products	2003	10 (6%)
Miscellaneous†	1998	3 (2%)

Note:
† Miscellaneous foods comprise yeast-based spreads.

Source: MFD.

Table 3. Number of folic acid fortified products and mean, minimum and maximum folate **concentration (µg/100 g) by food category, as reported in 2008 and 2011.**

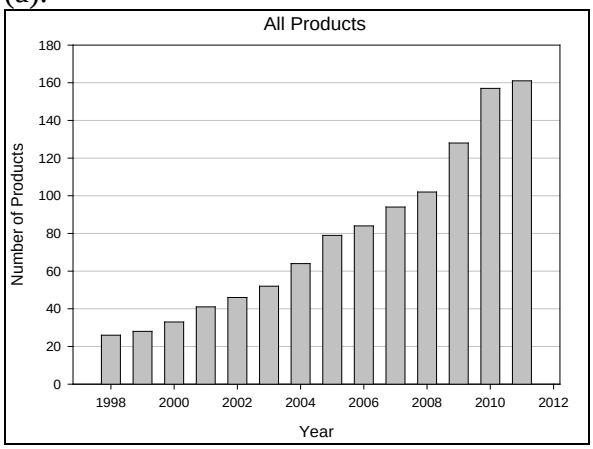
Food Category	2008		2011	
	Number	Mean (Range)†	Number	Mean (Range)†
Beverages, non-alcoholic	22	121 (8, 296)	22	127 (8, 370)
Breads	7	212 (200, 286)	26	175 (133, 200)
Biscuits	3	280 (280, 280)	3	280 (280, 280)
Breakfast cereals	49	214 (53, 333)	86	280 (50, 866)
Infant formulae	2	22 (22, 22)	2	22 (22, 22)
Infant cereals	2	140 (140, 140)	2	140 (140, 140)
Milk and milk drinks	3	20 (20, 20)	4	20 (20, 20)
Snack foods	1	38 (38, 38)	3	39 (38, 39)
Special therapeutic foods	10	242 (172, 300)	10	241 (155, 305)
Miscellaneous	3	2000 (2000, 2000)	3	2000 (2000, 2000)

Note:
† Mean (Range) of reported folate label value per 100 g.

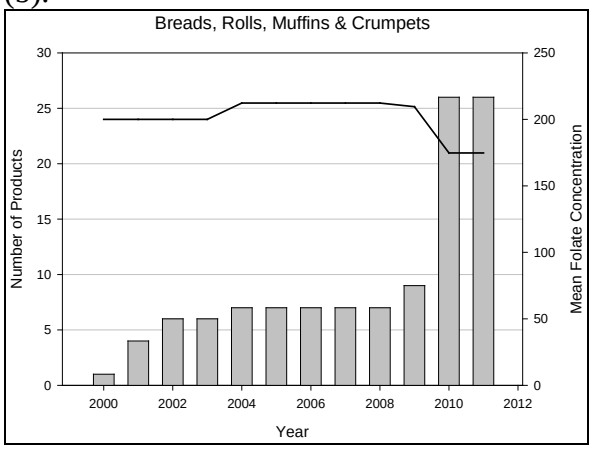
Source: MFD.

Figure 1. Products in the Manufactured food database recorded as being fortified with folic acid since 1997 (a), including subcategory analysis by total number and folate concentration (µg/100 g) (b-f).

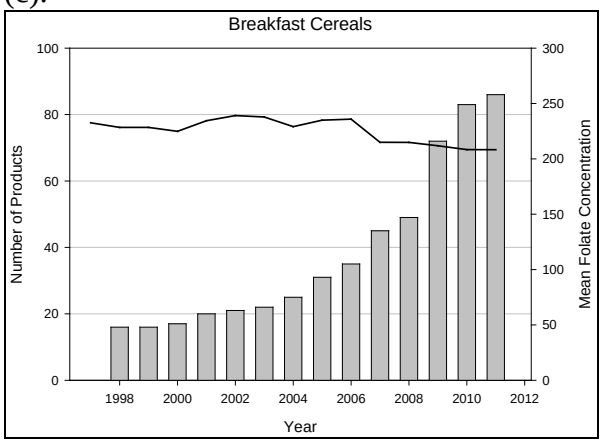
(a).



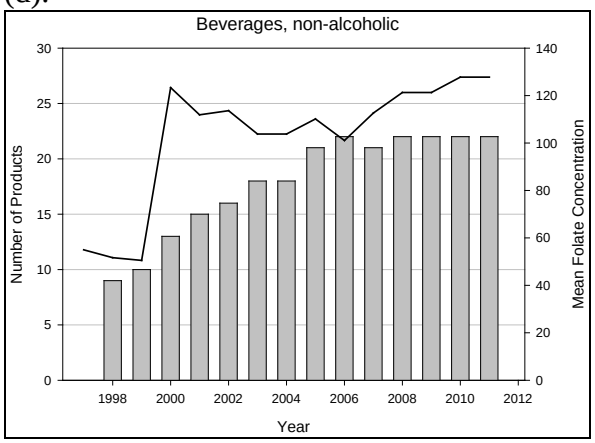
(b).



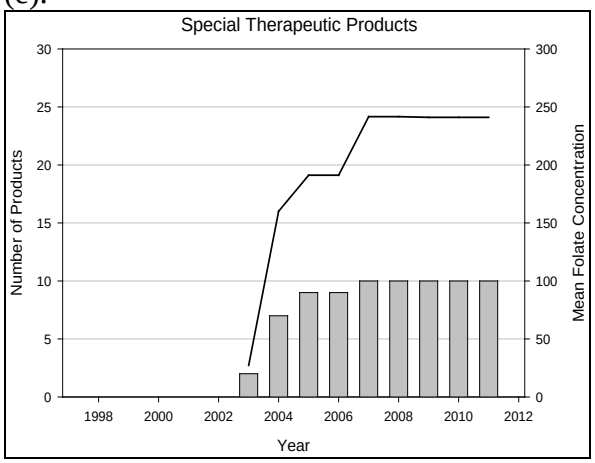
(c).



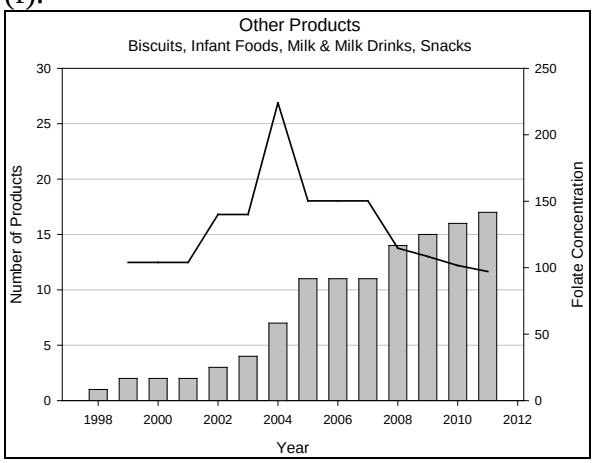
(d).



(e).



(f).



Source: MFD.

Table 4**. Main folic acid fortified food categories: median and mean folate concentration (µg/100 g) by year** (1997-2011).

Food Category	Year	Median	Mean
Beverages, non-alcoholic	1997	55	55
	1998	55	52
	1999	55	51
	2000	55	123
	2001	55	112
	2002	55	114
	2003	55	104
	2004	55	104
	2005	74	110
	2006	48	101
	2007	91	113
	2008	91	121
	2009	91	121
	2010	91	128
	2011	91	128
Breads, rolls, muffins, crumpets	2000	200	200
	2001	200	200
	2002	200	200
	2003	200	200
	2004	200	212
	2005	200	212
	2006	200	212
	2007	200	212
	2008	200	212
	2009	200	210
	2010	200	175
	2011	200	175
Breakfast cereals	1997	222	233
	1998	222	228
	1999	222	228
	2000	222	225
	2001	222	234
	2002	222	239
	2003	222	238
	2004	222	229
	2005	222	235
	2006	222	236
	2007	222	215
	2008	222	215
	2009	222	212
	2010	222	208
	2011	222	208

Source: MFD.

CONSUMER SURVEY OF WOMEN OF CHILDBEARING AGE 2010

The Consumer Survey of Women of Childbearing Age 2010 was commissioned by MAF to establish baseline quantitative data on women's awareness, understanding, and attitudes to folic acid in food and its relationship to health. The survey was carried out by Research New Zealand between September and October 2010.

Methods

This telephone survey focused on measuring New Zealand women's current knowledge of folate and folic acid, its importance and use particularly in the period in which women become pregnant, and opinions with regard to the addition of folic acid in bread. Several questions were also asked concerning bread consumption preferences. (11)

The sample design for the survey used a multi-stage random sampling approach. The primary sampling unit were the households of eligible electors, selected at random from the General and Māori Electoral Rolls, on the basis that they were aged 18-50 years. Once selected, a tele-matching exercise was conducted in order to match household addresses with a contact telephone number. Thirty-four percent were successfully matched. Respondents were then randomly selected from all those people usually living in these households, providing they were eligible to complete the survey (i.e. were females aged 16-44 years). Quotas were set by age to ensure that a sufficient number of younger women aged 16-29 years were interviewed.

Key Results

When asked how many slices of bread they have in an average day, 38% of respondents mentioned 2-3 slices per day (Table 5). This was the largest single category mentioned for bread consumption. Twenty-one percent mentioned 4-5 slices per day but no other categories were mentioned by more than 10% of respondents. Seven percent of respondents reported not eating any bread.

Three bread types, multigrain (41%), brown or wholemeal (31%) and white (21%) were chosen most often by respondents. There were no other bread types reported by more than 2% of respondents (Table 6).

Table 5. Self-reported daily bread intake in a proportion of women of childbearing age (n = 1,000)[†,‡].

Bread consumption	Number (%)
Less than 1 slice	30 (3%)
1-2 slices	90 (9%)
2-3 slices	380 (38%)
3-4 slices	90 (9%)
4-5 slices	210 (21%)
5-8 slices	70 (7%)
9-12 slices	0 (0%)
Other	50 (5%)
None/Don't eat bread	70 (7%)
Don't know	0 (0%)

Notes:

† Total may not sum to 1,000 (100%) due to rounding.

‡ In response to question *"About how many slices of bread do you have in an average day?"*

Source: Kalafatelis and Fryer 2010. (11)

Table 6. Self-reported bread type in a proportion of women of childbearing age (n = 933)[†,‡,§].

Bread type	Number (%)
Multigrain bread	383 (41%)
Brown or wholemeal bread (including rye bread)	289 (31%)
White bread	205 (22%)
Other	19 (2%)
Pita bread, flat breads or similar	9 (1%)
Gluten-free	9 (1%)
Homemade	9 (1%)
Mixed / range of types	9 (1%)
Sourdough breads	0 (0%)
Don't know	0 (0%)

Notes:

† Sub-sample based on those who eat at least some bread in an average day.

‡ Total may exceed 100% because of multiple responses.

§ In response to question *"And what type of bread do you usually have? Is it...?"*

Source: Kalafatelis and Fryer 2010. (11)

2011 FOLATE AND WOMEN'S HEALTH SURVEY

The 2011 Folate and women's health survey was commissioned by MAF to monitor the utility of voluntary fortification of bread with folic acid at improving the blood folate status of women of childbearing age. (12) The survey was carried out by the University of Otago from August 2010 to November 2011. The survey had two distinct parts; (i) the analytical determination of folic acid in bread; and (ii) the measurement of blood folate status in women of childbearing age.

Methods

For the analysis of folic acid content in bread, Bradbury *et al.* (12) report the selection of folic acid fortified brands of bread was based on a top-ten ranking of folic acid fortified breads by sales volume. The Baking Industry Research Trust (BIRT) gathered confidential information from the four main bread companies in New Zealand (George Weston Foods, Goodman Fielder, Couplands Bakeries, Yarrows) to generate two lists of the top-ten folic acid fortified breads, one for North Island and one for South Island breads, ranked by sales volume in each Island[‡]. All breads on the two lists were analysed, with one exception; two of the breads in the top-ten list for the North Island from the same brand differed only in the usage, one for "toast" and the other for "sandwich". Folic acid was only analysed in the "toast" version. Therefore, between 27 October 2010 and 8 February 2011, nine brands of bread were selected for analysis in the North Island and 10 in the South Island.

The packet of each new bread tested was checked to confirm that folic acid or folate was listed as an ingredient. The Baking Industry Association of New Zealand (BIANZ) website (http://www.bianz.co.nz/industry-news/folic-acid-fortified-breads-list.html) provides a list of folic acid fortified breads, and was accessed for additional confirmation that the breads were fortified with folic acid. All breads that were collected were listed as fortified on the BIANZ website. Subsequent to folic acid analysis, it was confirmed that two of the North Island breads, W 8 and W 9, did not list folic acid in the ingredient list. The results for breads W 8 and W 9 were excluded from the analysis.

‡ For a full list of available folic acid fortified breads refer to Appendix.

In studying the stability of folic acid fortified in bread during shelf-life, the top ranked folic acid fortified bread in the South Island – a white bread – and the top ranked folic acid fortified bread in the North Island – a brown bread – were used to assess the shelf-life of folic acid.

Folic acid extraction and isolation was conducted based on the method of Konings (13) modified for folic acid fortified bread. High-performance liquid chromatographic analysis of folic acid extracts from bread was conducted based on the method described by Verlinde *et al.* (14)

Key Results

Consumption of folic acid fortified bread, breakfast cereal, and spreads

Bread was consumed by 93% of the participants in the week prior to completing the telephone food frequency questionnaire (Table 7). Reported consumption of all bread was approximately 12 slices per week (Table 8). When only consumers of bread were considered this increased slightly to 13 slices (data not shown). Eighteen percent of women had consumed at least one slice of folic acid fortified bread in the past week. Seventy-five percent of women had consumed bread that was either not fortified with folic acid or could not be identified as fortified because the participant could not recall the brand name of the bread; of this latter group, 38 participants (13%) consumed one or more slices of bread of unknown brand. About half of women consumed a folic acid fortified spread.

Breakfast cereal was consumed by 72% of the participants in the week prior to completing the telephone food frequency questionnaire (Table 7). Forty-one percent of women consumed at least one bowl of folic acid fortified breakfast cereal in the past week and 31% consumed breakfast cereal that was either non-fortified or could not be identified as such; of this latter group, 15 participants (5%) consumed one or more bowls of breakfast cereal of unknown brand.

Folic acid content of folic acid fortified breads

In the North Island, four of the seven breads tested contained 100-300 µg folic acid per 100 g edible portion (Table 9), the other three breads contained less than 50 µg per 100 g edible portion. In the South Island, two of the 10 breads tested had folic acid concentrations that exceeded 400 µg per 100 g edible portion, six breads contained 100-300 µg folic acid per 100 g edible portion. The other two breads (D 8 and D 9) contained less than 50 µg per 100 g edible portion. The mean (SD) and median (interquartile range) for all 17 breads was 151 µg (131) and 144 µg (41, 189), respectively.

Folic acid stability over shelf-life of folic acid fortified bread

The stability of folic acid fortified white and brown bread during a five to six day shelf-life is shown in Table 10. As reported by Bradbury *et al.* (12) the folic acid content was marginally lower, by 1 µg (0.4%) – in white bread at the end of the shelf-life (i.e. best before date), but in brown bread had decreased by 18 µg (9.1%) compared to the content of folic acid at sales date.

Table 7. Prevalence of bread, breakfast cereal, and spread consumption in the previous week among women of childbearing age†.

	No. recruited	Bread consumers			Breakfast cereal consumers			Fortified spread consumers
		Fortified‡	Non-fortified/ unidentified§	Any	Fortified¶	Non-fortified/ unidentified††	Any	
All	288	18% (51)	75% (215)	93% (266)	41% (116)	31% (89)	72% (205)	53% (152)
Wellington	141	14% (20)	75% (106)	89% (126)	36% (50)	36% (50)	72% (100)	49% (69)
Dunedin	147	21% (31)	74% (109)	95% (140)	45% (66)	27% (39)	71% (105)	56% (83)

Notes:

† Values are percent of participants' recruited (n).

‡ Participants who consumed any folic acid fortified bread. To be included in this category, participants reported eating a brand of bread (at least one slice) known to be fortified with folic acid.

§ Participants who did not consume folic acid fortified bread. Participants in this category reported eating only non-fortified brands of bread or a combination of non-fortified and unidentified brands of bread.

¶ Participants who consumed any folic acid fortified breakfast cereal. To be included in this category, participants reported eating a brand of breakfast cereal (at least one bowl) known to be fortified with folic acid.

†† Participants who did not consume folic acid fortified breakfast cereal. Participants in this category reported eating only non-fortified brands of breakfast cereal or a combination of non-fortified and unidentified brands of breakfast cereal.

Percentages may not match to total recruited due to missing data.

Source: Bradbury *et al.* 2011. (12)

Table 8. Frequency of consumption† of all bread and breakfast cereals in the previous week.

Place	Bread (slices per week)	p value‡	Breakfast cereal (bowls per week)	p value‡
All	12 (9)		3.4 (2.8)	
Wellington	12 (9)	0.296	3.4 (2.8)	0.737
Dunedin	13 (8)		3.5 (2.9)	

Notes:

† Mean (SD) consumption amongst all participants.

‡ *p* values are for the difference between Wellington and Dunedin participants, tested using simple linear regression.

Source: Bradbury *et al.* 2011. (12)

Table 9. Folic acid content of folic acid fortified breads (µg/100 g edible portion)†.

Location	Bread Code No.	Mean (SD) folic acid in bread
North Island	W 1	156 (5)
	W 2	41 (23)
	W 3	133 (7)
	W 4	119 (4)
	W 5	6 (2)
	W 6	8 (4)
	W 7	246 (15)
South Island	D 1	189 (25)
	D 2	158 (19)
	D 3	452 (39)
	D 4	420 (21)
	D 5	105 (4)
	D 6	144 (6)
	D 7	190 (9)
	D 8	4 (1)
	D 9	4 (1)
	D 10	184 (8)

Note:

† Based on triplicate measurement from three loaves.

Source: Bradbury *et al.* 2011. (12)

Table 10. Folic acid content of folic acid fortified breads from start to end of shelf-life (µg/100 g fresh weight)[†,‡].

Bread code no.	Type of bread	Mean (SD) folic acid in bread	
		Sale date	*Shelf-life date*
NI 1	Brown	198 (12)	180 (15)
SI 1	White	256 (9)	255 (30)

Notes:
† End of shelf-life is equal to 'best before' date registered on the bread packaging.
‡ Based on triplicate measurement from four loaves.

Source: Bradbury *et al.* 2011. (12)

SUMMARY

Information on folic acid fortified foods supplied from major food manufacturers suggests a growing number of products are being made available to New Zealand consumers. Most of these foods are contained within four broad food categories i.e. breakfast cereals, breads, non-alcoholic beverages and specialist therapeutic products, thus limiting overall variety. The amount of folic acid being added to foods within and across categories is variable (according to nutrition information panel declarations).

Bread appears to be consumed by almost all women of childbearing age, with multigrain, brown or wholemeal, and white breads being the most popular choices. Commitments made by the bread baking industry to add folic acid at a level of 200 µg/100 g of bread to approximately one third of their range of breads have been partially implemented. The number of folic acid fortified breads has grown over the previous two years. There are at least 33 folic acid fortified breads for sale in New Zealand. It is not known whether this equates to approximately one third of their range of breads. Personal communications from the BIRT indicate that in November 2011 there were 719 sales units available in the 'Fresh Bake' category for key accounts (supermarkets). Ninety-two of these were private label. Loaf bread accounted for 323 sales units, buns and rolls another 116, and the rest were made up of hot plate and specialty bread products. (Watson T. Baking Industry Research Trust (NZ). Email to: David Roberts (Manager Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ). RE: Methodology for folic acid survey. 2012 February 24)

Analytical testing of folic acid fortified breads has highlighted significant variability in the folic acid levels of the highest selling folic acid fortified breads. The mean and median for folic acid fortified breads being 151 µg and 144 µg respectively, well below the stated objective of 200 µg/100 g.

There are several data gaps identified that could assist MPI to better respond to the monitoring questions relevant to this section. The MFD does not contain information on all packaged foods, particularly private label products. Information on these would assist in providing a better estimate of the number of folic acid fortified foods available to New Zealand consumers. MPI did not obtain sales data for any folic acid fortified foods. This would improve monitoring and evaluation by helping to identify the market share of folic acid fortified foods versus non-fortified foods within category, helping to demonstrate the reach of these products into New Zealand households. It is worthwhile noting that only a small proportion of women in the 2011 Folate and women's health study reported consuming a folic acid fortified bread. Additionally, MPI had no information about the geographical distribution of folic acid fortified breads in comparison with non-fortified breads. While it is known that

both North and South Island folic acid fortified breads are available, their distribution and access within metropolitan and provincial regions is unclear.

Consumer knowledge of folate and folic acid

Monitoring the knowledge of folate and folic acid among women of childbearing age may help to identify the success of health promotion messages regarding pregnancy, NTD risk and folic acid. It also has utility in explaining purchasing and dietary practices. As folic acid fortification of the food supply is voluntary in New Zealand, it may be necessary for women of childbearing age to make conscious changes to their diet in order to achieve a greater folic acid intake, including identifying and choosing folic acid fortified foods.

CONSUMER SURVEY OF WOMEN OF CHILDBEARING AGE 2010

Methods

Information on the methodology of the Consumer Survey of Women of Childbearing Age 2010 has been reported previously (p9) and is reported in full by Kalafatelis and Fryer. (11)

Key Results

Proportion of women of childbearing age aware of folate/NTD links and behaviours to increase folate intake

Those women who knew something about folate or folic acid were asked to identify which if any particular types of people needed to make sure they were getting the right amount. Sixty-two percent immediately thought of pregnant women, while 10% identified women planning to become pregnant. This represented 47% and 7% of the total sample of women.

When asked if they could think of any other specific groups, mention of pregnant women increased to 73%, and women planning to become pregnant to 20% (on a total sample basis, this represented 56% and 16%, respectively). Seventeen percent reported that folate or folic acid intake was important for ‘everyone’, while 14% believed it was important for children. On a total sample basis, this represented 13% and 11%, respectively (Table 11).

After prompting, 97% of those who knew something about folate or folic acid agreed that pregnant women and/or those who were planning to become pregnant need to make sure they were getting the right amount. This represented 74% of the total sample of women.

Those who agreed that pregnant women/women planning to become pregnant needed to make sure they were getting the right amount of folate, were asked to rate how important they believed this was on a scale of 0 to 10 (where 0 = not at all important and 10 = extremely important). On this basis, 87% provided a rating of 8 or higher (this represented 64% of the total sample) (Figure 2).

Two-thirds (68%) of those who agreed that pregnant women/women planning to become pregnant needed to increase their folate intake, reported that it was recommended that these women increase their folate and folic acid intake before they become pregnant (this equates to 50% of the total sample). Seven percent believed that this should happen when they discovered they were pregnant, while another 14% reported that pregnant women needed to increase their folate/folic acid intake within the first trimester. On a total sample basis, this represents 5% and 11%, respectively.

When asked to describe why it is recommended that pregnant women in particular, or women who are planning to get pregnant, increase their folate or folic acid intake, half (51% of those

who agreed that pregnant women/those trying to conceive need to make sure they are getting the right amount of folate/folic acid) said that it was important for babies nerve development or to minimise the risk of NTDs. Twenty-four percent said it was recommended because folate/folic acid helps with babies' general development and the avoidance of (unspecified) birth defects. This represented 38% and 18% of the total sample of women.

Overall those who were pregnant at the time of the survey or reported having had children in the past, aged 30+ years, and/or had higher educational status were significantly ($p < 0.05$) more likely to identify the associations between periconceptional folic acid and NTD-affected pregnancies. There were no notable differences between household income levels.

Proportion of women of childbearing age intentionally using folic acid fortified foods

At the time of the survey, 3% of all respondents said they were currently buying particular foods or drink specifically because they contained folate or folic acid. Two percent of all respondents (n = 45) reported actively checking to see if the food or drink they were buying had folic acid added to it. This was typically done by checking the ingredients label (76%), or nutrition information panel (36%).

Those who were pregnant at the time of the survey or reported having had children in the past, aged 30+ years, with higher household incomes and/or higher educational status were significantly ($p < 0.05$) more likely to know that folic acid is sometimes labelled on food products as folate. (11)

Ninety-seven percent of respondents reported not currently checking to see if their products contained folic acid. These respondents said that if they were going to do so, they would also check the ingredients label (73%) or the nutrition information panel (37%). (11)

Proportion of women of childbearing age aware of folate rich food sources

When asked to identify which types of foods and drinks were naturally good sources of folate, 22% of those who knew that pregnant women need to make sure they are getting the right amount of folate, identified vegetables (in general) as a good natural source of folate, one-third specifically mentioned green vegetables (33%), 17% mentioned fruit, 14% bread. However, another third (or 25% of the total sample) were unable to identify any foods or drinks that were naturally good sources of folate. (11)

Thirty-nine percent of all respondents did not know which types of food or drinks have folic acid added to them. Thirty percent mentioned bread. The next most commonly mentioned products were orange/fruit juice (19%), milk/dairy products (14%) and breakfast cereals (13%). (11)

Those who were pregnant at the time of the survey or reported having had children in the past, aged 30+ years, with higher household incomes and/or higher educational status were significantly ($p < 0.05$) more likely to identify specific types of food or drinks that are naturally good sources of folate. (11)

SUMMARY

As folic acid fortification of the food supply is voluntary in New Zealand, it may be necessary for women of childbearing age to make conscious changes to their diet in order to achieve a greater folic acid intake. The findings from the Consumer Survey of Women of Childbearing Age 2010 suggest that unprompted awareness of the need for periconceptional use of folic acid is high among those women with some pre-existing knowledge of folate or folic acid but low amongst all women combined.

Most women report not knowing why or how to identify folic acid fortified foods. Only a very small proportion of women report intentionally purchasing foods or drinks because they contain folic acid. This is accompanied by a lack of general knowledge on good food sources of folate.

A number of factors appear to characterise positive responses on knowledge and awareness including past or present pregnancy, age and socioeconomic variables such as household income and educational status.

The Consumer Survey of Women of Childbearing Age 2010 provides useful answers to the monitoring questions but further in-depth analysis of the findings is warranted. For example it would be worthwhile identifying whether awareness of the benefits of folic acid and having the specific knowledge of the benefits are predictive of the use of folic acid supplements or folic acid fortified foods in the periconceptional period.

Table 11. Percentage of women of childbearing age identifying specific population needs for folate or folic acid (Total unprompted) (%) (n = 809)[†,‡].

Question: Are there any types of people, if any, who need to make sure they are getting the right amount of folate or folic acid? Who are these people? Any other people?

Pregnant women	73
Women planning to become pregnant	20
Women who have just given birth	2
All women	11
Children	14
Older people	12
All people / Everyone	17
Women of childbearing age	2
People with existing health conditions/family history of health conditions	4
People who are undernourished	4
Breastfeeding women	2
Other	3
No types of people need to make sure/No others	2
Don't know/can't remember	8

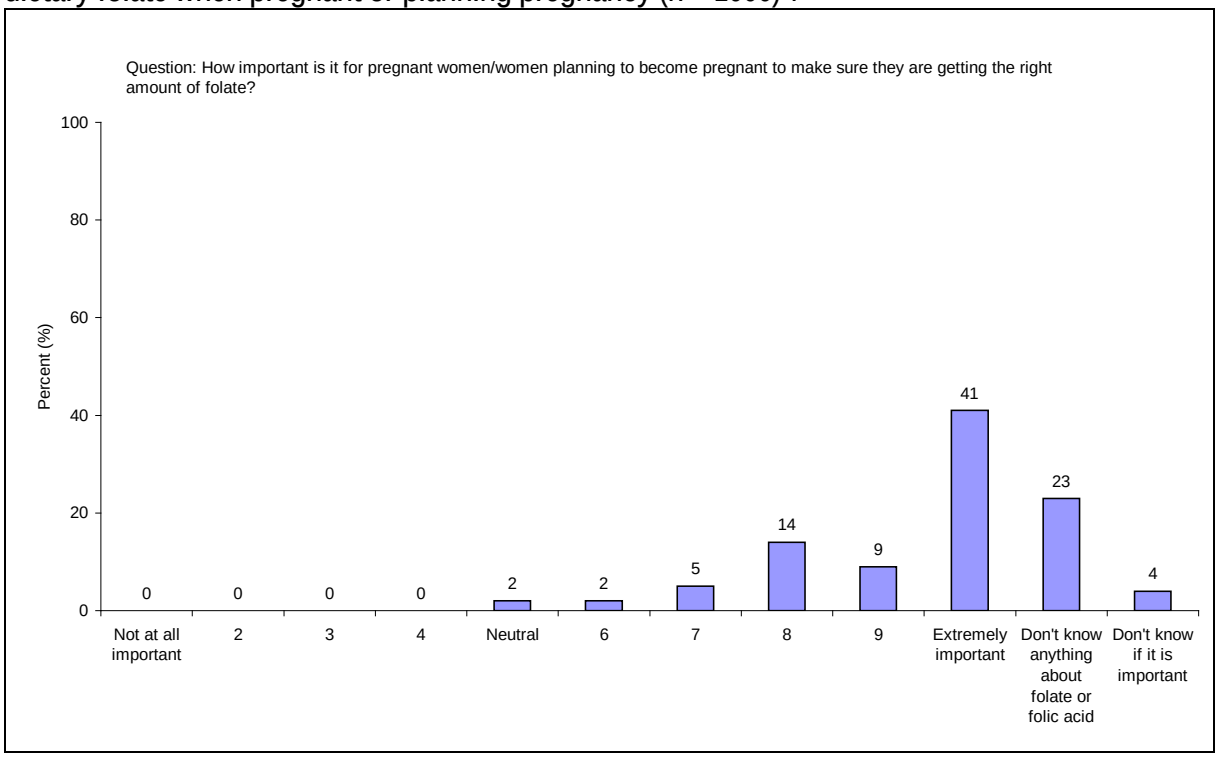
Notes:

† Sub-sample based on those who claimed to know at least something about folate or folic acid.

‡ Total may not sum to 100% due to rounding.

Source: Kalafatelis and Fryer 2010. (11)

Figure 2. Perceived importance among women of childbearing age of the need to get sufficient dietary folate when pregnant or planning pregnancy (n = 1000)[†].



Note:

† Total may not sum to 100% due to rounding.

Source: Kalafatelis and Fryer 2010. (11)

Folic acid intake and folic acid supplement use

The assessment of dietary folate intake is important in determining the mean, median and/or distribution of usual intake across a population. It can assist in identifying where the population might be at risk of folate deficiency or excess by comparing dietary folate intakes against established nutrient reference values. (15) The term dietary folate equivalents (DFE) has been introduced into nutrient reference values to accommodate for the varying bioavailability of naturally containing folate and added folic acid in foods. (15) The recommended dietary intake of folate for women of childbearing age is 400 µg/day DFE. This increases to 600 µg/day DFE during pregnancy. (15)

Measurement of dietary folate intake is complicated, relying on valid dietary assessment instruments and up-to-date food composition data. Few food composition databases in the world currently distinguish between naturally containing folate and added folic acid in foods. (16)

In addition to the increased dietary requirement from food, women who are at low risk of a NTD-affected pregnancy who plan to become pregnant, are recommended to take a 800 µg folic acid supplement (tablet) daily for at least four weeks prior to conception and for 12 weeks after conceiving to lower their risk of having an NTD-affected pregnancy. (17) Assessment of the quality of use of folic acid supplements periconceptionally is therefore also considered in the monitoring framework.

FOLIC ACID INTAKE

Adult nutrition survey 2008-09

The 2008-09 New Zealand adult nutrition survey (ANS09) was commissioned by the Ministry of Health to provide information for the development, implementation and monitoring of nutrition policies and programmes to improve the health of New Zealanders. The survey was carried out by the University of Otago from October 2008 to October 2009 and collected information about the eating habits and health characteristics of adult New Zealanders 15+ years. (18)

Methods

The survey was based on a complex multi-stage area-based sample design, consisting of random selection of primary sampling units, random selection of households within a primary sampling unit, and random selection of a single adult within a household. The survey included booster samples for Māori and Pacific adults. The survey sample was designed to be nationally representative. (18)

One day of food, beverage and supplement intakes were collected in 4721 adults using 24-hour diet recall methodology. A repeat 24-hour diet recall was collected in a subsample of 1180 adults within one month, so that nutrient intakes for each subgroup could be adjusted to obtain usual intake distributions. (18)

Nutrient intakes were determined by matching foods reported as consumed in the 24-hour diet recall with nutrients from either New Zealand food composition data, direct nutrient analysis or from an overseas database, including databases from Australia, the United States, Britain, Asia and the Pacific.

Key Results

It was expected that the ANS09 would calculate and report on dietary folate intakes. However, as reported by Parnell *et al.* (18) accuracy of nutrient estimates depends on two factors: (i) accuracy of information provided by the adults in the 24-hour diet recall, and (ii) accuracy of the food composition data. In this survey the authors determined that where food composition data were considered insufficiently reliable or incomplete (as was the case for folate), nutrient intake data would not be presented in the report. As such, no new data is available on adult's dietary folate intakes. (19)

The lack of any recently published data on the dietary folate intakes in New Zealand adults also precludes exploratory efforts to model the potential impact of the targeted voluntary bread fortification programme on the dietary folate intakes of adults, specifically women of childbearing age. It was MPI's intention to use the analytical folic acid content of the breads (Table 9), and the food consumption results from the ANS09 survey, to predict the population change in folic acid consumption with the introduction of the targeted voluntary fortification program. This will have to be deferred until the issues of reliability and/or completeness of the New Zealand folate food composition data can be addressed.

FOLIC ACID SUPPLEMENT USE

Adult nutrition survey 2008-09

Methods

Information on the methodology of the ANS09 has been reported previously (p19) and is reported in full by the University of Otago and Ministry of Health. (18) MAF commissioned the University of Otago to undertake post-hoc analysis of the ANS09 data to report on the proportion of New Zealand adults, including women of childbearing age, who reported consuming a dietary supplement containing folic acid. (20)

Supplement data were taken from the primary 24-hour diet recalls of 4721 New Zealand adults, including 1089 women 18-44 years. Supplements were described as those which the participant deemed to be a dietary supplement and included: folic acid supplements, multivitamins, and multivitamins/minerals. These data describe the proportion of New Zealand adults who reported consuming a dietary supplement containing folic acid.

Key Results

As reported by Parnell *et al.* (20) Table 12 summarises the above data. One hundred and ninety-one adults, 5.4% (95%CI: 4.3, 6.5) of the total survey sample, reported taking a supplement containing folic acid on the day of recall.

For the most part folic acid was derived from multivitamin and/or multivitamin and mineral supplements, 97.6% (95%CI: 96.6, 98.6). Women 51-70 years reported the highest use of supplements containing folic acid at 9.8% (95%CI: 5.8, 13.7), all derived from multivitamin and/or multivitamin and mineral supplements. Fifty-six women of childbearing age, 7.3% (95%CI: 5.0, 9.5), reported the use of supplements containing folic acid. In this group folic acid was derived mainly from multivitamin and/or multivitamin and mineral supplements. Only three women of childbearing age reported use of a folic acid only supplement. (20)

Calculated on an upper bound of the manufacturers recommended intake, the mean (SD) daily dose of folic acid would be approximately 296 (186) µg/d for all folic acid containing supplements (data not shown). The high standard deviation reflects the wide variability in folic acid which ranged from 5-1000 µg per daily dose (Table 13). Folic acid only supplements contained the highest median daily dose of folic acid at 550 µg. The lowest median daily dosage was reported in the B vitamin supplements at 200 µg. The highest single recommended daily dose of folic acid was 1000 µg found in a multivitamin supplement.

Table 12. Folic acid dietary supplement use among New Zealand adults 15+ years[†].

		Cell size[‡]	All dietary supplements[¶]	Contribution from multivitamins & minerals[††]
		(# folic acid)[§]	*Percent (95% CI)*	*Percent (95% CI)*
New Zealand Population (15+ yrs)		191 (# 0)	5.4 (4.3, 6.5)	97.6 (96.6, 98.6)
Males	15-18	7 (# 0)	1.2 (0.2, 2.2)	100 (0, 0)
	19-30	6 (# 0)	1.0 ([§§])	84.2 (0, 0)
	31-50	17 (# 0)	3.5 (1.6, 5.4)	100 (0, 0)
	51-70	11 (# 0)	4.3 (1.4, 7.1)	92.0 (0, 0)
	71+	15 (# 0)	2.6 (0.9, 4.4)	100 (0, 0)
	Total	56 (# 0)	2.9 (1.8, 4.0)	95.3 (0, 0)
Females	15-18	9 (# 0)	2.7 (0.7, 4.8)	100 (0, 0)
	19-30	23 (# 0)	8.4 (4.3, 12.4)	92.7 (90.2, 95.2)
	31-50	42 (# 0)	7.6 (4.6, 10.6)	99.5 (98.6, 100.5)
	51-70	29 (# 0)	9.8 (5.8, 13.7)	100 (0, 0)
	71+	32 (# 0)	5.1 (3.1, 7.1)	87.5 (83.2, 91.8)
	Total	135 (# 0)	7.7 (6.0, 9.4)	97.1 (96.4, 97.9)
Childbearing age[‡‡]		56 (# 3)	7.3 (5.0, 9.5)	96.5 (95.2, 97.8)

Notes:

† Details of all dietary supplement types containing folic acid are not reported as cell sizes are too small.

‡ Number reporting dietary supplement containing folic acid (Raw data cell sizes).

§ # number of participants reporting a supplement of folic acid.

¶ Data age adjusted and weighted to New Zealand population.

†† Proportion of reported supplements containing folic acid as part of a multi-vitamin/mineral.

‡‡ Women 18-44 yrs.

§§ Could not be reliably estimated.

Source : Parnell *et al.* 2011. (20)

Table 13. Compositional characteristics of folic acid dietary supplements by category, median, mean and range of recommended intakes **of folic acid (µg/d)**[†].

Category	Number	Median	Mean (Range)[†]
Folic acid only	2	550	550 (300, 800)
B vitamins	9	200	244 (20, 500)
Multivitamins	4	338	443 (96, 1000)
Multivitamins and minerals	72	300	287 (5, 800)

Note:

† Calculated on an upper bound of the manufacturers recommended intake.

Source: Adapted from Parnell *et al.* 2011. (20)

Consumer survey of women of childbearing age 2010

Methods

Information on the methodology of the Consumer Survey of Women of Childbearing Age 2010 has been reported previously (p9) and is reported in full by Kalafatelis and Fryer. (11)

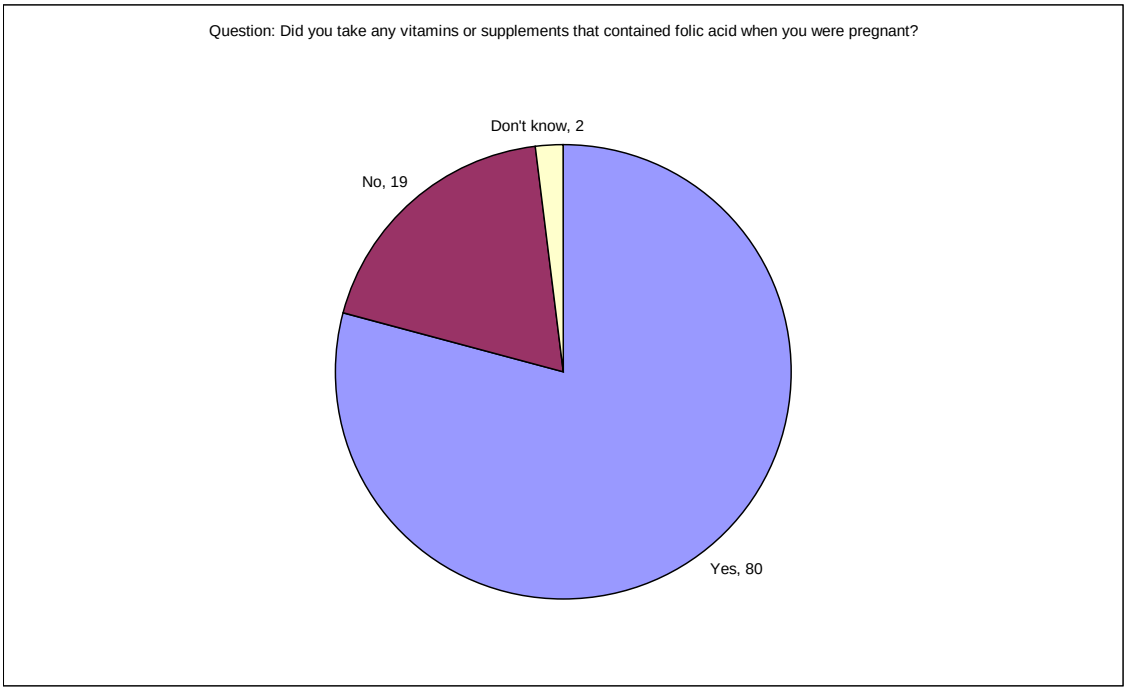
Key Results

One thousand women age 16-44 years were interviewed by telephone. The overall response rate was 49%. The data was then weighted by age and ethnicity to reflect the correct proportions in the population.

Fifty-nine percent of all the women interviewed for this survey were either currently pregnant, or had previously given birth. Kalafatelis and Fryer (11) found that 80% of those women reported taking vitamins or supplements containing folic acid while they were pregnant (Figure 3). Forty-one percent 41% reported taking them before they became pregnant, 18% within the first trimester and 38% when they discovered they were pregnant (Figure 4). This equated to 19%, 18% and 8% respectively, on a total sample basis.

Use of vitamins or supplements containing folic acid before pregnancy was significantly associated with older age (30+ years), tertiary level education and living in an urban centre ($p < 0.01$).

Figure 3. Self-reported use of folic acid dietary supplements during pregnancy among women of childbearing age (%) (n = 632)†,‡.



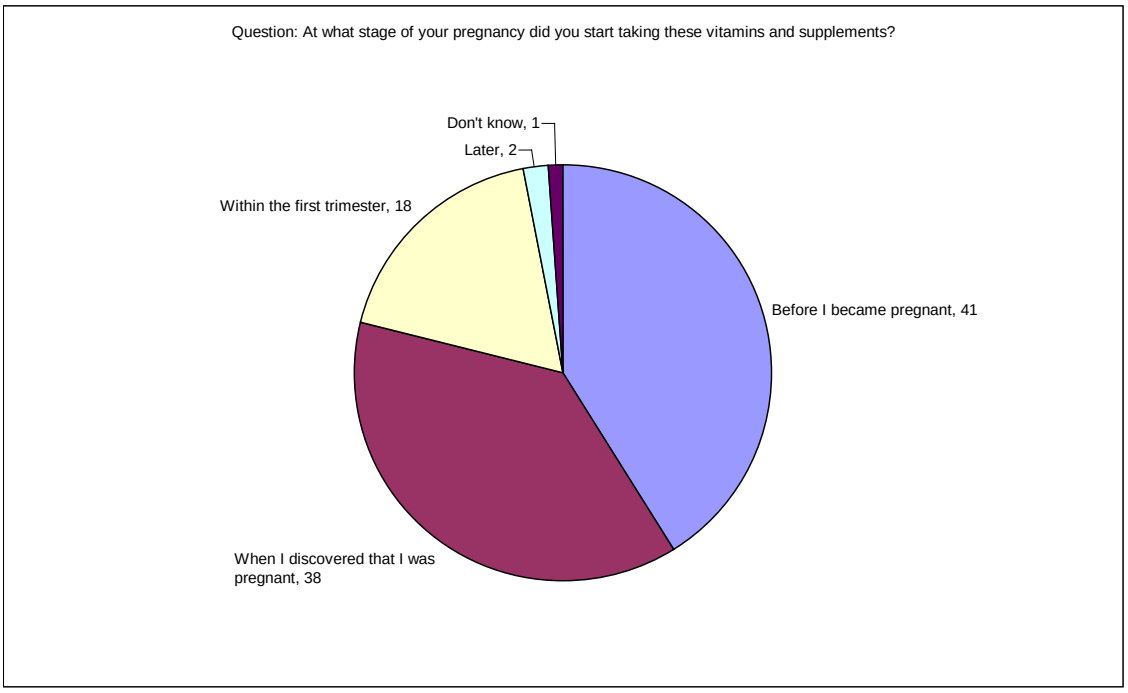
Notes:

† Sub-sample based on those who were pregnant at the time of the survey or who reported already having children.

‡ Total may not sum to 100% due to rounding.

Source: Kalafatelis and Fryer 2010. (11)

Figure 4. Self-reported use of folic acid dietary supplements during stage of pregnancy among women of childbearing age (n = 509)†,‡.



Notes:
† Sub-sample based on those women who took vitamins or supplements with folic acid while they were pregnant.
‡ Total may not sum to 100% due to rounding.

Source: Kalafatelis and Fryer 2010. (11)

Growing up in New Zealand study 2010

Growing up in New Zealand is a longitudinal study of approximately 7000 children and their families. The study aims to provide up-to-date, population relevant evidence about children growing up in New Zealand. (21)

Methods

Pregnant mothers were the contact point for recruitment of the cohort children. The sampling frame for the cohort was all expected births occurring in the regions covered by three District Health Boards (DHBs): Auckland, Counties-Manukau and Waikato within a defined time period. All pregnant women with an estimated delivery date (EDD) between 25 April 2009 and 25 March 2010, who lived within one of these three DHB areas during their pregnancy, were eligible to participate. There were no other inclusion or exclusion criteria.

The total sample size was based in particular on achieving adequate precision of statistical estimates for children identified as Māori throughout the study period. During pregnancy data was collected via face-to-face Computer Assisted Personal Interview (CAPI). Interviews for the Antenatal Data Collection Wave were completed in June 2010. Key health and wellbeing constructs that were measured at the antenatal interviews with mothers and partners included general health, exercise, diet, alcohol, and smoking questions. Mothers were specifically asked about vitamin and mineral usage before and during pregnancy, including prompting on folate and/or folic acid supplement usage.

Table 14. Self-reported maternal dietary supplement use in the 'Growing up in New Zealand Study 2010'.

	N	Never	Before pregnancy	Added during pregnancy
		n (Row %)	*n (Row %)*	*n (Row %)*
Planned				
Folate or folic acid	3719	284 (7.6%)	2167 (58.3%)	1268 (34.1%)
Vitamins/multivitamins/minerals	3719	1121 (30.1%)	1534 (41.2%)	1064 (28.6%)
Unplanned				
Folate or folic acid	2441	685 (28.1%)	217 (8.9%)	1539 (63.0%)
Vitamins/multivitamins/minerals	2442	1250 (51.2%)	321 (13.1%)	871 (35.6%)

Source: Morton *et al.* 2010 (21)

Key Results

Morton *et al.* (21) report that the use of dietary supplements during pregnancy was influenced by whether a pregnancy was planned or unplanned. Mothers who reported that their pregnancy was planned were more likely to have taken a folic acid containing dietary supplement before and throughout their pregnancy compared to mothers where the pregnancy was unplanned (Table 14). Of the planned pregnancies, 58% of mothers were taking a folic acid containing dietary supplement before their pregnancy, and almost all continued during pregnancy, while an additional 34% of mothers started taking folic acid during their pregnancy, usually from the first trimester onwards. Only 8% of mothers with planned pregnancies did not take folate at any time (Table 14). (21)

For pregnancies that were unplanned, 28% did not take folic acid at any time (before or during pregnancy). Nearly 9% were taking folic acid before and during their pregnancy and 63% took folic acid during their pregnancy, with approximately half beginning in the first trimester (Table 14).(21)

The vitamins and minerals in pregnancy survey 2011

The Vitamins and minerals in pregnancy survey (VAMPS) was a retrospective survey of postpartum women in birthing centres and hospitals located across New Zealand between 7 March and 15 April 2011. (22) Its primary aim was to extend existing knowledge on periconceptional folic acid use and maternal socio-demographic and behavioural characteristics by examining the effect of mandating the fortification of bread with folic acid.

Methods

Women were eligible for inclusion if they were aged 18 years or over, had delivered a healthy term infant, and could communicate in English. Dietary supplement use and bread intake prior to and during pregnancy were assessed using an anonymous, self-administered questionnaire.

Key Results

Of the 968 women invited to participate, 758 (78%) agreed. Of these, 35 women did not meet inclusion criteria for maternal age or gestational duration and were therefore excluded, resulting in a total sample of 723.

Only one-third (33.2%) of women surveyed reported taking folic acid as recommended, despite two-thirds of women indicating they were aware that folic acid should be taken periconceptionally. Mallard *et al.* (22) report that of the 56% of women who planned their

pregnancy, 56% took folic acid supplements (≥400 mg) as recommended compared with only 4% of women who reported their pregnancy was unplanned. Of the 33.2% reported to take folic acid supplements as recommended, approximately 61% were taking the prescribed 800 ug folic acid supplement recommended by the MoH (Houghton L. University of Otago. Email to: Michelle Gibbs (Advisor Science, Ministry of Agriculture and Forestry, Wellington, NZ). Re: Periconceptional folic acid supplement use. 2012 April 24). Socio-demographic factors associated with recommended folic acid intake included age, income, ethnicity ($p < 0.001$), parity ($p = 0.003$), and education ($p = 0.001$). (22)

SUMMARY

There is a lack of up-to-date information on the intake of DFE in the New Zealand population. This limits MPI's ability to investigate whether intakes in women of childbearing age have changed as a result of more widespread voluntary food fortification. It also precludes MPI from performing a more robust assessment of folic acid-related risk across the distribution of DFE intakes. Using predictive equations surrogate measures such as change in serum and red blood folate may be used to estimate dietary folic acid intakes.

Adherence to Ministry of Health policy guidelines for folic acid supplements (Tablets) is variable. At best, approximately 60% of some sub-groups report using a folic acid supplement during the periconceptional period. Women most likely to take a folic acid supplement are older, have higher incomes, are better educated and are more likely to have planned their pregnancy. However, there are many sub-groups of New Zealand women that report either starting a folic acid supplement once they know they are pregnant or never consuming a folic acid supplement at any time during their pregnancy.

Most surveys using self-reported data have not specifically identified the source of supplemental folic acid. There is considerable variability within and across dietary supplement types, with folic acid composition ranging from 5-1000 µg per daily dose. Data from the ANS09 suggests that most women appear to consume supplemental folic acid in the form of a multivitamin and/or a multivitamin and mineral supplement. Few women of childbearing age choose a folic acid only supplement. Approximately 20% of surveyed women who had delivered a healthy term infant reported using an 800 ug folic acid supplement as recommended during the periconceptional period.

Data gaps include the development of robust values for DFE. This would enable a more detailed examination of total DFE intakes and identify exposure pathways from foods. The variability in folic acid containing supplements would indicate that more work is needed to specifically identify the type of dietary supplement being consumed. Simply identifying women as either consumers or non-consumers of folic acid supplements will give a poor estimate of folic acid exposure given the wide variability in folic acid composition of dietary supplements.

Folate status

Measurement of folate status has historically included folate in serum and red blood cells. Serum (or plasma) folate concentrations are a sensitive indicator of recent folate intake, and fasting concentrations are a better indicator of short-term status. (23) Red blood cell folate concentrations are less sensitive than serum folate levels to short-term fluctuations in folate status and reflect long term tissue folate stores.

The monitoring question relates to whether the folate status of women of childbearing age has improved; so the mean or median value of serum and red blood cell folate can be used to assess changes over time. However, for an additional assessment, values can be compared with cutoff points for folate inadequacy or deficiency. (7)

It is recognised that there is no universally accepted cutoffs to define folate inadequacy or deficiency. In this report the same cutoffs as reported in the National Health and Nutrition Examination Survey are used to indicate folate deficiency (a red blood cell folate concentration of < 317 nanomoles per litre (nmol/L) and low serum folate concentrations (< 6.8 nmol/L). (18,24) To relate red blood cell folate concentration to risk of NTD-risk, cutoffs proposed by Daly *et al.* (25), whereby a red blood cell folate concentration < 339 nmol/L is used to categorise women at high risk of having a NTD-affected pregnancy, and a red blood cell folate concentration of ≥ 906 nmol/L is used to categorise women at very low risk of having a NTD-affected pregnancy.

ADULT NUTRITION SURVEY 2008-09

Methods

Information on the methodology of the ANS09 has been reported previously (p19) and is reported in full by the University of Otago and Ministry of Health. (18) The folate status measurements from the ANS09 reflect baseline values prior to the introduction of more widespread folic acid fortification of bread.

Key Results

The mean red blood cell folate concentration in New Zealand women 15+ years was 901 nmol/L (95%CI: 870, 932). Mean red blood cell folate ranged from 758 nmol/L (95%CI: 708, 808) for women 15-18 years to 1064 nmol/L (95%CI: 999, 1128) for women 71+ years. Only 2.5% (95%CI: 1.4, 3.6) of New Zealand women 15+ years had low red blood folate (< 317 nmol/L). (19) Pacific and Māori women had significantly lower mean red blood cell folate concentrations compared to non-Pacific and non-Māori women, -144.8 nmol/L and -86.3 nmol/L respectively ($p < 0.05$). (26,27)

Among all women of childbearing age, 27% had levels associated with low NTD risk (≥ 906 nmol/L) and 4% had red blood folate levels associated with high NTD risk (≤ 339 nmol/L). (19) There were no significant differences for either risk category between Pacific and Māori women compared to non-Pacific and non-Māori women. (26,27)

The mean serum folate concentration in New Zealand women 15+ years was 31.1 nmol/L (95%CI: 29.4, 32.8). Mean serum folate ranged from 24.4 nmol/L (95%CI: 22.4, 26.4) for women 15-18 years to 39.7 nmol/L (95%CI: 34.2, 45.1) for women 71+ years. Only 1.6% (95%CI: 0.8, 2.3) of New Zealand women 15+ years had low serum folate (< 6.8 nmol/L). (19)

2011 FOLATE AND WOMEN'S HEALTH SURVEY

Methods

For analysis of folate status following the introduction of more widespread folic acid fortification of bread, a cross-sectional survey of women of childbearing age was carried out from April to August 2011 in two city centres of New Zealand – a South Island centre, Dunedin, and a North Island centre, Wellington. The survey used a stratified random sampling technique with the electoral role as the sampling frame.

A sample size of 300 participants (150 in each city centre) would provide 90% power (alpha = 0.05, two sided) to detect a 64 nmol/L change in red blood cell folate concentrations – about one quarter of a standard deviation – and a change in the proportion of women with red blood cell folate concentrations ≥ 906 nmol/L from 33% to 46%. An additional consideration in choosing the sample size was the size of the confidence interval around the estimate of the proportion of women with a red blood cell folate concentration ≥ 906 nmol/L. For a prevalence of 50% of women ≥ 906 nmol/L, 300 participants would give a confidence interval ± 5-6%.

A self-administered questionnaire was used to collect information on socio-demographic characteristics and factors that may affect folate status. Participants also completed a telephone interview during which information about their frequency of consumption in the past week of breakfast cereals, breads, fortified spreads, and supplements was collected.

Participants attended a morning clinic at which anthropometric measures were taken and two fasting blood samples were drawn. Serum and whole blood folate were measured by microbiological assay and cut-offs used to indicate low serum folate concentrations (< 6.8 nmol/L) and folate deficiency (a red blood cell folate concentration of < 317 nmol/L). To relate red blood cell folate concentration to risk of NTD, cut-offs were again used, a red blood cell folate concentration < 339 nmol/L was used to categorise women at high risk of having a NTD-affected pregnancy, and a red blood cell folate concentration of ≥ 906 nmol/L was used to categorise women at very low risk of having a NTD-affected pregnancy.

Key Results

Invitations to participate in the study were delivered to 310 Dunedin women. The total response rate for Dunedin was 51%. In the Wellington sample, 300 women were invited to participate in the study. The response rate for the Wellington sample was 39%. Due to this low response rate a second Wellington sample of 114 women were invited to participate in the study. The response rate for the second Wellington sample was 32%. The overall response rate for the combined Wellington samples combined was 37%.

Serum and red blood cell folate concentrations of participants

As reported by Bradbury *et al.* (12) women in the survey had a mean (SEM) serum folate concentration of 36 (1) nmol/L and red blood cell folate concentration of 1096 (30) nmol/L (Table 15). After log-transformation the geometric mean for serum folate was 30 nmol/L (95%CI: 28, 32 nmol/L) and geometric mean for red blood cell folate was 996 nmol/L (95%CI: 945, 1049) nmol/L). The median serum folate concentration was 29 nmol/L (interquartile range: 20, 47 nmol/L) and the median red blood cell folate concentration was 989 nmol/L (interquartile range: 744, 1316). The prevalence of women with deficient serum and red blood cell folate concentrations, defined as < 6.8 nmol/L for serum and < 317 nmol/L for red blood cell, was 1%. Almost 60% of women in the survey had a red blood cell folate

concentration ≥ 906 nmol/L, a concentration associated with NTD risk similar to women taking a 400 µg/d folic acid supplement. (12)

The relation between bread and breakfast cereal consumption and serum and red blood cell folate concentrations

Participants who reported consuming folic acid fortified bread had a significantly higher mean serum folate concentration compared with participants who did not consume folic acid fortified bread according to Bradbury *et al.* (12) (Table 16). The ratio of geometric means after adjustment for use of folic acid supplements, consumption of folic acid fortified breakfast cereal, and city of residence was 1.24 (95%CI: 1.05, 1.48; $p = 0.012$). The same trend in serum folate concentration was apparent for consumers of fortified breakfast cereal relative to non-consumers with an adjusted ratio of 1.15 (95%CI: 1.00, 1.31; $p = 0.042$). Mean red blood cell folate concentrations were not significantly higher in consumers of folic acid fortified bread, however, there was a trend for higher concentrations amongst consumers; the adjusted ratio was 1.12 (95%CI: 0.99, 1.28; $p = 0.079$). Participants who ate folic acid fortified breakfast cereals had significantly higher red blood cell folate concentrations compared with those who did not consume folic acid fortified breakfast cereal; the adjusted ratio was 1.13 (95%CI: 1.02, 1.25; $p = 0.019$).

Comparison with serum and red blood cell folate status pre-voluntary folic acid fortification of bread

The blood folate results from the ANS09 and the 2011 Folate and women's health survey are compared in Table 17. Mean and geometric-mean serum and red blood cell folate concentrations were significantly higher (all $p < 0.001$) in the 2011 Folate and women's health survey compared to participants aged 18-44 years in the ANS09. The magnitude of difference for serum folate concentrations was 7.9 nmol/L (95% CI: 4.3, 11.4 nmol/L), and for red blood cell folate concentration it was 302 nmol/L (95% CI: 229, 374 nmol/L). The proportion of women in the 2011 Folate and women's health survey with red blood cell folate concentrations ≥ 906 nmol/L was 59% (95%CI: 53, 65), compared with 26% (95% CI: 22,31) of women of similar age in the ANS09.

A population-based survey of 212 women, 18-45 years living in Dunedin was conducted in 1999 and showed that median (interquartile range) red blood cell folate concentration was 787 nmol/L (616, 1073 nmol/L) (data not shown). (28) This is lower than the results of the present survey which show a median (interquartile range) red blood cell folate concentration of Dunedin women was 1042 nmol/L (778, 1381 nmol/L).

Based on the work of Daly *et al.* (25) and Wald *et al.* (29), the change in arithmetic mean serum folate concentration from the ANS09 to the 2011 Folate and women's health survey can be used to predict the decline in NTD rate. An 18% reduction in NTD rate would be predicted from the increase in serum folate concentration from 27.8 nmol/L to 35.6 nmol/L that occurred between 2009 and 2011. (12)

SUMMARY

From the data presented in this report it appears that the folate status has improved between the pre- and postfortification periods for women of childbearing age. Both red blood cell folate and serum folate concentrations increased significantly. Fifty-nine percent of women in the 2011 Folate and women's health survey returned a red blood cell folate measurement of ≥ 906 nmol/L, a level associated with a very low risk of having an NTD-affected pregnancy. This was up from 26% of women as reported in the ANS09.

There was a non-significant trend for average red blood cell folate levels to be higher in those women who consumed folic acid fortified breads.

These improvements in red blood cell folate status cannot be statistically attributed to the wider availability of folic acid fortified breads. However, after accounting for other factors, it does appear to have made a contribution to the increased folate status of women of childbearing age. Other factors that may have contributed to the increase in postfortification blood folate concentrations in women of childbearing age may have been the increased availability and consumption of folic acid fortified breakfast cereals and other foods.

Although there was no significant difference in terms of NTD risk for Pacific and Māori women compared to non-Pacific and non-Māori at baseline, testing of ethnic differences was not an objective of the 2011 Folate and women's health survey but does deserve further investigation.

Table 15. Serum and red blood cell folate status (nmol/L) of participants in the 2011 Folate and women's health survey.

	All	Wellington	Dunedin	Difference (95%CI)[§]	Ratio (95%CI)[¶]	Adjusted ratio (95%CI)[††]
Serum folate (nmol/L)						
Number	271	129	142			
Mean (SEM)	36 (1)	33 (2)	38 (2)			
Geometric mean (95%CI)	30 (28, 32)	27 (25, 30)	32 (29, 35)		1.17 (1.01, 1.35) $p = 0.033$	1.13 (1.00, 1.29) $p = 0.068$
Median (IQR)[†]	29 (20, 47)	25 (19, 37)	33 (20, 49)	8 (2, 13) $p = 0.004$		
< 6.8 nmol/L[‡]	1% (0, 2)	1% (0, 2)	1% (0, 2)			
Red blood cell folate (nmol/L)						
Number	271	129	142			
Mean (SEM)	1096 (30)	1034 (44)	1152 (42)			
Geometric mean (95%CI)	996 (945, 1049)	935 (866, 1010)	1054 (982, 1131)		1.13 (1.01, 1.25) $p = 0.025$	1.11 (1.00, 1.22) $p = 0.052$
Median (IQR)[†]	989 (744, 1316)	897 (675, 1251)	1042 (778, 1381)	157 (37, 276) $p = 0.011$		
< 317 nmol/L[‡]	1% (0, 2)	1% (0, 2)	1% (0, 2)			
≤ 339 nmol/L[‡]	1% (0, 2)	1% (0, 2)	1% (0, 2)			
≥ 906 nmol/L[‡]	59% (53, 65)	49% (40, 58)	68% (61, 76)			

Notes:
[†] Interquartile range (IQR), 1st and 3rd quartile.
[‡] Values are % (95%CI).
[§] Difference between medians of Dunedin and Wellington.
[¶] Ratio of the geometric means of Dunedin relative to Wellington.
[††] Ratio of the geometric means of Dunedin relative to Wellington adjusted for use of folic acid containing supplements (Y/N), and breakfast cereal consumption (Y/N).

Source: Bradbury *et al.* 2011. (12)

Table 16. Serum and red blood cell folate concentration (nmol/L) of participants in the 2011 Folate and women's health survey according to consumption of folic acid fortified bread or breakfast cereal.

	Bread				Breakfast cereal			
Measurement	Fortified[†]	Non-fortified, unidentified, or no bread[†]	Adjusted ratio (95%CI)[‡]	p value	Fortified[†]	Non-fortified, unidentified, or no bread[†]	Adjusted ratio (95%CI)[§]	p value
Serum folate	37 (32, 44)	28 (26, 31)	1.24 (1.05, 1.48)	0.012	33 (29, 36)	28 (25, 31)	1.15 (1.00, 1.31)	0.042
Red blood cell folate	1124 (990, 1276)	969 (906, 1026)	1.12 (0.99, 1.28)	0.079	1079 (991, 1176)	942 (883, 1006)	1.13 (1.02, 1.25)	0.019

Notes:

[†] Values are geometric mean (95%CI).

[‡] Ratio of the geometric means of folic acid fortified relative to non-fortified, unidentified or no bread adjusted for use of folic acid containing supplements (Y/N), city of residence (Wellington or Dunedin), and fortified breakfast cereal consumption (Y/N). For example, 1.24 can be interpreted as a 24% higher geometric mean serum folate concentration in consumers of fortified bread compared with non-fortified or unknown bread.

[§] Ratio of the geometric means of folic acid fortified relative to non-fortified, unidentified or no breakfast cereal adjusted for use of folic acid containing supplements (Y/N), city of residence (Wellington or Dunedin), and fortified bread consumption (Y/N).

Source: Bradbury *et al.* 2011. (12)

Table 17. Comparison of folate status between the 2008-09 New Zealand adult nutrition survey and the 2011 Folate and women's health survey.

	2008-09 New Zealand adult nutrition survey	2011 Folate and women's health survey	Mean difference (95% CI)	Ratio (95%CI)	p value
Serum folate (nmol/L)					
Mean (SEM)	27.8 (1.1)	35.6 (1.4)	7.9 (4.3, 11.4)		< 0.001
Geometric mean (95%CI)	23 (21, 24)	30 (28, 32)		1.31 (1.19, 1.45)	< 0.001
Red blood cell folate (nmol/L)					
Mean (SEM)	794 (21)	1096 (30)	302 (229, 374)		< 0.001
Geometric mean (95%CI)	720 (686, 755)	996 (945, 1049)		1.38 (1.29, 1.48)	< 0.001
≥ 906 nmol/L (95%CI)	26% (22, 31)	59% (53, 65)	33% (26, 40)		< 0.001

Source: Bradbury *et al.* 2011. (12)

Health benefits

The principal health benefit considered in this report is a reduction in the incidence of NTDs. Neural tube defects are a major group of birth defects where the brain, spinal cord, or the covering of these organs has not developed properly. Spina bifida and anencephaly are the most common types of NTDs.

Neural tube defects in humans result from the combined effects of genetic and environmental influences. (30) A meta-analysis of randomised and quasi-randomised trials has demonstrated that folic acid in doses ranging from 360 µg to 4000 µg/d alone or in combination with other vitamins and minerals, lowers the risk of first and second time occurrence of NTD-affected pregnancies. (1) The mechanism underlying the beneficial effects of folic acid is unclear. (30,31)

Not all cases of NTD are prevented by increasing folic acid intake. Further, Heseker *et al*. have demonstrated that the degree of reduction in NTD-affected pregnancies from folic acid is associated with the baseline prevalence of NTD and that there may be a 'floor effect' below which folic acid does not appear to be effective, regardless of folic acid intake. (32) This floor effect is estimated to be four to five cases at birth per 10000 births or seven to eight cases at birth or termination per 10000 births.

NEURAL TUBE DEFECTS

New Zealand Birth Defects Registry

Data on NTD prevalence in New Zealand are available from the New Zealand Birth Defects Registry (NZBDR) which collects data from the National Minimum Dataset for public and private hospital discharges (for live births) and the Adult and Perinatal Mortality Database (for stillbirths).

Children diagnosed with spina bifida, anencephaly or encephalocele are included in the data. Because children with spina bifida are not always diagnosed at birth in New Zealand, they have been added to the data set retrospectively for their birth year.

Data are collected on all live births with a diagnosed birth defect delivered or treated in a publicly funded hospital. Data on stillbirths are retrospectively added to the database, together will additional cases derived from the national perinatal and mortality databases.

From 2001-08 the number of live births and stillbirths affected by NTDs increased from 21 in 2001 to a peak of 41 in 2005, and has then decreased slightly to 34 in 2008 (Table 18). The highest prevalence rate was 7.1 cases per 10000 total births in 2005 and the lowest was 3.7 in 2001. The mean rate over this four year period was 5.4 cases per 10000 total births.

Comparison with baseline data is complicated by the absence of more recent data on NTDs diagnosed among terminations of pregnancy (TOPs). These are not available for the period since 2004 due to a change in the reporting method.

In February 2011, the NZBDR implemented a voluntary system for the notification of birth defects in TOP data. The data in Table 18 are only for live births and stillbirths reported to the NZBDR, as data on NTD number and/or rate are not yet available for the period following the introduction of the targeted voluntary bread fortification programme in 2009. (Borman B.

Centre for Public Health Research (Massey University, Wellington, NZ. Email to: David Roberts, Manager Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ, 2011 November 11).

Table 18. Neural tube defects, by birth outcome and year of birth, New Zealand, 2001-2008.

Year	Live births with neural tube defects	Fetal deaths* (stillbirths) with neural tube defects	Total live births and fetal deaths with neural tube defects	
	Number	*Number*	*Number*	*Rate*†
2001	14	7	21	3.7
2002	16	9	25	4.6
2003	14	13	27	4.8
2004	18	20	38	6.5
2005	22	19	41	7.1
2006	20	18	38	6.4
2007	15	15	30	4.7
2008	23	11	34	5.2
Total	142	112	254	5.4‡

Notes:
* Defined as fetal deaths of 20 weeks' or more gestation, or 400g or more birthweight
† Prevalence rates are per 10000 live births and fetal deaths
‡ Mean prevalence rate for the period 2001-2008

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.

Caveat: These data are from the New Zealand Birth Defects Registry (NZBDR) which has continuous ascertainment of cases. Therefore, if a child is born in 2006, but treated/diagnosed and reported to the NZBDR in 2010, that case is included in the 2006 birth cohort. Data on children initially considered to have an NTD may be later removed from the database if an alternate diagnosis is made, and similarly children diagnosed with an NTD some time after birth may be added to the database. Data are accrued according to the year the child was born, whether as a live birth or fetal death. Therefore, changes to diagnoses in the present may affect NTD data recorded against preceding years

SUMMARY

Based on the current NTD data it is impossible to answer the monitoring question for the pre- and postfortification periods. Rates of NTD prevalence are variable year-to-year with little discernable trend before the introduction of more widespread folic acid fortification of bread. More recent data on NTDs diagnosed among terminations of pregnancy (TOPs) is absent and will be important to capture the breadth of NTD outcomes. Due to the nature of reporting this information may not be available for several years.

Adverse health effects

As reported by AIHW, due to the emerging focus on cancer and folic acid in the media and academic literature the incidence and mortality of these cancers are reported here to enable monitoring change over time. (7)

There are many potential influences on cancer incidence and mortality. The collection of cancer data is ongoing, and provides a means for monitoring incidence and mortality, but not the effect of folic acid fortification on these. As such, these data have limited application/interpretability in the monitoring framework.

Concurrently MPI have also undertaken a systematic review of the literature on any potential association between folic acid supplementation and cancer.

CANCER

Incidence and Mortality in New Zealand

The New Zealand Cancer Registry is a population-based register of all primary malignant diseases diagnosed in New Zealand, excluding squamous cell and basal cell skin cancers.

The registry was set up in 1948, primarily using information sent by public hospitals to the National Minimum Dataset. Since the Cancer Registry Regulations 1994 came into effect, laboratory test results have been collected, and the data quality and completeness have significantly improved.

Data on deaths from cancer are sourced from the Mortality Collection held by the Ministry of Health Information Directorate. The Mortality Collection includes all deaths recorded in New Zealand for a particular year. Overseas deaths of cancer patients registered in New Zealand are not included in the collection.

The cancers are classified using the International Statistical Classification of Diseases and Related Health Problems (ICD), and the International Classification of Diseases for Oncology (ICD-O). All data are mapped to ICD-10 codes.

Age-standardised rates are presented in this report. More detailed data, including the number of cases, are available from the New Zealand Health Information Service publications.

This data is the most recently available final data and dates up to and including 2008. Some provisional cancer registration data from 2009 and 2010 data is available on the Ministry of Health's website (www.moh.govt.nz) but no provisional 2009 data is yet available. It takes a number of years for all deaths to have a cause of death identified and coded, and this has an impact on the ability to produce final cancer registration data. (Lewis C. Analytical Services (Ministry of Health, Wellington, NZ). Email to: David Roberts (Manager, Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ). Cancer incidence and mortality. October 2011 19)

Colorectal Cancer

Age-standardised incidence and mortality rate data for colorectal cancer are presented in Table 19 and Figure 5, and a summary of these results is provided below.

Incidence

Males
From 1994 to 2008 the age-standardised incidence rate for males decreased by an average of 1.7% per year, from 63.5 cases per 100000 population in 1994 to 49.2 in 2008 (Figure 5). The highest rate was in 1994.

Females
From 1994 to 2008 the age-standardised incidence rate for females decreased by an average of 1.8% per year, from 50.3 cases per 100000 population in 1994 to 38.6 in 2008 (Figure 5). As with males, the highest rate was in 1994.

Mortality

Males
From 1994 to 2008 the age-standardised mortality rate for males decreased by an average of 1.7% per year, from 30.0 cases per 100000 population in 1994 to 23.2 in 2008 (Figure 5). The highest rate was in 1994.

Females
From 1994 to 2008 the age-standardised mortality rate for females decreased by an average of 2.3% per year, from 21.9 cases per 100000 population in 1994 to 15.6 in 2008 (Figure 5). The highest rate was in 1994.

Prostate Cancer

Age-standardised incidence and mortality rate data for prostate cancer are presented in Table 20 and Figure 6, and a summary of these results is provided below.

Incidence

From 1994 to 2008 the age-standardised incidence rate increased by an average of 0.7%, from 100.5 cases per 100000 population in 1994 to 103.3 in 2008 (Figure 6). The highest rate was 132.9 in 2000.

Mortality

From 1994 to 2008 the age-standardised mortality rate decreased by an average of 1.1% per year, from 25.8 cases per 100000 population in 1994 to 21.5 in 2008 (Figure 6). The highest rate was 27.3 in 1995.

Breast Cancer

Age-standardised incidence and mortality rate data for breast cancer are presented in Table 21 and Figure 7, and a summary of these results is provided below.

Incidence

From 1994 to 2008 the age-standardised incidence rate increased by an average of 0.4%, from 89.0 cases per 100000 population in 1994 to 93.3 in 2008 (Figure 7). The highest rate was 97.2 in 2000.

Mortality

From 1994 to 2008 the age-standardised mortality rate decreased by an average of 1.9% per year, from 25.5 cases per 100000 population in 1994 to 19.1 in 2008 (Figure 7). The highest rate was 28.6 in 1996.

Table 19. Age-standardised incidence and mortality rates for colorectal cancer, New Zealand, 1994–2008 (ICD-10 codes: C18-C20)[†,‡,§].

Year	Incidence			Mortality		
	Male	*Female*	*Persons*	*Male*	*Female*	*Persons*
1994	63.5	50.3	56.2	30.0	21.9	25.6
1995	59.8	48.1	53.4	28.8	21.0	24.2
1996	60.3	46.2	52.8	28.4	20.6	24.0
1997	55.0	43.0	48.4	26.5	18.0	22.0
1998	56.1	43.9	49.4	25.3	18.7	21.7
1999	58.2	44.4	50.7	25.6	18.9	21.9
2000	53.3	44.9	48.7	24.2	18.5	21.1
2001	55.6	44.0	49.2	25.2	17.9	21.1
2002	54.4	41.6	47.6	23.8	16.5	19.8
2003	54.2	42.5	48.0	21.9	16.8	19.1
2004	52.7	43.2	47.5	21.5	17.5	19.3
2005	50.4	42.5	46.2	22.5	17.3	19.7
2006	54.7	39.3	46.5	20.3	16.9	18.6
2007	51.0	39.4	44.7	22.4	16.3	19.1
2008	49.2	38.6	43.5	23.2	15.6	19.1

Notes:

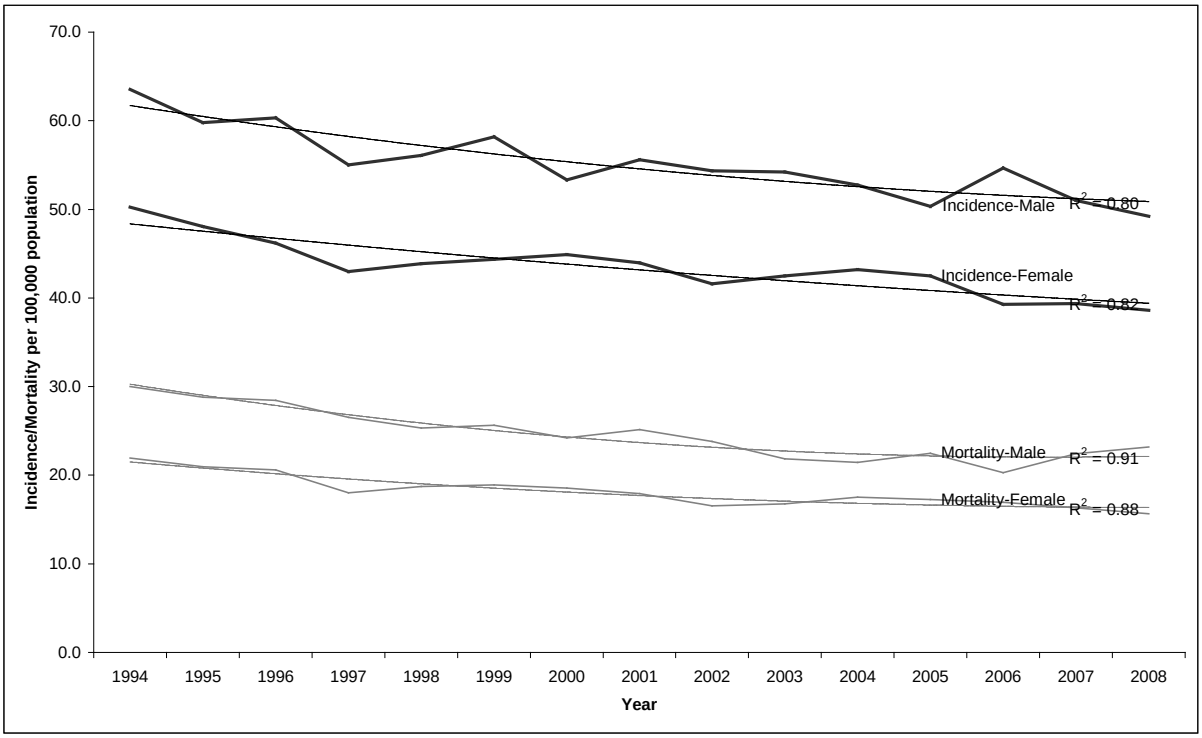
† Rates are the number of cases per 100000 population.

‡ Mortality data are tabulated by the year of registration.

§ Rates are standardised to the 2001 World Health Organization standard population.

Source: Lewis C. Analytical Services (Ministry of Health, Wellington, NZ). Email to: David Roberts (Manager, Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ). Cancer incidence and mortality. October 2011 19.

Figure 5. Age-standardised incidence and mortality rates for colorectal cancer, New Zealand, 1994–2008 (ICD-10 codes: C18-C20)[†].



Note:

† Age-standardised to the 2001 World Health Organization standard population.

Source: Lewis C. Analytical Services (Ministry of Health, Wellington, NZ). Email to: David Roberts (Manager, Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ). Cancer incidence and mortality. October 2011 19.

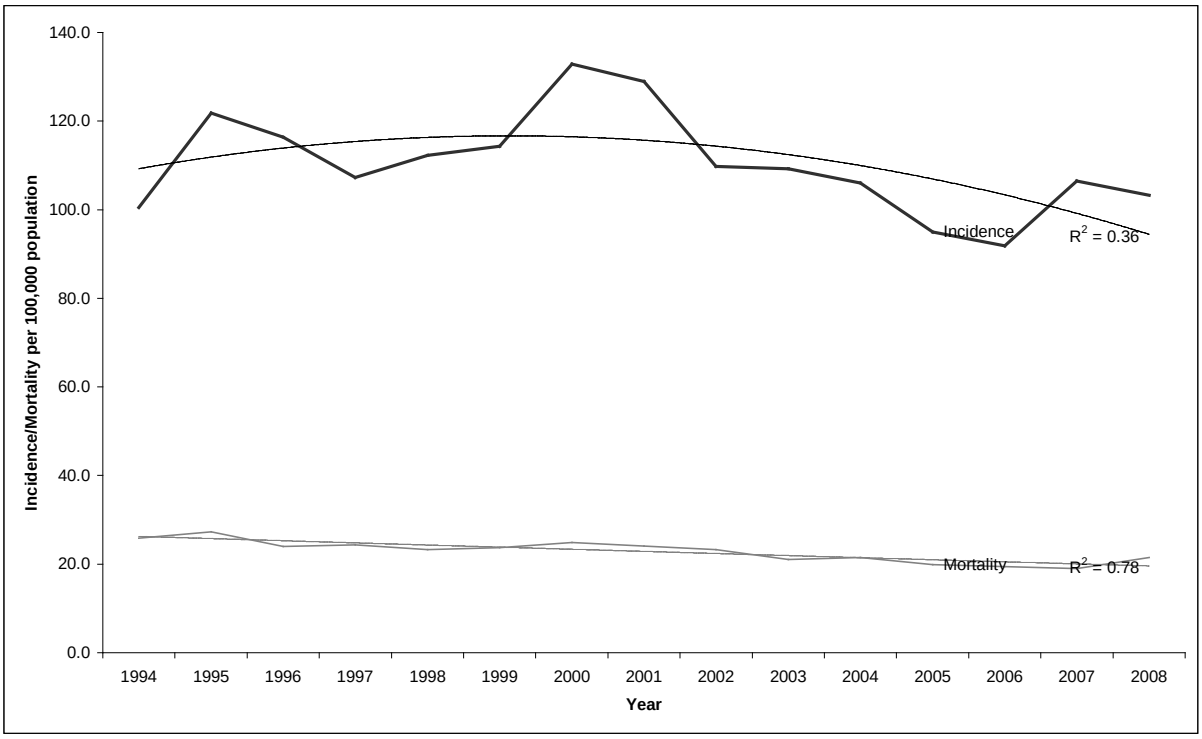
Table 20. Age-standardised incidence and mortality rates for prostate cancer, New Zealand, 1994–2008 (ICD-10 code: C61)[†,‡,§].

Year	Incidence	Mortality
1994	100.5	25.8
1995	121.8	27.3
1996	116.4	24.0
1997	107.3	24.3
1998	112.3	23.3
1999	114.3	23.8
2000	132.9	24.9
2001	128.9	24.1
2002	109.8	23.3
2003	109.3	21.0
2004	106.1	21.5
2005	95.0	19.9
2006	91.8	19.4
2007	106.5	19.0
2008	103.3	21.5

Notes:
† Rates are the number of cases per 100000 population.
‡ Mortality data are tabulated by the year of registration.
§ Rates are standardised to the 2001 World Health Organization standard population.

Source: Lewis C. Analytical Services (Ministry of Health, Wellington, NZ). Email to: David Roberts (Manager, Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ). Cancer incidence and mortality. October 2011 19.

Figure 6. Age-standardised incidence and mortality rates for prostate cancer, New Zealand, 1994–2008 (ICD-10 code: C61)[†].



Note:
† Age-standardised to the 2001 World Health Organization standard population.

Source: Lewis C. Analytical Services (Ministry of Health, Wellington, NZ). Email to: David Roberts (Manager, Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ). Cancer incidence and mortality. October 2011 19.

Table 21. Age-standardised incidence and mortality rates for breast cancer, New Zealand, 1994–2008 (ICD-10 code: C50)[†,‡,§].

Year	Incidence	Mortality
1994	89.0	25.5
1995	87.5	28.4
1996	87.5	28.6
1997	87.4	25.8
1998	88.8	25.2
1999	95.4	25.3
2000	97.2	23.6
2001	94.2	22.7
2002	93.6	22.4
2003	89.3	23.1
2004	88.5	22.4
2005	92.0	21.7
2006	92.1	20.3
2007	90.3	20.8
2008	93.3	19.1

Notes:

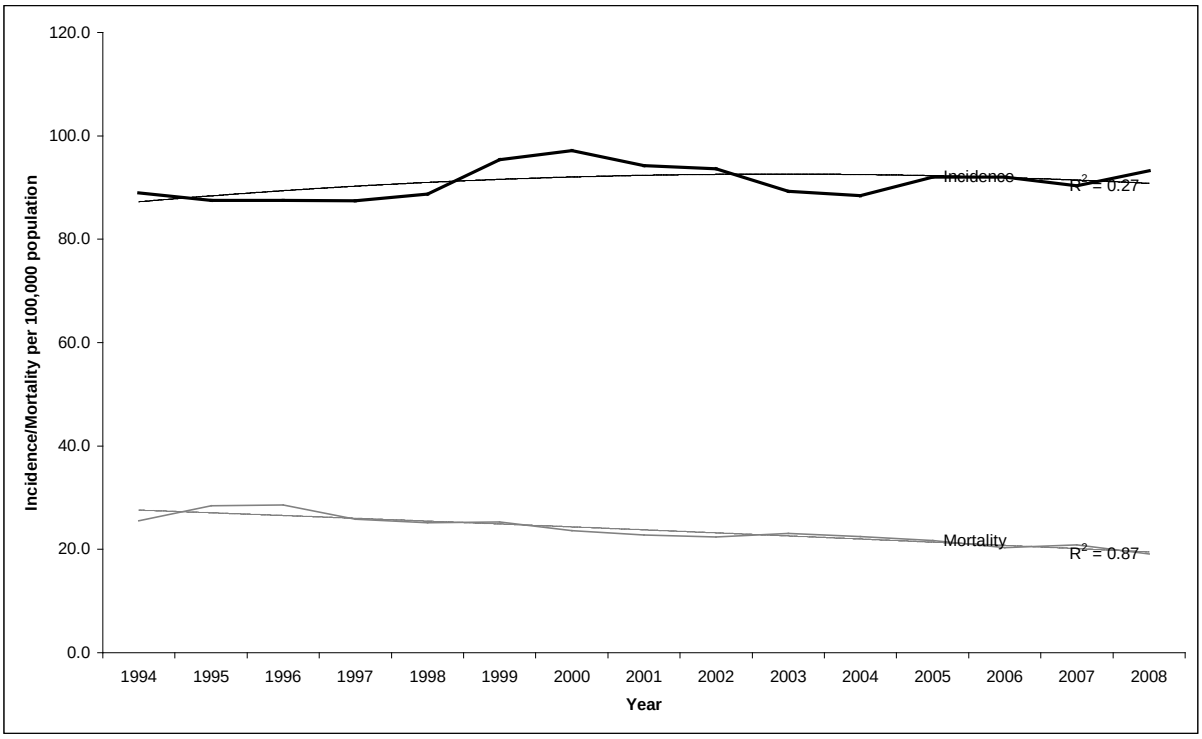
† Rates are the number of cases per 100000 population.

‡ Mortality data are tabulated by the year of registration.

§ Rates are standardised to the 2001 World Health Organization standard population.

Source: Lewis C. Analytical Services (Ministry of Health, Wellington, NZ). Email to: David Roberts (Manager, Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ). Cancer incidence and mortality. October 2011 19.

Figure 7. Age-standardised incidence and mortality rates for breast cancer, New Zealand, 1994–2008 (ICD-10 code: C50)[†].



Note:

† Age-standardised to the 2001 World Health Organization standard population.

Source: Lewis C. Analytical Services (Ministry of Health, Wellington, NZ). Email to: David Roberts (Manager, Nutrition, Ministry of Agriculture and Forestry, Wellington, NZ). Cancer incidence and mortality. October 2011 19.

Review of the association between folic acid and cancer

Background

Food Standards Australia New Zealand (FSANZ) has previously conducted a review of the relationship between folic acid and cancer as part of the risk assessment to inform the P295 Final Assessment Report (33) and again in May 2007 in the First Review Report. (34) Currently FSANZ are in the process of conducting a meta-analysis of the literature. The aim of MPI's review is to provide an update of the evidence that has been published since the FSANZ First Review Report published in 2007.

At the time of the First Review Report the published literature examining folic acid and cancer was mostly limited to cohort and case control studies. However, since this time the results of several large randomised controlled trials (RCTs) of folic acid supplementation and other B vitamins have been reported. These trials have been designed primarily to study the use of folic acid supplements to either prevent cardiovascular disease or recurrence of colorectal adenomas in high risk groups of patients rather than the general population. Few trials have specifically been designed to investigate the effect of folic acid and cancer incidence. It is also important to note that the folic acid supplement doses of these trials range from 0.5 to 5 mg per day in the trials reviewed. Under mandatory fortification in New Zealand it is estimated that folic acid intake would increase by approximately 0.2 mg in 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. (34)

Methods

A systematic search of Scopus and the MEDLINE database via PubMed from 1 January 2007 through to February 2012 was conducted. The following search terms were used: "folate" or "folic acid" in combination with one of the following "cancer" or "prostate cancer" or "colorectal cancer" or "colorectal adenoma" or "bowel cancer" or "breast cancer". In addition to this, reference lists of studies were hand-searched to identify additional relevant studies.

The search was limited to studies that were published in English, human trials, and were either RCTs or meta-analyses. Only trials that used folate in the form of folic acid within the supplement were included, one RCT used 5-methylytetrahydrofolate in supplement form and has been excluded from this review. (35) Site-specific cancers were limited to colorectal, breast and prostate cancer in keeping with the AIHW monitoring and evaluation baseline report.

Results

Seven RCTs (36-42) and six meta-analyses (43-48) were identified which reported folic acid and risk of total cancer and/or site-specific cancer incidence (Table 22 and Table 23). A further paper (49) was identified which conducted a secondary analysis of the original RCT published by Cole *et al.* (36)

For the seven RCTs which reported folic acid and cancer incidence outcomes, trial duration ranged from 3-8 years. Treatment was folic acid either alone or in combination with aspirin or B-vitamins. Folic acid treatment ranged from 0.5-5 mg/day. The RCTs were conducted in several different countries, some of which had mandatory folic acid fortification. These trials were either designed to prevent cardiovascular disease in at risk patients (39-41), or to reduce the recurrence of colorectal adenomas in patients with a previous history of colorectal adenomas. (36,38,42)

Four RCTs (36,38,42,50) and three meta-analyses (46,47,51) were identified that specifically assessed the association between folic acid and recurrence of colorectal adenomas. Participants in each of these trials had a prior history of colorectal adenomas at recruitment and each trial was specifically designed to assess recurrence of colorectal adenomas as the primary outcome.

Total Cancer Incidence

In general, the results of RCTs and meta-analysis report that folic acid has no significant effect on cancer incidence. Table 22 and Table 23 provide a summary of all published RCTs and meta-analyses since the last review FSANZ conducted in 2007. Results from the seven large RCTs published since 2006 have generally reported either no effect of folic acid or a slight non-significant increase in the incidence of cancer with folic acid supplementation (38,39,41), with only one study reporting a significant increase in incidence with folic acid supplementation. (36)

Results from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) collaborative group provide the most compelling evidence from an individual randomised controlled trial. (39) It is the largest study that has been conducted and randomised 12064 survivors of myocardial infarction to placebo or a supplement containing 2 mg of folic acid and 1 mg of B_{12} supplement a day for 6.7 years. The study took place across multiple study centres in the UK at a time when voluntary fortification of selected foods was permitted, but prior to implementation of mandatory fortification of bread. Thus this study provides a good example of the effect of folic acid supplementation in a non mandatory setting similar to New Zealand. After almost seven years of follow-up there was a non-significant slight increase in the incidence of cancer (RR 1.07; 95% CI: 0.96-1.19).

The most thorough analysis of the randomised trials that has been conducted to date is that of Clarke *et al.* of the B-Vitamin Treatment Trialists' Collaboration. (44) The group consists of almost all researchers involved in folic acid supplementation trials to lower plasma homocysteine. The B-Vitamin Treatment Trialists' Collaboration conducted an individual participant data meta-analysis which included seven large RCTs, involving a total of 35603 individuals. Of these trials, one has not published the effect of folic acid on cancer outcomes. 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. As such, none of the trials examining the effect of folic acid on recurrence of colorectal adenomas were included in this meta-analysis. Although vascular disease was the primary outcome assessed by the meta-analysis there was a substantial number of incidents of cancer (n = 3010) upon which to conduct the analysis. There was found 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. Furthermore, there was no heterogeneity between the trials despite the range of folic acid supplement doses and duration of trials.

Prior to the publication of Clarke *et al.* (44), a pooled analysis of two Norwegian RCTs (37,52) suggested that there was an adverse affect of folic acid on the incidence of cancer (HR 1.21; 95% CI: 1.03-1.41) and cancer mortality (HR 1.38; 95% CI: 1.07-1.79). (43) However, when these two RCTs (37,52) were included in the pooled analysis of Clarke *et al.* (2010) (44) no significant effect was found nor was there evidence of heterogeneity between studies. It is likely the Norwegian trials reflect the random variation amongst the studies around a relative risk of '1'.

A meta-analysis has recently been published online ahead of print reporting a significant increase in the incidence of cancer after supplementation with folic acid (RR 1.21; 95% CI: 1.05-1.39). (45) This meta-analysis was designed primarily to assess cancer incidence, and also includes populations with a prior history of colorectal adenomas which were not included in the meta-analysis of Clarke *et al.* (44) Although it is advantageous to include these studies, the methodology of this meta-analysis is of sub-optimal quality. Firstly, the Women's Antioxidant and Folic Acid Cardiovascular study (WAFACS) (41) which reported a decreased risk in the incidence of cancer was excluded for reasons not identified a priori. The justification for excluding this study was that plasma folate levels at the end of the study were slightly higher than reported in previous studies. However, the WAFACS (41) reported similar mean plasma folate status at the end of the study compared to other US folic acid supplementation trials conducted during mandatory fortification. (36,42) It therefore seems unwarranted to exclude this study which has both a large sample size and long study duration. A second issue with the meta-analysis of Baggott *et al.* (45) is that study duration served as the only weighting factor. As a result of this, the Aspirin Folate Polyp Prevention study (AFPPS) (36) with one of the lowest number of events and the only trial to demonstrate a significant increase in cancer incidence has the greatest weighting and strongly impacts the results.

One further meta-analysis has been conducted and reported findings of RCTs and controlled observational studies separately (48). In this meta-analysis of RCTs all folic acid supplementation trials were included. The relative risk of folic acid supplementation on cancer incidence was 1.07 (95% CI: 1.00, 1.1) which is similar to the results of the individual participant data meta-analysis of Clarke et al (44). The meta-analysis of controlled observational studies also reported a slight non-significant increase in the incidence of cancer (RR 1.03; 95% CI: 0.92, 1.16). (48)

The evidence that has accumulated since the last review is suggestive that folic acid supplementation does not have an adverse effect on overall cancer incidence. Almost all RCTs have had a non-significant effect with relative risks close to 1, and assessment of participant level data of almost all relevant trials also results in a null effect regardless of folate status at baseline or mandatory fortification. This provides some reassurance that fortification with folic acid will not result in an increased risk of cancer, but research will continued to be monitored in this area.

Site-specific cancer incidence

Although some individual RCTs have reported an increase in the incidence of some cancers only one meta-analysis has yet specifically assessed site-specific cancers other than colorectal cancer. A collaborative individual participant data meta-analysis of all folic acid supplementation trials by the B-Vitamin Treatment Trialists' Collaboration is currently underway and will provide more robust evidence as to the association, if any, between folic acid and site-specific cancers.

Colorectal cancer

Of the five RCTs (36,38,39,41,42) and four meta-analyses of RCTs (43,46-48) published on colorectal cancer incidence none have reported a significant association with folic acid supplementation. All RCTs published from 2007 onward report a non-significant reduced risk of colorectal cancer incidence with folic acid (36,38,39,41,42), only one RCT was published before 2007 and reported a non-significant increase in colorectal cancer incidence. (53) Mixed results were reported for the meta-analyses, the pooled analysis of the Norwegian trial reported a null effect (43), a meta-analysis of trials in populations with a prior history of colorectal adenomas reported a non significant decrease in incidence (47) and the third meta-

analysis reported a slight increase in colorectal cancer with supplementation with B-vitamins. (46) Of these meta-analyses none have included all relevant studies, only containing data from two or three trials, so do not provide an overview of the evidence to date. The meta-analysis of Wien et al which has assessed all folic acid supplementation trials published to date also reports a null effect which is in agreement with all literature published to date (RR 1.00; 95% CI: 0.83, 1.21). (48)

Meta and pooled analyses of cohort studies with up to 20 years of follow-up duration report a reduced risk of colorectal cancer with higher folic acid intakes from both dietary folate and total folic acid sources. (48,54,55)

The totality of evidence published to date does not indicate that there is an increased risk of colorectal cancer with folic acid intake.

Breast cancer

Only two RCTs have been published reporting incidence of breast cancer since the time of the last review conducted by FSANZ. (41,42) Both RCTs have reported a non-significant decrease in incidence upon supplementation, however the Nurses' Health Study/Health Professionals Follow-up Study (NHS/HPFS) only contained 11 events to conduct the analysis. (42) The only trial to assess breast cancer as a principle outcome is the WAFACS trial which randomised 5442 women to either a B vitamin supplement containing 2.5 mg of folic acid or placebo for a period of 7.3 years. (41) These women were health professionals with pre-existing cardiovascular disease or coronary risk factors, but were not at an increased risk of cancer at baseline. At the end of the study there were 184 cases of breast cancer to conduct the analysis. Supplementation with folic acid had no significant effect on breast cancer incidence in this population (HR 0.83; 95%CI: 0.6-1.14; p = 0.24). (41)

Only one other RCT published in 2006 has reported breast cancer incidence, the Heart Outcomes Prevention Evaluation-2 (HOPE-2) study reported a non-significant increase (RR 1.11; 95%CI: 0.47, 2.61). (53) However there were only a very small number of cases (n=22) in addition to very wide confidence intervals ranging from a decrease in risk of 53% to an increase of up to 261%. The meta-analysis of Wien *et al.* has conducted an analysis of folic acid and breast cancer based on these three trials reporting a non-significant decrease in breast cancer upon supplementation 0.86 (0.65, 1.14). (48)

In addition to results from RCTs, results from a meta-analysis of prospective cohort studies also report no association between folic acid and cancer assessed by either total folate intake (RR 1.00, 95% CI: 0.87-1.14); or comparison of high and low quintiles of blood folate status (OR 0.81, 95% CI: 0.59-1.10). (56)

There does not appear to be an association between folic acid and breast cancer incidence based on the current evidence from RCTs and meta-analyses of prospective cohort studies.

Prostate cancer

Concerns that folic acid supplementation may increase the risk of prostate cancer arose after the publication of the AFPPS in which the increase in cancer incidence was primarily attributed to the increase in prostate cancer in the treatment group. (36) 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; $p = 0.02$). (49) The authors noted that the results may in fact be spurious due to the small number of cases over the follow-up period (33 cases). (36)

Since the AFPPS three more papers have published results for prostate cancer. (39,42,43) Of these trials, one has reported a small non-significant decrease in risk (42), and two papers have reported a non-significant increase of around 20% in the treatment groups. (39,43) A meta-analysis of these trials reports a borderline significant effect of folic acid supplementation on prostate cancer incidence (RR 1.24; 95%CI: 1.03, 1.49) (48) yet there are still a limited number of cases included within this analysis to conclusively determine the true effect of folic acid on prostate cancer incidence.

To summarise data on prostate cancer are inconclusive; however the limited data available is suggestive of a small increase in risk, of borderline significance. 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.

Recurrence of Colorectal adenomas

It is generally accepted that most colorectal cancer arise from colorectal adenomas, however not all adenomas progress into carcinomas. (57) Several trials have examined the relationship between folic acid and colorectal adenomas. At the time these studies were conducted it was believed that folic acid played a protective role particularly with colorectal cancer. However there has been concern raised that folic acid may in fact have a dual role in carcinogenesis, preventing the initiation in healthy individuals but promoting progression of tumour growth in those with established adenomas. (58)

Four RCTs have been published since 2007 to examine the relationship between folic acid and recurrence of colorectal adenomas in populations with a prior history of colorectal adenomas. (36,38,42,50) These RCTs have assessed the recurrence of colorectal adenomas as a primary study outcome. Patients were randomly allocated to placebo or folic acid (0.5-5 mg/day) for a minimum follow-up of three years. Advanced adenomas are classified in these trials as either a large adenoma (> 1 cm diameter), an adenoma with villous components, high grade dysplasia, or invasive carcinoma. Table 21 and Table 22 summarise the RCTs and meta-analyses of these trials since 2006 on the association between folic acid and recurrence of colorectal adenomas and advanced adenomas.

After three or more years of supplementation there was no significant effect of folic acid supplementation on the recurrence of one or more colorectal adenomas or advanced adenomas in these studies. (36,38,42,50) Half of the studies to date reported a non-significant increase in the recurrence of colorectal adenoma of 7% (38) and 9% (36), whereas the other half of studies reported a non-significant decrease of 13% (42) and 36% (50) in those receiving folic acid supplements. There is some suggestion of adverse effects with longer duration of supplementation. In the AFPPS when only the results at the time of the second follow-up colonoscopy were analysed there is a significant increase in the recurrence of advanced adenomas (RR 1.67, 95% CI: 1.00-2.80; $p = 0.05$) and multiple adenomas (RR 2.32, 95% CI: 1.23-4.35; $p = 0.007$) in those randomised to folic acid supplementation. (36) It is worth noting that only 59.5% of participants underwent a second colonoscopy and there were relatively few cases of advanced adenomas and multiple adenomas at the second follow-up. When the relative risk of advanced adenomas in participants with information for both follow-up periods is presented the relative risk is lower and non-significant (RR 1.35, 95% CI: 0.98-1.86; $p = 0.07$). The NHS/HPFS also followed-up participants for an extended duration of between five and six and a half years. (42) There was no significant increase in the risk of advanced adenomas upon folic acid supplementation at the end of the study (RR 1.03, 95% CI: 0.53-1.98; $p = 0.94$) despite supplementation in a similar population with an equivalent dose of folic acid. (42) Furthermore, there was no association found when

recurrence of adenoma and folic acid supplementation were analysed by time to endosocopy. (42) Both these RCTs were large multi-centre trials in populations with similar baseline plasma folate status. (36,42)

Pooling the individual level data of the three largest, higher quality trials also finds no significant effect on the recurrence of colorectal adenomas (RR 0.98; 95% CI: 0.82-1.17; p = 0.81) or advanced adenomas (RR 1.06; 95%CI: 0.81-1.39; p = 0.65). (47) However in this pooled analysis follow-up time was limited to three and a half years despite the longer duration of follow-up in two of the trials. Therefore, an adverse effect on the number of advanced adenomas cannot be addressed.

One further meta-analysis has been published which has specifically attempted to determine if an association between folic acid and advanced adenomas after three years of follow-up exists. (51) The results of which should be interpreted with caution as only two studies were included. At the time this meta-analysis was conducted only the AFPPS (36) had published data on recurrence of colorectal advanced adenoma. The second study (HOPE-2) (53) was conducted in a population which did not have a prior history of colorectal adenomas and only reported the recurrence of colorectal cancer, which was classified as an advanced adenoma in this meta-analysis. It is therefore difficult to interpret the outcome of this meta-analysis as the two studies measured different outcomes in substantially different populations and other studies measuring colorectal cancer recurrence were not included. The meta-analysis reported a 50% increase in advanced adenomas in these two studies with more than three years of follow-up (OR 1.50; 95% CI: 1.06-2.10). (51)

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.

SUMMARY

Monitoring cancer incidence and mortality through use of a population-based register has little utility in helping to answer the monitoring question. Causality will never be possible to demonstrate however it does enable monitoring of changes in incidence and mortality over time.

The association between folic acid and cancer is an emerging area of research. Since the last FSANZ review of the area the results of several large randomised controlled folic acid supplementation trials and meta-analyses of these trials have become available. While these trials have been designed primarily to study the use of folic acid supplements to either prevent cardiovascular disease or colorectal adenomas (colorectal cancer precursors), both in high risk groups of patients rather than the general population, their findings have been used to examine for cancer risk in these groups as well.

Based on these trials, and of meta-analyses of prospective cohort studies, the evidence suggests that folic acid supplementation has no significant effect on the incidence of total cancer, colorectal cancer, or breast cancer. Data on prostate cancer are inconclusive; however the limited data available suggests a small increase in risk, of borderline significance. Similarly the results of trials investigating folic acid and recurrence of colorectal adenomas are inconsistent and it is unclear if a significant effect is apparent with longer duration of supplementation in populations with a prior history of colorectal adenomas.

A limitation of all studies reviewed is that the duration of follow-up may not be sufficient due to the long latency period of cancer. None of these trials have specifically assessed cancer

outcomes as a primary outcome and screening and reporting of cancer incidence has not been standardised across studies. Furthermore, caution must be employed when evaluating the evidence from sub-group analysis. Large sample sizes are required to detect an effect between folic acid and cancer outcomes and sub-group analyses on small populations can lead to spurious results.

In summary, the weight of evidence available to date does not indicate that folic acid supplements would increase the risk of total cancer incidence, colorectal cancer, or breast cancer. As yet, there is insufficient evidence to evaluate the effect of folic acid supplements and either the risk of prostate cancer, or the risk of colorectal cancer among people with established adenomas. Estimated folic acid intakes at the level proposed for mandatory fortification would be lower than those consumed by participants in folic acid supplement trials, for the majority of the population.

Table 22. Summary of RCTs assessing folic acid and risk of total cancer and site-specific cancer incidence.

Author, year, study, country, fortification status	Eligibility criteria	n	Treatment Dose folic acid (mg/day) and duration	Baseline plasma folate	Total cancer & mortality	Colorectal cancer	Other cancer
				(Median)†	*Incidence reported as RR‡ (95% CI) unless otherwise stated*		
Cole 2007 AFPPS¶ (36), US & Canada, mandatory fortification introduced mid-trial	Inclusion: Aged 21-80 years with a histologically confirmed colorectal adenoma removed either 3 months before recruitment, or 16 months before recruitment with a history of at least 2 adenomas or if the adenoma was > 1cm. Exclusion: History of familial polyposis syndromes, large intestine cancer, malabsorption syndromes, conditions that could be worsened or treated with either aspirin or folic acid, B12 deficiency.	1021	Aspirin, and/or folic acid Dosage 1 mg/day Duration 6-8 years	Placebo, folic acid, mean: 10.4, 10.5 ng/mL	Non-colorectal cancer Placebo, folic acid: 6.3%, 10.5% (p = 0.02)	Colorectal cancer Placebo, folic acid: 0.8%, 0.6% (p = 0.72)	Prostate cancer Placebo, folic acid: 2.8%, 7.3% (p = 0.01)
Figueiredo 2009 AFPPS (49)	Secondary analysis of male participants in the AFPPS.	643 males	..	..	..	..	Prostate cancer Age-adjusted HR‡ 2.58 (1.14, 5.86; p = 0.02)
Logan 2008 ukCAP¶ (38), UK & Denmark, no mandatory fortification	Inclusion: Less than 75 years of age with a colorectal adenoma >0.5 cm removed 6 months before recruitment, or before this time if an adenoma of any size had been removed 6 months before randomization. Exclusion: Serious medical conditions, regular treatment with non-steroidal anti-inflammatory drugs, intolerance to aspirin, patients with a resectioned bowel, or incomplete adenoma removal.	945	Aspirin, and/or folic acid Dosage 0.5 mg/day Duration 3 years	..	Non-colorectal cancer Placebo, folic acid: 1.7%, 1.9% Mortality Placebo, folic acid 1.5%, 0.2% (p > 0.05)	Colorectal cancer Placebo, folic acid: 1.2%, 1.1%	..
Ebbing 2008 WENBIT¶ (37), Norway, no mandatory fortification	Inclusion: Aged 18 years or older undergoing coronary angiography for suspected coronary artery disease and/or aortic valve stenosis. Exclusion: Unavailability for follow-up, participation in other trials, alcohol abuse, serious mental illness, or cancer.	3096	B vitamins Dosage: 0.8 mg/day Duration 3.2 years	Placebo, folic acid: 4.5, 4.3 ng/mL	Total cancer 1.25 (0.91, 1.71; p = 0.18) Mortality 1.27 (0.90, 1.79; p = 0.18)	..	..

Table 22 (continued). Summary of RCTs assessing folic acid and risk of total cancer and site-specific cancer incidence.

Author, year, study, country, fortification status	Eligibility criteria	n	Treatment Dose folic acid (mg/day) and duration	Baseline plasma folate	Total cancer & mortality	Colorectal cancer	Other cancer
				(Median)	*Incidence reported as RR‡ (95% CI) unless otherwise stated*		
Zhang 2008 WAFACS¶ (41), US, mandatory fortification	Inclusion: Women aged 40 years plus, either postmenopausal or no intention of becoming pregnant, history of CVD or at least 3 coronary risk factors Exclusion: History of cancer (except melanoma) within last 10 years, serious non-CVD illness, using warfarin or other anticoagulants.	5442	B vitamins Dosage 2.5 mg/day Duration 7.3 years	Placebo, folic acid: 8.9, 8.8 ng/mL§	Total cancer HR 0.97 (0.79-1.18; *p* = 0.75) Cancer mortality HR 0.82 (0.56-1.21; *p* = 0.32)	Colorectal cancer HR 0.81 (0.43- 1.50; *p* = 0.50)	Breast cancer HR 0.83 (0.60-1.14; *p* = 0.24) Lung cancer HR 1.04 (0.58, 1.87; *p* = 0.89)
Wu 2009 NHS/HPFS¶ (42), US, mandatory fortification introduced mid-trial	Participants recruited from the Nurses Health Study and Health Professionals follow-up study Eligibility: History of colorectal adenoma confirmed by medical record, endoscopy planned < 4 years after initiation of trial, agreed not to take supplements during the trial, cancer free at time of enrolment.	672	Folic acid Dosage 1.0 mg/day Duration 3-6.5 years	Placebo, folic acid, mean: 9.3, 9.7 ng/mL	Total cancer Placebo, folic acid: 7% vs. 7% (*p* = 0.97) Mortality Placebo, folic acid: 4%, 2% (*p* = 0.08)	Colorectal cancer Placebo, folic acid: 0.9%, 0.3% (*p* = 0.37)	Placebo, folic acid: Breast cancer 2%, 1% (*p* = 0.75) Prostate cancer 2%, 1% (*p* = 0.75)
Hodis 2009 (40), US, mandatory fortification	Inclusion: Aged 40 years and older, fasting homocysteine > 8.5 µmol/L and no clinical signs of CVD. Exclusion: Diabetes, elevated fasting serum glucose or triglycerides, elevated blood pressure, untreated thyroid disease, > 5 alcoholic drinks/day	506	Folic acid Dosage 5 mg/day Duration 3.1 years	Placebo, folic acid: 9.2, 9.7 ng/mL	Total cancer Placebo, folic acid: 6.0%, 6.3% (*p* = 1.00)	..	..
SEARCH¶ 2010 (39), UK, no mandatory fortification	Inclusion: Aged 18-80 years with a history of myocardial infarction, blood cholesterol of at least 135 mg/dL on statin medication or 174 mg/dL if not. Exclusion: Chronic lever, renal or muscle disease; history of any cancer (except melanoma); and use of potentially interacting medicines.	12064	B vitamins Dosage 2 mg/day Duration 6.7 years	Placebo, folic acid 6.2, 6.1 ng/mL	Total cancer 1.07 (0.96, 1.19) Cancer mortality 1.03 (0.87, 1.23)	Colorectal cancer 0.95 (0.71, 1.27)	Prostate cancer 1.18 (0.94, 1.49) Lung cancer 0.95 (0.74, 1.23)

Notes:

† To convert conventional units (ng/mL) to SI units (nmol/L), multiply by 2.265.

‡ RR Relative Risk; HR Hazards Ratio

§ Baseline plasma folate status retrieved from Clarke *et al.* (44)

¶ AFPPS Aspirin Folic Acid Polyp Prevention Study; NHS/ HPFS Nurses Health Study and Health Professionals follow-up study, SEARCH Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine, ukCAP United Kingdom Colorectal Adenoma Prevention; WENBIT Western Norway B Vitamin Intervention Trial

Table 23. Summary of meta-analyses assessing folic acid and risk of total cancer and site specific cancer incidence.

Author, year	Design	Trial eligibility	Trials included	n	Total cancer incidence & mortality *Incidence reported as RR‡ (95% CI) unless otherwise stated*	Site-specific cancer *Incidence reported as RR‡ (95% CI) unless otherwise stated*
Ebbing 2009 (43)	Pooled analysis of Norwegian homocysteine lowering trials to reduce vascular outcomes	Combined analysis of two Norwegian RCTs with similar study design with an observational 38 months post-trial follow up	NORVIT (Norway) WENBIT (Norway)	6837 2 RCTs	Total cancer (cases = 629) HR 1.21 (1.03, 1.41) Cancer mortality (cases = 236) HR 1.38 (1.07, 1.79) All cause mortality (cases = 1021) HR 1.18 (1.04, 1.33)	Colorectal cancer (cases = 95) HR 1.00 (99% CI: 0.59, 1.69) Lung cancer (cases = 92) HR 1.59 (99%CI: 0.92, 2.75) Prostate cancer (cases = 165) HR 1.21 (99%CI: 0.81, 1.81)
Clarke 2010 (44) B vitamin trialists' collaboration	Individual participant data meta-analysis of homocysteine lowering trials to reduce vascular outcomes	Search strategy: Collaborative project between B vitamin researchers, plus grey literature search and experts consultation Eligibility: Double blind randomised B-vitamin supplement trial for the prevention of vascular disease. Trials with at least 1000 participants with at least 1 year follow up.	HOST (US) WENBIT (Norway) NORVIT (Norway) VISP (US) WAFACS (US, fortification) HOPE-2 (Canada, US, Brazil, Western EU, Slovakia) SEARCH (UK)	35603 7 RCTs	Total cancer (cases = 3010) 1.05 (0.98-1.13; $p = 0.14$) Heterogeneity $\chi^2_6 = 4.68$, $p = 0.6$ Cancer mortality 1.00 (0.85, 1.18; $p = 0.99$) Mortality (cases = 5125) 1.02 (0.96, 1.08; $p = 0.46$)	..
Carroll 2010 (46)	Meta-analysis of folic acid plus B vitamins trials	Search strategy: 8 databases searched with no limitations. Eligibility: RCT of folic acid in population with prior history of colorectal adenomas	HOPE-2 (Canada, US, Brazil, Western EU, Slovakia) WAFACS (US, fortification) Zhu et al 2003 (China)	3 RCTs	..	Colorectal cancer (cases = 128) RR 1.13 (95% CI: 0.77, 1.64; $p = 0.54$) Heterogeneity $\chi^2 = 2.14$ ($p = 0.34$), $I^2 = 7\%$
Figueiredo 2011 (47)	Pooled analysis of individual data	Search strategy: PubMed and contacting colleagues. No inclusion/exclusion criteria established	AFPPS Study (US & Canada) ukCAP (UK & Denmark) NHS/HFPS (US)	2632 3 RCTs	..	Colorectal cancer Placebo vs. folic acid 0.8% vs. 0.6%; $p = 0.64$ Heterogeneity not reported

Table 23 (continued). Summary of meta-analyses assessing folic acid and risk of total cancer and site specific cancer incidence.

Author, year	Design	Trial eligibility	Trials included	n	Total cancer incidence & mortality	Site-specific cancer
					Incidence reported as RR‡ (95% CI) unless otherwise stated	
Baggott Epub 2011 (45)	Meta-analysis of folic acid supplementation on cancer incidence	Search strategy: Pubmed Eligibility: Randomised placebo controlled trials, published in English with a minimum follow-up of 1 year	HOPE-2 (Canada, US, Brazil, Western EU, Slovakia) NORVIT (Norway) AFPPS (US) WENBIT (Norway) ukCAP (UK & Denmark) SEARCH (UK)	6 RCTs	Total cancer (cases = 2416) 1.21 (1.05, 1.39) Heterogeneity not reported	..
Zhou 2011 (59)	Meta-analysis of folic acid supplementation and cardiovascular outcomes	Search strategy: Medline, EmBase, Cochrane Central Register of Controlled Trials. Eligibility: RCTs, published in English regardless of publication status. Studies were limited to folic acid supplementation examining cardiovascular disease and homocysteine lowering	Unclear which RCTs were used to examine cancer outcomes as referenced incorrectly.	6 RCTs	Total cancer 1.08 (0.98, 1.21; p = 0.135) Heterogeneity: I^2=26.7% (p = 0.234)	..
Wien 2012 (48)	Meta-analysis of folic acid supplementation on cancer incidence	Search strategy: 11 Databases searched with no limitations. Eligibility: Systematic reviews, RCTs, controlled observational studies of cancer incidence/mortality in any population taking supplements 0.4mg/day.Studies of folic acid supplementation as part of high dose cytostatic regimen of cancer treatment were excluded.	ukCAP (UK & Denmark) AFPPS (US) NHS/HPFS (US) HOST (USA) VISP (US) WAFACS (US, fortification) Ebbing 2009 (WENBIT & NORVIT) SEARCH (UK) Charles (Scotland) Zhu (China)	10 RCTs	Total cancer (cases = 3515) 1.07 (1.00, 1.14) Heterogeneity: χ^2=7.8 (p=0.45), I^2=0% Cancer mortality (cases = 1134) 1.09 (0.92, 1.30) Heterogeneity: χ^2=7.22 (p = 0.12), I^2=45%	Prostate Cancer (cases = 632) 1.24 (1.03, 1.49) Heterogeneity: χ^2=4.82 (p=0.31), I^2=17% Breast cancer 0.86 (0.65, 1.14) Colorectal cancer 1.00 (0.83, 1.21)

Table 24. Summary of RCTs assessing folic acid and risk of recurrence of colorectal adenomas in populations with a prior history of colorectal adenomas.

Author, year, study, country, fortification status	Eligibility criteria	n	Treatment	Recurrence of colorectal adenomas RR (95% CI) unless otherwise stated	Notes
Cole 2007 AFPPS (36), US & Canada, mandatory fortification introduced mid-trial	Inclusion: Aged 21-80 years with a histologically confirmed colorectal adenoma removed either 3 months before recruitment, or 16 months before recruitment with a history of at least 2 adenomas or if the adenoma was >1cm. Exclusion: History of familial polyposis syndromes, large intestine cancer, malabsorption syndromes, conditions that could be worsened or treated with either aspirin or folic acid, B_{12} deficiency	1021	Dosage 1 mg/day Duration 1st follow-up: 3 years 2nd follow-up: 6-8 years	1st follow-up (n = 987) One or more adenomas 1.04 (0.90, 1.20; *p* = 0.58) Advanced adenoma 1.32 (0.90, 1.92; *p* = 0.15) 2nd Follow up (n = 607) One or more adenomas 1.13 (0.93, 1.37; *p* = 0.23) Advanced adenoma 1.67 (1.00, 2.80; *p* = 0.05) Both follow-up periods One or more adenomas 1.09 (0.98, 1.21; *p* = 0.12) Advanced adenoma 1.35 (0.98, 1.86; *p* = 0.07)	96.7% underwent colonoscopy at 1st follow-up 71.4% consented to 2nd follow-up period 59.5% underwent colonoscopy at 2nd follow-up Originally 3 year follow-up, extended for an additional 3-5 years
Jaszewski 2008 (50), US fortification	Inclusion: aged 18-80 years, agreed in advance to participate if at least one adenoma >0.5 cm was detected at baseline colonoscopy screening. Exclusion: severe co-morbid conditions, diseases causing contraindications for colonoscopy, malabsorption, hereditary predisposition to colorectal cancer, pregnant and nursing mothers.	177	Dosage 5 mg/day Duration 3 years	One or more adenomas Recurrence twice as high in placebo group compared to folic acid. Advanced adenoma Folic acid reduced risk (*p* = 0.02)	..
Logan 2008 ukCAP (38), UK & Denmark, no mandatory fortification	Inclusion: Less than 75 years of age with a colorectal adenoma >0.5 cm removed 6 months before recruitment, or before this time if an adenoma of any size had been removed 6 months before randomization. Exclusion: Serious medical conditions, regular treatment with non-steroidal anti-inflammatory drugs, intolerance to aspirin, resectioned bowel.	945	Dosage 0.5 mg/day Duration 3 years	One or more adenomas 1.07 (0.85, 1.34; *p* = 0.58) Advanced adenoma 0.98 (0.68, 1.40; *p* = 0.89)	90.8% underwent follow-up endoscopic examination
Wu 2009 NHS/HPFS (42), US, mandatory fortification introduced	Participants recruited from the Nurses Health Study and Health Professionals follow-up study Eligibility: history of colorectal adenoma confirmed by medical record, endoscopy planned <4 years after baseline, agreed not to take supplements during the trial, cancer free at time of enrolment.	672	Dosage 1 mg/day Duration 3-6.5 years	One or more adenomas 0.87 (0.65, 1.16; *p* = 0.33) Advanced adenoma 1.03 (0.53, 1.98; *p* = 0.94)	71% underwent follow-up endoscopic examination Follow-up extended to 5-6.5 years.

Table 25. Summary of meta-analyses assessing folic acid and risk of recurrence of colorectal adenomas in populations with a prior history of colorectal adenomas.

Author, year	Design	Trials included	n	Treatment	Recurrence of colorectal adenomas RR (95% CI) unless otherwise stated
Fife 2010 (51)	Meta-analysis	AFPPS Study (US & Canada) ukCAP (UK & Denmark) HOPE-2 (Canada, US, Brazil, Western EU, Slovakia)	3 RCTs	Dosage 0.5-2.5 mg/day Duration 3-8 years	Follow-up less than 4 years One or more adenomas OR† 1.07 (95% CI: 0.88, 1.30) Advanced adenoma OR 1.14 (95% CI: 0.85, 1.53) Follow-up of 4 or more years Advanced adenoma OR 1.50 (95% CI: 1.06, 2.10) Heterogeneity $\chi^2 = 0.50$ ($p = 0.48$)
Carroll 2010 (46)	Meta-analysis	AFPPS Study (US & Canada) ukCAP (UK & Denmark) Jaszewski (US)	3 RCTs	Dosage 0.5-5 mg/day Duration 3 years	One or more adenomas RR 0.93 (95% CI: 0.61, 1.41; $p = 0.27$) Heterogeneity $\chi^2 = 8.65$ ($p = 0.01$) $I^2 = 77\%$
Figueiredo 2011 (47)	Pooled analysis of individual data	AFPPS Study (US & Canada) ukCAP (UK & Denmark) NHS/HFPS (US)	3 RCTs n = 2632	Dosage 0.5-1.0 mg/day Duration 3.5 years	One or more adenomas RR 0.98 (95% CI: 0.82, 1.17; $p = 0.81$) Heterogeneity Q = 3.34 ($p = 0.19$) $I^2 = 70$ Advanced adenoma RR 1.06 (95%CI: 0.81, 1.39; $p = 0.65$) Heterogeneity Q = 2.04 ($p = 0.36$) $I^2 = 2.0$ Mortality Placebo vs. folic acid 1.7% vs. 0.5%; $p = 0.002$

Note:
† OR Odds Ratio

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Appendix

Table 26. Folic acid fortified breads available in New Zealand as at 22 December 2011.

Bread Manufacturer	Bread Description
Couplands	Classic Wholemeal breads (sandwich, toast, long cut),
Couplands	Daily Bread (600g white)
Couplands	Daily Grain (600g grain)
George Weston Foods	Super Soft Multigrain
George Weston Foods	Super Soft Honeygrain
George Weston Foods	Budget Multigrain (South Island and Upper North Island Only)
George Weston Foods	Original Swiss Goodness grain
George Weston Foods	Sunflower Poppy Seed Goodness Grain
George Weston Foods	Soya Linseed Goodness Grain
George Weston Foods	9 Grain Goodness Grain
George Weston Foods	Burgen Soya Linseed
George Weston Foods	Pams Soy Linseed (South Island and Upper North Island Only)
George Weston Foods	Pams Mixed Grain (South Island and Upper North Island Only)
George Weston Foods	Pams Barley Sunflower (South Island and Upper North Island Only)
George Weston Foods	Pams Multigrain (South Island and Upper North Island Only)
George Weston Foods	Bazaar Garlic loaf 360g
George Weston Foods	Bazaar Cheese with Garlic Loaf 425g
George Weston Foods	Bazaar Garlic Baguette Single 200g
George Weston Foods	Bazaar Garlic Baguette Twin 400g
Goodman Fielder	Giant Multi Grain Toast 600g
Goodman Fielder	Giant Multi Grain Sandwich 600g
Goodman Fielder	Giant Wheatmeal Toast 600g
Goodman Fielder	Giant Wheatmeal Sandwich 600g
Goodman Fielder	Sunny Crust Multigrain Toast 600g
Goodman Fielder	Sunny Crust Wholemeal Toast 600g
Goodman Fielder	Golden Bake Wheatmeal Toast 600g
Goodman Fielder	Golden Bake Wheatmeal Sandwich 600g
Goodman Fielder	River Mill Wheatmeal Toast 600g
Goodman Fielder	River Mill Wheatmeal Sandwich 600g
Goodman Fielder	River Mill Nature's Grain Toast 600g
Goodman Fielder	River Mill Sunflower & Barley Toast 600g
Goodman Fielder	Export Meat Warehouse Nature's Grain Toast
Goodman Fielder	Export Meat Warehouse Wheatmeal Toast

Source: Baking Industry Association of New Zealand 2011. (6)