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A REPORT TO FSANZ

INFORMING A STRATEGY FOR INCREASING FOLATE LEVELS TO PREVENT NEURAL TUBE DEFECTS:

A COST-EFFECTIVENESS ANALYSIS OF OPTIONS

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Summary

The Centre for Health Economics, Monash University was asked by Food Standard Australia New Zealand (FSANZ) to undertake a comparative cost effectiveness analysis of alternative strategies for reducing the incidence of neural tube defects (NTDs). This was in response to a Ministerial request to FSANZ in the context of consideration of mandatory fortification of bread/bread making flour with folic acid. Considerable documentation already exists in the form of a comprehensive report by FSANZ on mandatory fortification of bread with folic acid together, extensive supporting documentation and submissions by interested parties (www.foodstandards.gov.au). This work is not repeated here.

This report seeks to provide a framework for comparing the performance of alternative strategies to increase folate consumption and reduce the rate of NTDs. The broad purpose is to support the development of an optimal strategy to reduce the rate of NTDs.

Approach

The broad approach adopted is that of comparative cost-effectiveness analysis; the expression of performance in terms of cost to achieve a specified health outcome. The steps followed in completing this task were i) selection of interventions to include in the research exercise; ii) collection of literature from which to draw evidence about costs of interventions and effectiveness in terms of impact on folate levels and NTDs; iii) Extract data on impact of interventions from seminal studies, a technique used where meta-analyses are not available and/or where individual interventions vary. The seminal study is used to describe the intervention and the source of evidence for both costs and outcomes; iv) Model outcomes and costs to estimate performance in terms of $/NTD averted, and $/QALY (or DALY) (quality or disability adjusted life year); v) conduct sensitivity analyses – in this one-way sensitivity analyses, involving the variation of a single parameter at a time to determine the effect on performance; vi) Analyse performance with respect to other criteria of *s*afety, equity and sustainability. (This was achieved at indicative level only); vii) Compare performance across interventions in terms of cost/NTDs prevented, and cost/DALY, and the secondary criteria; viii) Discuss findings, considering issues such as data quality and data gaps and possible synergies or conflict between intervention options.

NTDs prevented have been estimated, using Bower, DeKlerk et al (2006) model, calibrated for Australian and New Zealand women, with a separate Indigenous model. Estimated mean changes in folic acid levels for each intervention is the primary input to the model.

Intervention Options

Four broad types of intervention options for reducing the incidence of NTDs were selected for analysis, each of which have a small number of variations. Whilst each option is considered in isolation, it is recognised, that interventions might best be implemented in combination. Four intervention options were subject to economic analysis:

i. *Promoting the use of folic acid supplement*s at least one month prior and three months post conception through; a) a multi-faceted general population campaign, b) a targeted campaign to disadvantaged women, c) brief clinician advice to women 18-48 at an O&G visit;
ii. *Mandatory fortification* of bread/bread making flour with folic acid
iii. *Extending (and maintaining) Voluntary fortification* of the food supply with folic acid;
iv. *Promoting consumption of folate rich foods* – naturally and fortified through:
    a) a population-wide marketing campaign
    b) a targeted approach delivered in a clinical setting.

Key Findings

Key findings are summarised in tables S1 and S2, where we report the estimated effect ('base-case') of each intervention, if applied across the entire target population, calculated separately for Australia and New Zealand. We summarise here i) NTD cases prevented per year, ii) cost per NTD prevented – calculated over the 10 year model period and with both costs and NTDs discounted at 5% pa, iii) cost/DALY across the 10 year model period and iv) cost per DALY with NTDs accrued over 10 years but DALYs calculated out to life expectancy.

It is important to note that in considering these estimates all are subject to uncertainty given the quality of the data that has been drawn upon in their calculation. The limitations are described fully in the text.

Our analysis suggests for Australia and New Zealand, a health promotion campaign to promote supplement use and mandatory fortification will have the greatest impact on NTDs. But even these interventions are estimated to prevent only around 8% of current NTDs. In terms of cost per NTD prevented, extending voluntary, by supplying more fortified products to the market place appears highly cost-effective for both Australia and New Zealand, as do all approaches to promoting supplement use amongst women who may become pregnant. Mandatory fortification in New Zealand does not appear cost effective and in Australia, performance depends on the cost of implementation – which is uncertain. Even applying the lower cost estimate, mandatory fortification appears less cost effective than other options. Dietary interventions generally do not appear cost effective, but those targeting all folate rich foods (including those which are fortified) perform better. If wider benefits were also included, from folate and dietary changes the relative performance may alter. However, this wider analysis is outside the scope of this study.

We have not explored possible negative consequences, other than to report, in Chapters 3 and 4 the number of persons who are estimated to reach the NHMRC defined Upper Limits for folic acid intake. With mandatory fortification it is estimated that 200,000+ persons in Australia would be at or above the daily upper limits. We do not attempt to interpret this finding.

In terms of cost per DALY, most intervention options, appear cost-effective and in some cases highly cost-effective relative to societal norms[1]. We report both cost/DALY achieved within the 10 year model period but also with life years and quality of life modelled out to full life expectancy, (but based on NTDs and costs accrued over the 10 year model period). The latter is common in cost-utility analyses. Only Mandatory fortification under the high cost option and the targeted dietary campaign (natural folate only) perform poorly in terms of cost per DALY.

In short, the economic analysis suggests that investment in several of the interventions analysed to prevent cases of neural tube defects, would fall well within accepted societal norms for the funding of health interventions, suggesting a strategy to reduce NTDs employing cost-effective options would meet societal goals.

We do note, however, that confidence in the estimates of effect and costs is compromised by the quality of the studies on which the analysis rests. These studies are few and generally of poor study design. A detailed one-way sensitivity analysis is reported in chapter 6 highlights the impact on performance of assuming alternative plausible parameter values.

In relation to equity the interventions most favourable to women at high risk and who are poorly educated, will be ones that specifically target these groups.

If proceeding to implement a NTD reduction strategy, it will be highly desirable to collect high quality baseline data and monitor outcomes over time, which can then be used to modify the strategy to maximise impact for resources allocated.

[1] In Australia cost/QALY of less than $40,000 is generally considered 'good value' and as a pharmaceutical almost certain to receive funding through the PBS, given high quality evidence.

Table S.1 Key results 'base case' estimates - Australia

Intervention	**NTDs prevented (per year)**	**Cost per NTD prevented $**	**Net Cost per DALY** (10 years) **$**	**Net Cost per DALY** Modelled to life expectancy* **$**
SUPPLEMENT USE				
Health promotion campaign	27.1	55,000	21,500	6,400
Minority young women	5	60,500	24,000	7,200
Physician advice	13.1	23,100	6,700	2,000
EXTENDED VOLUNTARY				
Medium estimate	7.07	14,900	2,900	900
Industry lower estimate	1.8	58,600	23,100	6,900
Higher estimate	11.2	9,400	300	100
MANDATORY FORTIFICATION#				
200ug/100g flour lower cost	23.81	84,400	35,000	10,500
200ug/100g flour higher cost	23.81	617,400	281,200	83,900
DIETARY FOLATE				
Targeted campaign- natural folate	2.17	619,700	278,500	83,100
Targeted campaign- all folate	5.26	255,700	114,100	34,000
National health promotion campaign-natural	4.41	338,600	152,400	45,500
National health promotion campaign- all	9.74	153,300	66,800	19,900

Net cost Costs net of estimated downstream savings to the health sector related to fewer NTD births
* Average life expectancy 80 years: average of males 78 year and females 82 years
\# Higher cost – developed by a consultant commissioned by industry, Lower cost developed by a consultant commissioned by FSANZ

Table S.2 Key results base case estimates New Zealand

Intervention	**NTDs prevented (per year)**	**Discounted cost $ per NTD prevented**	**Cost per DALY $ (Net cost offsets)**	**Cost per DALY $ (Net cost offsets)** - Modelled to life expectancy*
SUPPLEMENT USE				
Health promotion campaign	8.72	38,400	13,700	4,100
Physician advice	4.21	16,100	3,400	1,000
EXTENDED VOLUNTARY PERMISSIONS				
Medium estimate	3.01	7,900	Cost saving	Cost saving
Industry lower estimate	1.89	12,500	$1,800	$500
Higher estimate	3.86	6,100	Cost saving	Cost saving
MANDATORY FORTIFICATION				
135ug bread	6.94	553,600	251,600	75,000
DIETARY FOLATE				
Targeted campaign- natural folate	0.47	641,600	292,300	87,200
Targeted campaign- all folate	1.13	266,900	119,200	35,600
National health promotion campaign-natural	0.95	352,500	158,800	47,400
National health promotion campaign- all	3.33	100,600	42,400	12,700

*average life expectancy 80 years: average of males 78 year and females 82 year

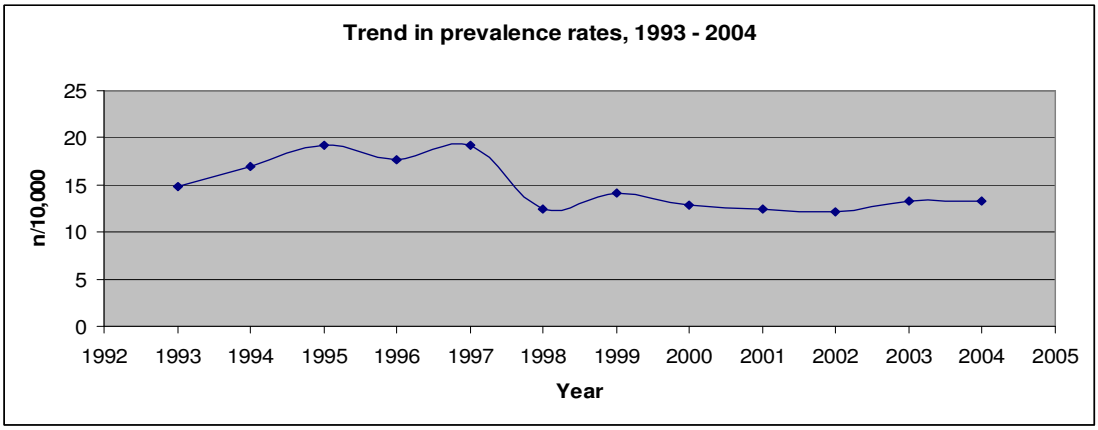
CHAPTER 1 INTRODUCTION

1.1 Background

Neural Tube Defects (spina bifida, anencephaly, and encephalocoele) are a group of birth defects, which occur in utero during the development of the brain and spinal cord. Observational studies and randomised trials have demonstrated a preventative effect of folic acid supplementation[2] during the periconceptional period on the occurrence of neural tube defects (NTDs). The recent Cochrane Review by Lumley et al. 2006 estimates a 72% reduction in the incidence of NTDs with peri-conceptional folate supplementation, relative risk of 0.28 (95% CI 0.13 to 0.58).

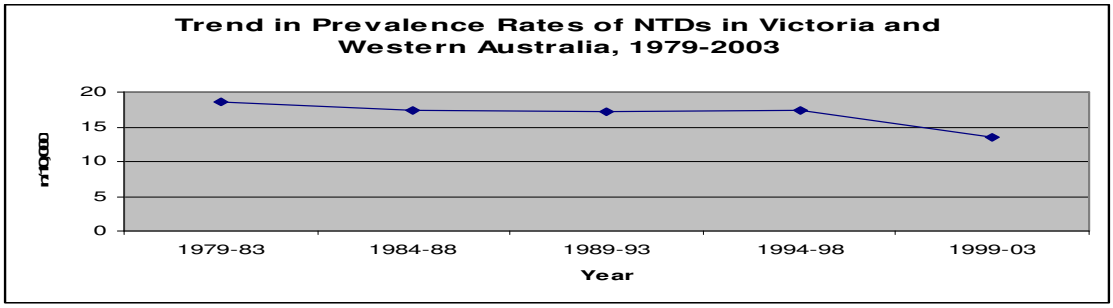
While national and regional birth defects registers and monitoring programs report the occurrence of NTDs, comparison of reported rates across countries and over time is compromised by variable definitions for reporting foetal deaths and differences in ascertainment and notification, prenatal diagnosis and termination of pregnancies. (Lancaster P *et al,* 2001). Still, data from Birth Defect Registries in South Australia (SA), Victoria and Western Australia (WA) suggest a reduction in the rate of NTDs of ~30% between the 1980s/early 1990s and late1990s/early 2000s, (terminations, still births and live births)[3]. Figure 1.1 displays the trend in NTD prevalence from 1993 to 2004 in Victoria. (Birth Defects in Victoria 2003, 2004). A longer term picture of NTD rates is illustrated in Figure 1.2, (live births, stillbirths, terminations) for 1979 to 2003 for WA and Victoria.

Figure 1.1 Trend in prevalence rates, 1993 – 2004 in Victoria



Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Total	96	110	123	112	120	78	89	81	78	77	85	85
N/10,000	14.8	16.9	19.2	17.7	19.2	12.5	14.1	12.9	12.5	12.1	13.3	13.3

Figure 1.2 Prevalence of NTDs in Western Australia and Victoria, 1979-2003



[2] Folate is a water soluble B vitamin which plays an essential role in metabolism and cell division. The need for folate is greater when cell turnover is increased, as in foetal development. (NHMRC, 2006).

[3] Mean annual cases of NTDs/10,000 births decreased in SA from a mean 19 in 1986-1996 to 15 in 1997-2001, in WA from 19 in 1980-1995 to 14 in 1996-2002 and in Vic from 18 in 1992-1996 to 2001-2002. (PHAA AGM, 2004)

Source: International Clearinghouse for Birth Defects Surveillance and Research, 2005.

In total, NTDs constitute a small proportion of live births, still births and terminations as shown in Table 1.1.

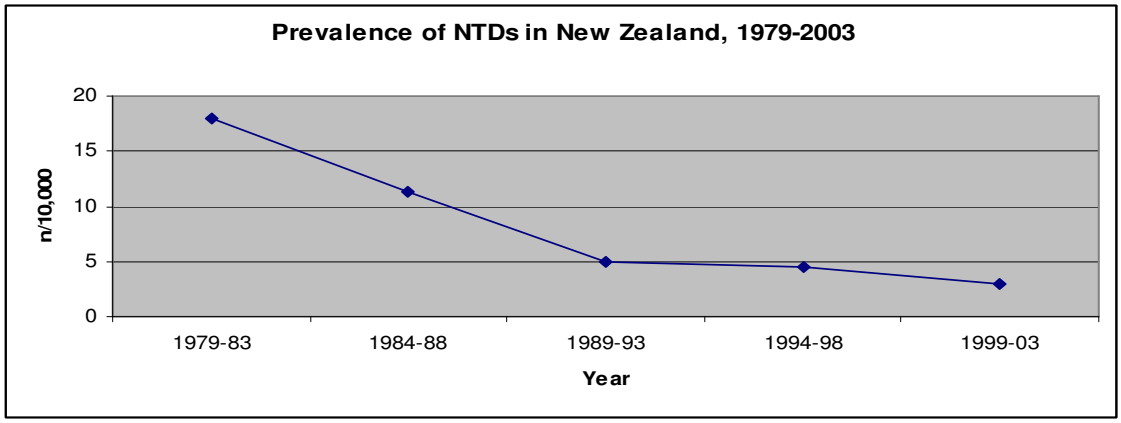
Table 1.1 Livebirths, stillbirths and terminations; Total and number affected by NTD 1999-2003, SA, Vic, WA

	1999	2000	2001	2002	2003
Total Livebirths	106,187	104,936	104,040	104,908	105,226
NTD live births	33	37	25	22	21
Total Stillbirths	753	716	701	688	746
NTD stillbirths	13	12	15	17	18
Total terminations*	13,883	13,909	13,950	13,496	13,021
NTD terminations	107	103	98	93	86
Total Births	106,940	105,652	104,741	105,596	105,972
Total NTDs	153	152	138	132	125

Source: adapted from FSANZ (2005), based on the Birth Defect Registries.
Notes: * not including total terminations of pregnancy in Victoria, but including terminations of pregnancy for NTD affected foetuses for all three states.

In 1999, the prevalence of NTDs in New Zealand was 9.1 per 10,000 total births (live births, stillbirths and abortions) or 5.0 per 10,000 births (live births and stillbirths only). (Ministry of Health, 2003) Figure 1.4 shows the trend in NTD (live and stillbirths) prevalence in New Zealand over the period from 1979 to 2003.

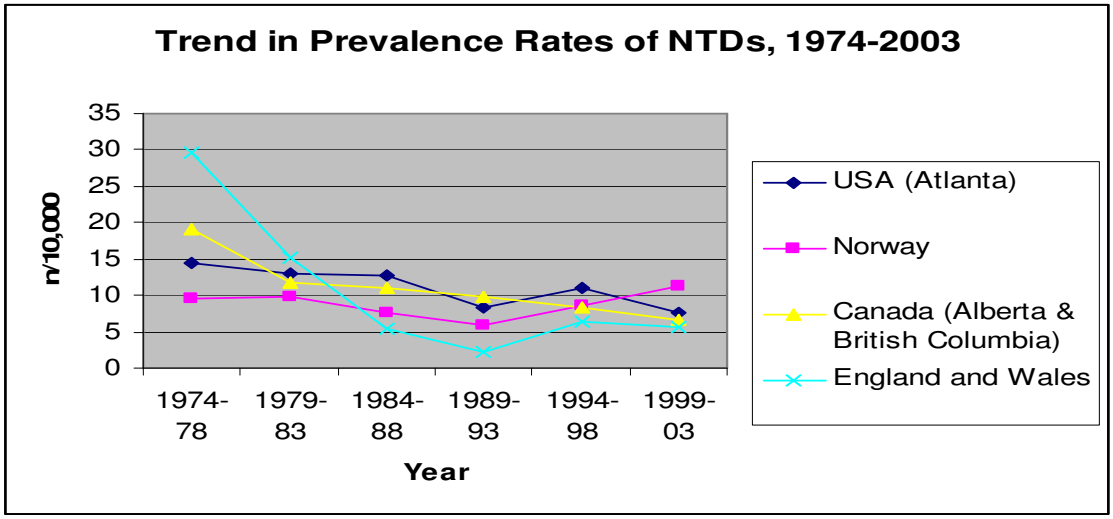
Figure 1.4 Prevalence at birth of NTDs (live & stillbirths only) New Zealand 1979–2003



Source: International Clearinghouse for Birth Defects Surveillance and Research, 2005

The prevalence of NTDs from 1974 to 2003 in the USA, Norway, Canada, England and Wales are displayed in Figure 1.5 based on data from the International Clearinghouse for Birth Defects Surveillance and Research, 2005. Prior to 1994 the birth prevalence rates in Norway, England and Wales do not include terminated births. The data for Alberta, Canada does not include terminated births until 1997. The data suggests a very large drop in incidence of NTDs in England and Wales between the mid 1970s and mid 1980s and to a lesser extent in Canada. We are not aware of a formal analysis and explanation of the reported data.

Figure 1.5 Prevalence of NTDs, USA, Norway, Canada, England and Wales, 1974-2003



Source: International Clearinghouse for Birth Defects Surveillance and Research, 2005

Folate Consumption

The mean daily folate intake in Australia for females aged 19-44 years, according to the 1995 National Nutrition Survey, was 230.0ug. In New Zealand, the daily mean intake of folate from food for the same population group was 211.0ug. (ABS, 1998 and NZ Food: NZ People, 1999). These estimates include only folate from natural sources, that is excluding additional folate from fortified food and beverages. There is considerable variation around the mean values as shown in Table 1.2.

Table 1.2 Percentile distribution of daily folate intake (ug) females 19-44 years, Australia & NZ

AUSTRALIA	Percentile				
Age group (years)	**10**	**25**	**50**	**75**	**90**
19-24	164.1	188.2	224.3	260.1	311.1
25-44	166.1	188.9	218.4	253.8	295.9
NEW ZEALAND	**Percentile**				
Age group (years)	**10**		**50**		**90**
19-24	125		195		290
25-44	141		213		307

Source: ABS, 1998 and NZ Food: NZ People, 1999

The NHMRC recommends that women capable of/planning a pregnancy should consume folic acid as a supplement or in the form of fortified foods at a level of 400ug/day for at least one month before and three months after conception, in addition to consuming food folate from a varied diet. (NHMRC, 2006)

New Zealand recommends that women planning a pregnancy take 800ug folic acid daily for four weeks prior to conception and for 12 weeks after conceiving to reduce the risk of NTDs. (Ministry of Health, 2003)

In Australia and New Zealand folate can be obtained through naturally occurring dietary sources, folic acid supplements or through folic acid fortified foods (such as breads and cereals). Voluntary fortification of specified foods with folate was first approved in Australia and New Zealand in 1995 and 1996 respectively. In 1999, more than 100 folate-fortified foods (e.g. breakfast cereals, juices, breads) were reported to be available in Australia. (Bower C *et al,* 2002)

1.2 Economic Evaluation

Research question

The Centre for Health Economics, Monash University was asked by Food Standard Australia New Zealand (FSANZ) to undertake a comparative cost effectiveness analysis of alternative strategies for reducing the incidence of neural tube defects (NTDs). This was in response to a Ministerial request to FSANZ in the context of consideration of mandatory fortification of bread with folic acid. That is, options are to be compared with mandatory fortification.

Considerable documentation already exists in the form of a comprehensive report by FSANZ on mandatory fortification of bread with folic acid together, extensive supporting documentation and submissions by interested parties (www.foodstandards.gov.au). This work is not repeated here.

This report seeks to provide a framework for comparing the performance of alternative strategies to increase folate consumption and reduce the rate of NTDs. The broad purpose is to support the development of an optimal strategy to reduce the rate of NTDs.

Approach to Assessment and Comparison of Performance

The broad approach adopted is that of comparative cost-effectiveness analysis. This involves the expression of performance in terms of cost to achieve a specified health outcome. This is the approach typically employed in the economic evaluation of health interventions[4] . It is clearly pertinent here where the research question concerns the comparison of competing and/or complementary interventions for reducing the incidence of NTDs. There are seven distinct steps in completing this task[5]:

a. ***Select interventions*** to include in the research exercise. This selection needs to reflect the objective of research and ideally be as comprehensive as possible to cover all major options – current and potential and can include those expected to be both more and less cost-effective. (See below).

b. ***Collate literature*** from which to draw evidence about costs and effectiveness. Ideally this will include seminal studies or meta-analyses based on randomised control trials of the subject interventions, with measured outcomes covering behaviour change, change in clinical markers and impact on 'final' endpoints (in this case number/rate of NTDs).

c. ***Extract data on impact of interventions from selected seminal studies*** (and other pertinent sources)***:***

- Costs: normally calculated from resource use to which unit costs are applied described
- Effectiveness: mean change (and confidence intervals) for primary outcomes – eg behaviour, folate status, NTDs

The seminal study technique is most suitable where meta-analyses are not available and/or where interventions vary in content. The seminal study is used to describe the intervention and as the source of evidence for both costs and outcomes. Whilst generalisations may be problematic, ad hoc departures from the details of the seminal study undermines the claim that the analysis is evidence-based

[4] Drummond M et al., *Methods for the Economic Evaluation of Health Care Programmes*, 3rd Edition, Oxford University Press, NY

[5] Segal L and Mortimer D.'A population-based model for priority setting across the care continuum and across modalities' *Cost Effectiveness and Resource Allocation* 2006, 4: 6 (28 March)

d. ***Model outcomes and costs to estimate performance***

- Select suitable primary measure of performance - in this case:
  - $/NTD averted,
  - $/QALY (or DALY)
- Model outcomes using published epidemiological data based on cohort studies etc.
- Model extensive one-way sensitivity analyses- involving the variation of a single parameter at a time to determine the effect on cost effectiveness

e. ***Analyse performance with respect to other criteria*** (other than efficiency and effectiveness) and typically:

- safety
- equity
- sustainability.

In the context of this study, and in view of the short time frame for conduct of this work these secondary criteria will be assessed at an indicative level, based on a priori analysis.

f. ***Compare performance across interventions.*** Comparison will be made in terms of:

- the primary criteria - considering also uncertainty and confidence in estimates
- secondary criteria
- conduct sensitivity analyses to explore the effect of uncertainty around parameter values on performance.

g. ***Discussion***

Consider other issues such as:

- data quality and data gaps – recommend critical data gathering requirements,
- issues in developing a strategy – possible positive and/or negative synergies between intervention elements.

These steps have been followed in this analysis and reported here. Task 1 Selection of interventions is reported on below. Tasks 2, 3 & 4 represent the core tasks of the cost-effectiveness analyses. This work is reported on in Chapters 2 to 5, one chapter for each broad intervention option analysed. Chapter 2 covers promoting the use of peri-conceptual folic acid supplements, Chapter 3 is on extended voluntary fortification. Chapter 4 draws together the material on mandatory fortification and in chapter 5 we cover the promotion of folate rich foods. In chapters 6 and 7 we compare the performance of the intervention options with separate analyses for Australia and New Zealand and conclude with Chapter 8 in which we identify key qualifications and priorities for further research.

Intervention Options

The first task in determining comparative performance is to select and describe a set of interventions that might be employed to reduce NTDs. Ideally this choice will be comprehensive and include all feasible interventions, both options which it is thought might perform poorly, as well as those thought to perform well. This process helps identify key data gaps and recommendations to support interventions that perform well, whilst discouraging resource allocation to interventions that perform poorly. The set of interventions to be analysed can include both complementary and substitutable options. Ideally sets of strategies would be described for analysis that cover all feasible combinations of interventions. This however expands considerably the number of options to be evaluated and the data demands.

Our capacity to consider various combinations of interventions is restricted both by the nature of the available evidence and resource constraints on the evaluation. We had no choice but to analyse each intervention in isolation, even though we know that a combined strategy – that includes various elements of the components is likely to be the best way forward. An analysis of the possible negative and positive synergies between interventions is an important and a gap in our work and ideally would be explored in an extension to this analysis.

Four broad types of intervention option for reducing the incidence of NTDs have been selected for analysis, each of which also has a small number of variations. Whilst each option is considered in isolation, it is recognised, that interventions might best be implemented in combination. That is it for an option to be considered, it does not have to be capable of providing a 'complete' answer.

The intervention options subject to economic analysis are:

1. ***Promoting the use of folic acid supplement*s** at least one month prior and three months post conception through:
   a) multi-faceted general population campaign
   b) targeted campaign to disadvantaged women
   c) brief clinician advice to women 18-48 at O&G visit
2. ***Extending (and maintaining) Voluntary fortification*** of the food supply with folic acid
3. ***Promoting consumption of folate rich foods*** – naturally and fortified through:
   c) a population-wide marketing campaign
   d) a targeted approach delivered in a clinical setting.
4. ***Mandatory fortification with folic acid***

1.3 Terminology

Consistent terminology has been used throughout this report.

Folate – is a water soluble B-group vitamin. The term *folate* is used generically to refer to all forms of the vitamin, both naturally-occurring and synthetic, and its active derivatives

Folic Acid –is used to refer to synthetic folate which is used in food fortification and supplements

Natural Folate – used to refer to folate found naturally in food and does not include folic acid added to food

Dietary Folate – used to refer to folate that is consumed via the diet, both naturally occurring and folic acid added through fortification. This term does not include folate consumed through supplements

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Source: Green T and Green E, 2005

Chapter 2 Promote use of folic acid supplements peri-conceptually

2.1 Current supplement availability and use

Availability

The New Zealand ministry of Health recommends 800µg/day folic acid for women peri-conceptually, as the formulation available as a registered medicine over the counter at pharmacies; despite noting that 400µg/day is sufficient to reduce the risk of NTDs (Ministry of Health, 2006). Dietary supplements available from supermarkets, pharmacies and health food shops contain doses ranging from 30-350µg/day with regulations specifying a 300µg/day upper limit (FSANZ, 2006).

In Australia folic acid supplements and multivitamin supplements containing folate can be purchased at supermarkets, health food shops and pharmacies at a cost of around $2.99 to $3.39 per 100 tablets (Megafol, Alphapharm, Feb 2007). Folic acid supplements usually contain 500µg/day doses and multivitamins for pregnancy and breast feeding contain folic acid levels ranging between 200 and 800µg/day (FSANZ, 2006). Folic acid is also listed on the PBS and a 200 tablet script can be obtained by concession card holders for $4.90, or for free once a concession holder reaches the safety net. (It is possible for non-concession holders to obtain a folic acid script although the price will exceed the off the shelf price.)

Current use of folate supplements

A small number of Australian and New Zealand surveys and studies have assessed self-reported supplement use. These were identified through a simple Medline (OVID) search performed in January 2007 using the subject headings "folic acid", "neural tube defect" and "dietary supplements". This search identified 203 studies. of which based on a title (or abstract) review 29 were found to be possibly relevant and were examined in detail. From these seven Australian studies that reported peri-conceptional folic acid supplement use were identified. Key data from these seven studies are summarised in Table 2.1.

Table 2.1 Estimated use of folic acid supplements peri-conceptually (≥1 month prior + 3 months following conception)

Study Population (Year conducted)	**No. of women in sample**	**% taking folic acid supplements**	**Dose**	**Reference**
South Australian women attending antenatal clinic (2001)	211	33%	Unknown	Maats & Crowther 2002
Western Australian case control study-NTDs & folic acid (1997-2000)	578	28.5%	≥200µg	Bower & Miller et al, 2004
New Zealand, Dunedin women in hospital following birth (2004)	104	39%	800µg	Dobson et al, 2006
New Zealand, Christchurch, women's antenatal visits (date?, but pre 1999)	191	17%	Unknown	Schader & Corwin, 1999
South Australian survey of pregnant women (2005)	304	36%	400µg/d	Conlin et al, 2006
Victorian survey of recent mothers (2000)	1593	36%	Unknown	Watson et al, 2006
NSW child health survey (2001)	647	46%	Unknown	Watson et al, 2006

All studies used interview or survey techniques to gather information from pregnant or recently pregnant women, such that all reported supplement use data is based on self report. Self reported supplement use has been shown to correlate well with actual plasma and serum folate levels.

The reported use of folate supplements more recently (post 2000) is reasonably consistent across studies, with estimated periconceptional use varying between 33% and 46%. Some of the variation between studies might be explained by differences in study populations.

We have used the figures presented by Conlin et al. (2006) to define current use of folic acid supplements by women peri-conceptually. These data are the most recent and also the most detailed. On the other hand they are based on a survey of women who were younger and more single than the Australian population and thus may underestimate current use. (Increasing age and being married has a positive relationship with supplement use, Bower et al, 2005). Conlin et al report the proportion of women taking supplements periconceptionally and identify those who take them once per day and at the correct dose. Thirty-six percent of pregnant women reported taking supplements periconceptionally with 94% taking them every day and of these 92% comply with the dosage recommendations. This suggests some 30% of pregnant women achieved full compliance for timing and dose. We have thus used 30% as the base line to which the estimated effect of interventions to promote use of folic acid supplements is added. We apply 36% in sensitivity analysis. We note that Bower and DeKlerk in their application of the Wald model (Bower, DeKlerk, 2006) assume that 36% of women take folate supplements peri-conceptually.

Use of folate supplements by Indigenous Australians

We are not aware of any published data on the use of supplements in the Indigenous populations of Australia or New Zealand. The Bower, DeKlerk et al (2006) model linking increased folic acid to NTDs prevented assumes no supplement use in their Indigenous model. This is certain to be an underestimate. In the Bibbulung Gnarneep study (as cited by Bower et al 2004) 55% of Indigenous women knew that folate was important in pregnancy (38% for teenage mothers). This compares to 67.5% knowledge of the link between Spina Bifida and folate in the WA survey in 1995 (with 49% knowledge for young women; Bower et al, 2004). Unfortunately the Bibbulung Gnarneep study did not measure supplement use. A USA study reporting supplement use by young Indigenous women, in the Houston intervention study reported 9% supplement use at the recommended dose (500ug/day) (Chacko et al, 2003). We have used this as our base case.

Bioavailability of folic acid supplements

There is little published data on the bioavailability of folic acid dietary supplements. Taking supplements with food is known to reduce bioavailability of folic acid compared to when taken without food, with the loss estimated by Gregory (2001) at 15%. For the purposes of this work we will assume that folic acid supplements are normally taken on their own, to yield have 100% bioavailability, but 85% bioavailability is modelled in sensitivity analyses.

Proportion of pregnancies that are planned

A factor affecting the use of folate supplements is the proportion of pregnancies that are planned, due to the requirement to take folic acid for at least one month prior to as well as 3 months post conception to minimise the risk of NTDs. Table 2.2 summarises some of the literature on the proportion of pregnancies that are planned. (This information was found incidentally, we did not do a specific literature search for planned pregnancies in Australia and New Zealand). The results for 5 of 6 studies are highly consistent and suggest the proportion of pregnancies in Australia and New Zealand that are panned lies between 60 and 64%. Although, it should be noted that the studies do not describe precisely what is meant by a "planned" pregnancy. This can be defined narrowly to include only couples actively trying to conceive, or defined more broadly to include also persons who are not taking contraceptive measures and not minding the outcome.

Table 2.2 Proportion of pregnancies planned in Australia and New Zealand

Reference	Description	% of pregnancies planned
Dobson et al, 2006	Dunedin, New Zealand, 104 interviews of women who had just given birth	64
Schader & Corwin, 1999	191 pregnant women in Christchurch, NZ in 1999 interviewed during antenatal visits	44
Conlin et al, 2006	South Australian survey of 304 pregnant women	60.2
Watson et al, 2006	The NSW Child Health Survey 2001 (n=647)	63
Bower et al, 1997	Survey of 128 women attending first antenatal visit around the end of the Western Australian campaign to promote use of folate supplements	62.6
Bower, Miller et al, 2005	Western Australian control group (n=578) from case control study 1997-2000	60

2.2 Effectiveness of interventions

Search and selection

Only a small number of intervention studies have been conducted in Australia or internationally with the aim of increasing folic acid supplement that have attempted to evaluate program impact. A simple Medline (OVID) search performed in January 2007 using the subject headings "folic acid", "neural tube defect" and "dietary supplements" identified 203 studies. Of these 29 were identified as potentially relevant and examined in detail. Only five intervention studies were identified with reported results, where the aim was to increase supplement use to decrease NTDs. Most relate to interventions introduced in the mid 1990s. The interventions use differing approaches, delivery settings and population subgroups. The five interventions are summarised in Table 2.3 and the four used to model the cost-effectiveness described more fully in Table 2.4. These studies all report supplement use prior to and following the intervention, with only one employing a randomised control trial study design – and this was flawed by contamination. In short the available data on trials to promote supplement use is both limited and of poor quality.

Studies that aimed to establish the relationship between supplement use and NTDs were outside scope.

The interventions identified use differing approaches, content, settings and target groups. But fall broadly into three categories. Each study is subject to its own set of limitations and potentials for bias.

We have used these studies to model:

1. *A comprehensive Folate health promotion campaign*- based on the Western Australian and South Australian interventions
2. *A campaign targeted at disadvantaged groups* - based primarily on the Houston USA campaign, which offered education and free supplements for minority young women visiting reproductive health clinics. The Georgia-based program was used also to confirm level of effect.
3. *Physician counselling/advice (+/- free supplements)* - based on the Arkansas USA study

Table 2.3 Interventions aimed at increasing use of folate supplements peri-conceptually- Summary Description (a) and Results

Intervention year	Sample frame for evaluation	N women surveyed	% taking folic acid supplements(b)			Timing	Reference
			Baseline	Follow up %	Follow up +% point		
Comprehensive Folate health promotion campaign WA, 1992-95	Pregnant women attending first antenatal visit	1993: 143 1995: 121	14.0	30.6	+16.6	Before & early pregnancy	Marsack et al, 1995; Bower et al, 1997
Folate health promotion campaign-SA; 1994-95	Hospitalised women following birth	1995: 158 1996: 187 1998: 167	10.1	26.7 46.1(c)	+15.6 +36	Daily before + 1st 3 months of pregnancy	Chan et al, 2001
Advice + Free folic acid supplement in family planning clinics-Georgia USA; 2000-01	Women visiting family planning clinic 18-45 years	68	23	42	+19	within 2 days of their visit	Watkins et al, 2004
Education and free supplements for minority young women-Houston US 1999-2000	Young women 13-22 years visiting reproductive health clinics	387	9	27(d)	+18	> 21x last month	Chacko et al, 2003
Counselling and supplements from Physician- Arkansas US (unknown)	Women 18-45yrs during routine gynaecologic visit	I: 139 C: 140	23.7 23.6	39.6 36.4(e)	+15.9 +12.8	At least a few times per week	Robbins et al, 2005

I= intervention, C= control (But major contamination as most of the control group also received physician advice)
(a) for more complete description see Table 2.2 below
(b) 400ug where stated
(c) may incorporates the effect of a Commonwealth campaign
(d) 27% reported that they took supplement at least 21 times in last month
(e) reported taking supplements at least a few times per week

Quality of Trial evidence

The Western Australian campaign was comprehensive and has been well described. There are limitations of the design, notably the lack of a control group, necessitating a simple pre-post study design. This means that attribution of change to the intervention is uncertain, with the possibility that confounders are in part responsible for observed changes in reported supplement use. Further, a different group of women were surveyed in 1993 and 1995, although there characteristics were similar. The intervention had just begun in 1993 when the baseline data were collected, such that base-line may already incorporate some campaign effect. The study provides little detail on how often women took supplements and at what doses. The study relies on self-report data which may be in error. We also cannot be certain about the generalisability of study results. One issue is the increase in the proportion of women taking supplements since this intervention, which has occurred for a variety of reasons. Whether similar results would be achieved with the current cohort of women is not clear and cannot be established without new studies. However the seminal study methodology relies on the use of study costs and outcomes as described. Our approach has been to also model alternative levels of supplement use.

The evaluation of the South Australian campaign is subject to similar limitations. The baseline assessment occurred after the trial began, potentially reducing the measured effect. As above, the pre-post study design is subject to possible confounders. The study relies on self report data and provides little detail on frequency and dose of supplement use. The study does not report characteristics of the women surveyed in 1995 and 1996, so we do not known if they differ in ways potentially relevant to supplement use. As with the WA campaign, the possible transferability of findings is unknown, especially in view of the current higher level of supplement use.

Table 2.4 Details of intervention and participants

	Target and sample frame for evaluation	Intervention Details	Actual/potential settings
WA Health promotion campaign	Target: All women in WA of child bearing age or considering becoming pregnant. Sample frame: *1993:* Age 17-43 years (mean 28.7), 86% married/de facto, 83% born in Australia, NZ or UK, 58% high school only, 11% Technical/further, 29% university, 36% first pregnancy, 61% planned pregnancy *1995:* Similar to above	Key message: raise aware-ness of folate & NTDs, ↑ women's folate intake Physicians, pharmacists, dieticians, community and child health workers- information sheets, pamphlets, posters, articles in journals, newsletters and bulletins, presentations, training & continuing education, stickers for folic acid bottles, printed paper bags, consumer newsletter General community- seminars, message on Medicare cheques, magazine articles, newspaper, radio and TV ads, editorials, taxi back ads, information sheet to public libraries, displays and food demonstrations, cooking program & education package, information to Education Dept and schools, incorporating material into curriculum, public launch, stamp, stickers, price tags.	Media, pharmacists, supermarkets, professional seminars/workshops, general practitioners, paediatricians, obstetricians and gynaecologists, child health nurses, schools, child care centres, libraries, family planning clinics
SA Health promotion campaign (1994-95)	Target: All women in SA of child bearing age or considering becoming pregnant. Sample Frame: Information not reported	Key message: folate/folic acid reduces risk of NTD, green leafy vegetables, fruit, cereals good source of folate, adequate folate/folic acid needs to be taken periconceptionally + 1st 3 months of pregnancy. Health professionals (pharmacists, GPs, dieticians, nursing, medical staff) posters, NHMRC guidelines, information leaflets, information in professional newsletters, presentations. Wider community- posters/pamphlets to school librarians, health education teachers, womens community groups, fruit & vegetable vendors, health food shops, libraries, shopping centres, childcare centres, preschools. Newspaper, magazine, TV & radio advertising.	
Houston Program Education & free supplements for minority young women (1999-2000)	Target: Young women from minority groups sample frame Age 13-22 (mean 18), 93% single, 72% black, 28% Hispanic, 59% education appropriate for age, 43% previous pregnancy, 86% sexually active in last 3 months & not pregnant	A trained health educator saw young women and asked them to complete an assessment questionnaire that assessed baseline knowledge or NTDs, folic acid and intake. Young women were seen in hospital or community based free reproductive health clinics. The young women received personalised education regarding NTDs, NTD prevention by folic acid, importance of taking daily supplements & increasing consumption of natural & fortified folate rich foods. Young women also received a free 3 month supply of multivitamin tablets.	Health or community centres where young minority women present for visits with health workers of any type
Physician advice - Texas	Target: Women presenting for routine O & G consultation Sample frame: Intervention-Mean age 29 years 52% black, 45% single, 50% college education, 15% graduate school, 58% income <US$30,000. Control group: similar except_9.3% graduate school	Women attending routine gynaecologic consultation received brief (30-60 second) counselling regarding folic acid, a starter bottle of 30 supplements and a pamphlet about benefits of folic acid. Women received a booster phone call from the research nurse 1-2 weeks after their visit. Control women received 30-60 seconds of counselling on another preventative health behaviour and a pamphlet on folic acid containing a voucher for free supplements. Physicians were not prohibited from including folic acid advice to control women.	Public & private O & G practices & clinics in the community & hospital/ outpatients settings. Other providers of O & G care such as GPs, specialist nurses and midwives

The Houston intervention was conducted in free reproductive clinics (hospital and community based) in Houston Texas, USA. The intervention targeted low income young women aged between 13 and 22 years, 66% of whom were black and 25% Hispanic with advice and free folic acid supplements. The intervention enrolled women who indicated an interest in taking multivitamins which represented 98% of women approached. Results of the study are based on 3 month follow up of a random sample of young women yielding data from 33 out of 387 women. This means we have no information about possible longer term effect, and cannot be sure whether the sample is representative. Further, given some discrepancies in responses regarding supplement use, the self report data may not be entirely reliable. Given these limitations wide estimates of effect around the base case have been modelled in sensitivity analysis. This intervention has been modelled for indigenous Australians using a sub-model developed by Bower and de Clerk et al (2006).

The physician advice intervention conducted in Arkansas, USA targeted women aged 18 to 45 years attending routine gynaecological visits. Four separate clinics were involved in the trial two were affiliated with a medical school and two private practices. Women were randomised into the folic acid intervention group or 'control group', with the same physicians giving advice to both groups. Women in the intervention group received 30-60 seconds of brief counselling, a folate pamphlet and a starter bottle of 30 folic acid tablets. The control group received 30-60 seconds brief counselling on preventative health behaviours, a folic acid pamphlet and a coupon for free supplements. Physicians were not prevented from giving advice on folate to the control group. Contamination is evident; 85% of control subjects reported receiving physician counselling about folic acid and 15% mailed for the free supplements. Both groups improved significantly in their reported intake of folic acid. In essence this trial reports on the difference between brief counselling plus free supplements and brief counselling and coupons for supplements.

For all interventions supplement use is defined as full compliance – that is consuming the recommended dose of folic acid supplements, 1 month prior to and 3 months post conception. It is however possible that some benefit is still obtained for women who start using folic acid supplements very early in pregnancy, or who use supplements peri-conceptionally at a lower than recommended dose, or who take supplements at the recommended time and dose but occasionally miss a day. For the purpose of our evaluation these possible additional benefits are conservatively excluded.

Results - Trial outcomes

Key trial results were summarised in Table 2.3. In short for the Western Australian campaign self reported supplement use before and in early pregnancy in women attending their first antenatal visit rose from 14% in the 1993 baseline survey to 30.6% in the 1995 follow up survey. The South Australia campaign reported supplement use increasing from 10.1% in 1995 shortly after the program began to 26.7% in 1996 after the program concluded and 46% in 1998, incorporating also the effect of a national campaign. The Houston program for minority young women showed 'daily' 400 μg folic acid supplement use was 9% at baseline and 27% reported taking supplements at least 21 times in the previous month after the trial period of three months. Supplement use rose from 23.7% to 39.6% in the intervention group of the Physician counselling study in Arkansas and from 23.6% to 36.4% in the 'control' group which was in effect a brief intervention group – without free supplements.

Scenarios

The scenarios used in the economic analysis are outlined in Table 2.5. Results as reported in the trials are used for the base case analysis. But high and low estimates are also used in sensitivity analysis, reflecting considerable uncertainty in the transferability of this data to current populations, especially in view of the increase in supplement use that has already been achieved.

Table 2.5 Proposed scenarios for change in supplement use

Scenario	Baseline %	Follow up %	Absolute % point change	Application
Population wide Health promotion campaign				
WA Results as presented	14	30.6	16.6	Base case#
WA Results minus women with planned pregnancies	2.1	12.2	10.1	Sensitivity estimate
Results from SA campaign (+ national campaign)	10.1	46.1	36.6	Sensitivity alternative
Houston program				
At least 21 times per month	9	27	18	Base case#
Base case halved			9	Sensitivity lower estimate
Results from Georgia study	23	42	19	Sensitivity alternative
Physician advice				
Intervention group results	23.7	39.6	15.9	Base case#
Control group results	23.6	36.4	12.8	Sensitivity alternative

As reported in the seminal trial. It is also similar to the reported result of a 1995 population based campaign in the Netherlands to promote folic-acid supplement use (De Walle et al 1999).

NTDs prevented

We estimate NTD cases prevented per year by the subject intervention - in this case campaigns to promote folic acid supplement use if applied across the entire target population, calculated separately for Australia and New Zealand. In estimating performance we have modelled results over a 10 year period, summing NTDs avoided (discounted at 5% pa) over 10 years.

The annual cases of NTDs prevented was estimated using an excel spreadsheet replicating the Bower and DeKlerk et al (2006) model, calibrated for Australian and New Zealand women. A separate model for indigenous Australians is described by Figure 2.1. The primary input to the models is the mean increase in folic acid intake. (The model does not allow NTDs prevented to be estimated directly by varying folic acid supplement use). The estimated increase in supplement use is thus translated into a change in mean folic acid level in pregnant women, assuming a dose of 500µg in Australia and 800µg in New Zealand, and 100% bioavailability of folic acid. (We also model 85% bioavailability in sensitivity analysis). The percentage point change in supplement use, together with dosage information is then used to calculate the total increase in folic acid intake which is applied to the 70% of the population not previously taking supplements (see above) to yield the mean change in folic acid intake as an input to the model.

We have used this approach to estimate the annual number of NTD cases prevented for each of the three interventions, for the base case and for the alternative scenarios. The results are reported in table 2.6. For instance, for Australia we estimate annual NTDs prevented at 26 to 27 for either a comprehensive population health campaign or physician advice and ~ 5 for a program targeting indigenous women – base case estimate. With considerable variation possible around that value as indicated in other reported scenarios.

We note that with the Bower, DeKlerk et al (2006) model it is not possible to differentiate by individual baseline levels of folic acid intake. This is a weakness of the model, given studies show an increase in folate from low levels is more beneficial than the same increase from higher levels (Daly et al, 1995). This places some uncertainty on the estimated reduction in NTDS based as they are on mean changes in folate levels.

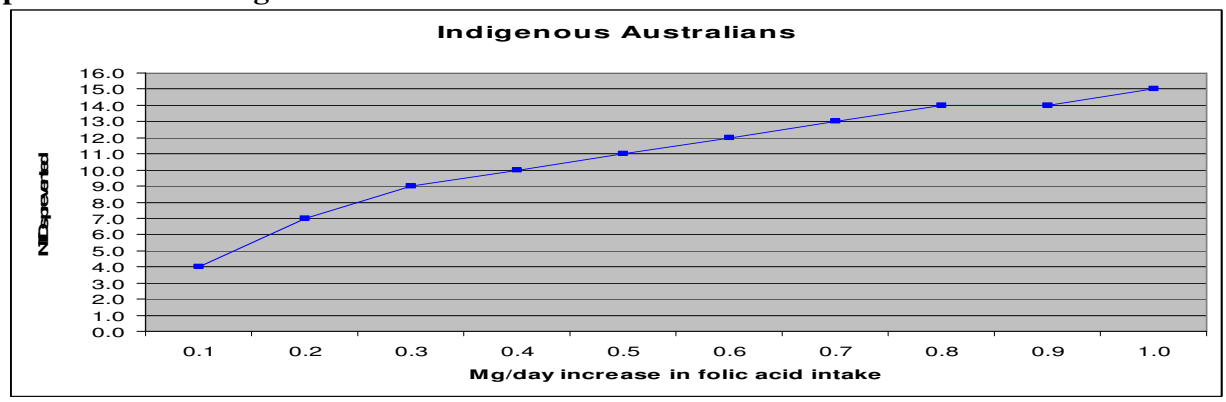
Further, as noted above current use of folic acid supplements is higher than when the seminal studies were conducted. We have no evidence to know whether the observed gains are still achievable. However, it is interesting that in the USA, even after nearly 10 years of mandatory fortification and current use of folic acid supplements by women estimated at 33%, the Centre for Disease Control commenting that increasing this is important is developing a program to promote supplement use amongst College students, presumably in the belief that further gains are achievable. (CDC 2005).

Table 2.6 Estimates of mean increase in folic acid consumption and NTDs prevented

Scenario	Australia		New Zealand	
	Mean increase in folic acid*	Est. NTDs prevented	Mean increase in folic acid*	Est. NTDs prevented-
Health campaign				
'Base case' per WA results	***119ug***	***27***	***190ug***	***8.7***
Lower estimate	72µg	17	116µg	5.7
Results from SA campaign	257µg	52	411µg	15.8
Houston program				
'Base case' supplements taken >21 times per month	***129 µg***	***5.0***	***-****	***-***
Results from Georgia study	136 µg	5.15	-	-
Physician advice				
Intervention group results	***114 µg***	***26***	***182 µg***	***8.4***
Control group results	91 µg	21	146 µg	7.0

Notes: * Not modelled for NZ in the absence of a minority specific model

Figure 2.1 Estimated relationship between increase in folic acid intake and NTDs prevented for Indigenous Australians



2.3 Cost of intervention

Health promotion

There are two possible approaches to estimating the costs of rolling out a campaign similar to the WA or SA campaign across all of Australia and New Zealand. Firstly we can take the actual costs of conducting these campaigns and extend them, or secondly we can assess the costs of other similar scale National campaigns for different health issues and use these as an indication of the cost of conducting the national campaign.

The chief investigators from the WA campaign received $185,000 from the WA Department of Health from 1992-1994 and a research grant of $62,400 in 1994. This covers only part of the campaign costs. It does not include the costs of the chief investigators or considerable in-kind support, sponsorship and un-paid student time.

The direct cost of the SA campaign was $40,000 with an additional $10,000 allocated for evaluation. This covered only a half time project officer, and dose not reflect other program costs. To cost all the components of this type of campaign and extrapolate across Australia is probably less reliable than drawing costs from other national campaigns, which is the approach taken. (See Table 2.7). It is still the case that the benefits of the WA and SA campaign were achieved at modest financial cost, but these are not necessarily generalisable.

Table 2.7 Summary of costs of selected high profile national public health campaigns

Campaign	**Costs** (current dollars)
National Tobacco Campaign 1997	$9 million
National Go for 2&5 Campaign 2005	$4.76 million
Skin Cancer Awareness 2006-07	$5.5 million
TAC Road safety* advertising 1990-1992	$4.05-$6.83 million per year

*drink driving, speeding, concentration

A 'reasonable' cost estimate for a national folate education program is set at $5 million up front costs plus an ongoing annual investment of $1 million for Australia. This would fund a high profile campaign with a combination of media and community-based elements. In sensitivity analysis we model alternative lower and upper estimates of $3 million up front + $500,000 ongoing and $7 million upfront + $2 million ongoing. We assume a national campaign in New Zealand would cost ~ one fifth that for Australia (on a simple population pro-rata basis), giving the base case estimate of NZ$1.12 million up-front plus NZ$225,00 on-going.

Houston style Program- targeting high risk group

This program was implemented by trained health educators who we assume to be clinical nurse educators. We have prepared an indicative costing for Australia, to illustrate the possible cost-effectiveness of an intervention targeting young indigenous women. The costing presumes a high profile intensive activity, including for instance 3 months of free supplements each year for young indigenous women in the target age group. Cost components are described in table 2.8

Table 2.8 Cost of targeted intervention for minority young women (15-24 yrs)

Description	**Units**	**Cost inputs $AU**	**Total cost $AU**	
			Year 1	**On-going**
Personnel to conduct education campaign to engage/train health workers + program management	0.5 -1.0 educator per state/territory year 1 + 1-2/year Australia ongoing	5.6 x $72,000* (year 1) 1.6 x $72,000 (ongoing)	403,000	115,000
Education campaign materials	1 information pack per health worker ongoing	Distribute to ~1,200 health workers serving ATSI communities + 400 annually @ $10/pack	12,000	4,000
Starter bottles of supplements	100 folic acid tablets	@ $3.39 per bottle** 43,500 indigenous women aged 15-24 years***	147,000	147,000
Total Australia			$562,000#	266,000#

Source/Notes:

* Clinical nurse educator current award (March 2007) $1133.20/week (~ $70,000/an incl. wage on-costs).

\# In 2003–04, OATSIH funded 140 organisations to provide/ facilitate access to primary health care for Aboriginal and Torres Strait Islander peoples, additional to services through the community health centre network, AIHW Australia's Health, 2006

** e-pharmacy price for Megafol 0.5mg 100 tablets

***ABS- 458,000 indigenous Australians 50% female, 19% aged 15-24 years

\# assumes provision of advice is not time intensive and included in normal consultation time

Physician advice

The core costs of this intervention are those associated with promoting the strategy to clinicians, including materials, along with the costs of the folic acid starter bottles. As brief physician counselling concerning the use of folate supplements in this initiative is specified as 30-60 seconds and forms part of the standard physician role during a gynaecological consult, we have assumed no additional cost in clinician time. Table 2.9 summarises the relevant costs. It assumes that women in the target group will attend an O&G specialist ~ once every 3 years.

We note that the trial reported considerable success in encouraging physicians to talk briefly to patients about folate supplements and NTDs, despite what seems to be a low cost approach to this task. This is evident in the reported results, that even most 'control group' patients recalled receiving a message about folic acid and NTDs, with many reporting changing their behaviour.

Table 2.9 Indicative costs for a physician counselling intervention- Australia

Description	Units	Cost inputs $AU	Total cost $AU	
			Year 1	ongoing
Personnel to conduct education campaign targeted at obstetricians and gynaecologists	0.5 to 1 educator per state/territory year 1 + 1.5/year (Australia-wide) ongoing (incl program management)	4.8x $78,000 (year 1) 1.5 x $78,000 (ongoing)	376,000	117,000
Education campaign materials	1 information pack per physician per year	1189 Australian O&G Fellows* @ $10 per pack	12,000	4,000
Starter bottles of supplements	30 folic acid tablets	$1.13 per bottle** x 150 bottles/yr /physician***	170,000	144,000
Total Australia			558,000	265,000
Total New Zealand#			NZ$126,000	NZ$ 59,000

Source/notes

* The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (in sensitivity include also 2,807 clinicians with an O&G Diploma)

** 1/3 e-pharmacy price for Megafol 0.5mg 100 tablets

*** For women who may become pregnant and not already taking supplements [@50% (assumed % of women in target (~1,000,000) visiting an O&G each 2 years) x 70% not now taking supplements] year 1 @ 85% in 2nd and subsequent years.

\# 20% of cost for Australia

2.4 Cost effectiveness – dollars per NTD prevented

Assumptions/ Base Case

The following is a list of the key assumptions used in the base case to model the cost effectiveness of these interventions:

- Costs discounted at 5% pa. Outcomes discounted at 5% pa base case (0% alternative)
- Time horizon of the model 10 years
- AU$ for Australian NZ$ for New Zealand
- 100% bioavailability folic acid base case (85% sensitivity)
- At baseline 30% of target group currently take supplements, 9% indigenous
- Average dose of folic acid 500ug Australia, 800ug New Zealand
- Costs include a combination of year 1 costs plus on-going costs to maintain the impact
- Link between increased folic acid intake to NTDs calculated using the Bower & deKlerk et al model by allocating extra supplement use across the 70% of women assumed not to be taking supplements

Table 2.10 Cost per NTD prevented for the interventions targeting supplement use

Intervention	Present Value costs* $	Mean NTDs prevented /year 10 yrs		Cost (disc@5%) per NTD prevented $	
				NTDs not discounted	NTDs disc @5% pa
Australia $AU					
Health promotion campaign	11,530,000	27.1	271	42,500	55,000
Education and free supplements for young indigenous women	2,340,000	5.0	50	46,700	60,500
Physician counselling + free supplements	2,330,000	13.0	131	17,800	23,000
New Zealand $NZ					
Health promotion campaign	2,590,000	8.7	87	29,700	38,400
Physician counselling and free supplements	520,000	4.2	42	12,400	16,000

* Present value costs: costs per year over 10 years, discounted and summed.

Sensitivity analysis
Sensitivity analyses are reported in chapter 6 (Table 6.2). For a fuller description of the methodology and interpretation of sensitivity analysis refer to chapter 6. Cost-effectiveness estimates are most sensitive to the dose of supplement assumed to be taken, the cost of the intervention and the confidence intervals around the translation of folic acid into NTDs.

2.5 Safety – upper limit excedences

There are likely to be minimal safety issues associated with supplement use as these interventions target women capable of or planning to become pregnant. Such use will be time limited and will not occur for instance in children where excedences are most likely, given the relatively low upper limits specified for children.

2.6 Equity

The extent to which interventions to promote supplement use will differentially reach persons from differing educational, ethnic and income backgrounds is of interest. It is widely reported from several studies (eg CDC 2005, De Walle et al 1999), that women with more formal education, older women and those who are married and are more likely to take folate supplements peri-conceptually. This is consistent with other findings about health promoting behaviours. What however is also reported is that interventions to promote supplement use can be highly effective across all population groups, not just in high income or better educated women. Thus for instance the Houston program described in this Chapter achieved a large increase in use of folate supplements in young, low income, 'minority' mostly single women. Similarly a Netherlands population-based campaign to promote folic acid supplement use in women, whilst confirming the differential in use by education level, reported a large and significant increase in supplement use after the campaign by all women, including those in the lowest educated group, (up from 2.4% per advice to 16.5%). (De Walle 1999). These studies suggest that while population-based campaigns may not reduce differentials, they can achieve substantial benefits across all groups. Further, interventions, especially clinician-based, can be used to target 'at risk' groups to achieve a differential impact for this group, if this is a priority.

2.7 Overview

The limited evidence that is available suggests that interventions to promote supplement use are potentially effective and if so will almost certainly be cost-effective under a range of plausible assumptions. Both physician-based and population-based interventions may perform well.

These results are however based on only a small number of trials of mediocre quality, few of which are recent and for which costing data is generally quite imprecise; although interestingly they do report similar results. Still it would be desirable to collect additional data through the evaluation of a new supplement campaign..

A comparison with other intervention options is provided in Chapter 6 and a more comprehensive discussion of the limitations of this research is provided in Chapter 7.

Chapter 3 Extend voluntary fortification

3.1 Introduction

This chapter draws extensively on the work of FSANZ; specifically:

- discussions with industry to determine potential options for extending voluntary permissions and their uptake,
- the modelled effect of three extension options, a low estimate from industry, a medium and an optimistic scenario, on the mean folic acid intake and consequently on the number of NTDs.

Our task has primarily been to put these results in a comparative context with the other options reviewed. It has not been possible to prepare detailed costings of the voluntary scenarios, which are rather indicative. The challenges with costing are both conceptual and empirical.

3.2 Current voluntary fortification permissions

Voluntary folate fortification of certain foods was introduced in Australia in 1995 and in New Zealand in1996. Folic acid is permitted to be voluntarily added to the following foods:

- breakfast cereals
- breads
- flour
- vegetable and meat extracts
- fruit and vegetable juices and drinks
- beverages derived from legumes
- pasta
- savoury biscuits

Folic acid (in small amounts) may also be added to legume analogues of dairy foods and meat. Voluntary folate fortification permissions were recently extended to cereal based beverages. (FSANZ. *Final Assessment Report*. Proposal P295. Consideration of Mandatory Fortification with Folic Acid, October 2006).

These permissions have been widely taken up by industry, with a high proportion of cereals, breads and orange juice fortified. See Table3.1. FSANZ estimate that 149 foods in Australia and 101 foods in New Zealand are fortified with folic acid (based on data from the 1995 Australian and 1997 New Zealand National Nutrition Surveys). The extensive take up of voluntary permissions by industry has meant considerable folic acid is now being consumed through fortified foods. FSANZ estimates the mean intake of folic acid from voluntarily fortified foods among women aged 16-44years is now 108ug in Australia and 62ug in New Zealand. This represents a considerable effect. FSANZ estimates the impact to be 60 to 160 fewer NTD cases per year. (FSANZ 2006, Figure 1 p 35).

We note that the precise impact of voluntary permissions on folate levels and NTDs and other health outcomes is uncertain. Data from Lancaster and Hurst (2001) and the Victorian Perinatal Data Collection Unit (2005) indicate a fall in NTD rates of 10 – 30% since the introduction of voluntary folate fortification. Recent declines in prevalence of NTDs are thought to be associated with increased periconceptional intake of folate in response to health promotion campaigns and fortification of selected foods. (Bower C *et al,* 2002). However, it is not possible to ascertain the precise impact of folic acid fortification, given other possible influences on NTD rates and the lack of well constructed experiments. Simple observation of historic data is at best indicative. In many (but not all) counties the incidence of NTDs had been decreasing in the years prior to the advent of fortification (Busby et al 2005, Eurocat 2007). It is postulated that factors such as improved nutrition may be relevant or pre-natal diagnosis and termination (where these are not fully recorded - a data capture issue). (Kim YI, 2004). However a comprehensive analysis of historic trends is yet to be completed.

3.3 Proposed extensions to permissions

It was proposed in the P295 *Draft Assessment Report* that "industry could in the future apply to have further voluntary folic acid permissions considered". Extension of voluntary fortification permissions across a broader range of food groups has the potential to provide more folic acid in the food supply and subsequent increased folate intake. The possible extensions to voluntary permissions are paradoxically limited by the success of the strategy to date. FSANZ after discussion with industry described a low, medium and optimistic scenario of extended voluntary fortification. Current as well as postulated increases under the three scenarios are described for Australia and New Zealand in Tables 3.1A and 3.1B

Table 3.1A Current folic acid fortification through voluntary permissions and projected changes under 3 alternative scenarios – Selection of products, Australia

Commodity	% market share fortified product			
	Current	Industry proposal	Moderate scenario	Optimistic scenario
Bread	15-20	20	25	30
Flour (wholemeal)	0	No change	5	5
Pasta	0	No change	2.5	5
Breakfast cereal	High	No change	no change	No change
Low/reduced fat milk	5	No change	10	20
Low/reduced fat plain yoghurt	0	100%	100%	100%
Low/reduced fat fruit yoghurt	0	No change	50	100
Juices	50 (orange)	No change	Small increase	Small increase
Low fat, low sugar biscuits	0	No change	5	10

Source:FSANZ. *First Review*. Proposal P295: Consideration of Mandatory Fortification with Folic Acid, March 2007

Table 3.1B Current folic acid fortification through voluntary permissions & projected changes under 3 alternative scenarios – Selected products, New Zealand

Commodity	% market share fortified product			
	Current	Industry proposal	Moderate scenario	Optimistic scenario
Bread	varied	As is + 20% those not now fortified	As is + 25% those not now fortified	As is + 30% those not now fortified
Flour (wholemeal)	0	No change	5	5
Pasta	0	No change	2.5	5
Low/reduced fat milk	0	No change	10	20
Low/reduced fat plain yoghurt	0	100%	100%	100%
Low/reduced fat fruit yoghurt	0	No change	50	100
Juices	25	No change	40	50
Low fat, low sugar biscuits	0	No change	5	10

Source:FSANZ. *First Review*. Proposal P295: Consideration of Mandatory Fortification with Folic Acid, March 2007

3.4 Estimated impact of postulated extensions on folate levels and incidence of NTDs

FSANZ has modelled the impact of these two scenarios on folic acid consumption and the rate and number of NTDs. These estimates are reported in Table 3.2 as well as the impact of current permissions.

Table 3.2 Estimated folic acid intake and NTDs prevented from extended voluntary permissions and up-take

	Australia		New Zealand	
Mean folate intake (ug)		x85%(a)		x85%(a)
▪ *Current voluntary*	108	92	62	53
▪ *Estimated mean folate intake after extensions*				
o Medium estimate ('base case')	136	116	119	101
o Industry estimate (sensitivity low estimate)	115	98	97	82
o Optimistic Scenario (sensitivity high estimate)	153	130	136	116
▪ *Estimated Additional mean folic acid intake extended voluntary (adjusted for 85% bioavailability)*				
o Medium estimate ('base case')		24		48
o Industry estimate (sensitivity low estimate)		6		29
o Optimistic scenario (sensitivity high estimate)		38		63
Estimated number of NTDs prevented (NTDs/year)				
o Medium estimate (base case)		7.1		3.0
o Industry estimate (sensitivity low estimate		1.8		1.9
o Optimistic scenario (sensitivity high estimate)		11.2		3.9

Source: FSANZ. *First Review*. Proposal P295: Consideration of Mandatory Fortification with Folic Acid, March 2007.

Note: a) adjusted for 85% bioavailability given consumption of folic acid with food

3.5 Cost of extending voluntary fortification

The cost of extending voluntary permissions mainly falls on the food and grocery industry and would normally be passed on to consumers in the form of higher prices. (While the costs will fall in the first instance on industry they represent costs to society in the form of resources forgone). The types of costs that may be incurred by industry may include labelling changes, packaging, product development, production costs, ingredient costs and monitoring/ testing costs. Submissions from various food companies have shown a wide range of cost estimates depending on the types of costs included. We note that product development and label change could be considered part of the normal product cycle, especially where new products are introduced at the discretion of companies after assessing their market potential. This is the position taken by most companies and seems reasonable.

Despite considerable cooperation from industry at very short notice, in forwarding estimates of the costs of proposed extensions to voluntary fortification covering a range of products, it is beyond the scope of this exercise to conduct a detailed micro costing of the three distinct voluntary fortification scenarios. This is in part a reflection of the number of possible product lines involved. The best that can be achieved at this time is an indicative costing based broadly on industry estimates, varied widely in sensitivity analysis. The costs in Table 3.3 draw on the evidence provided by industry and in the middle scenario focus on identifiable additional costs, specific to folic acid supplementation. We note that in contrast to the mandatory scenario, tolerances are less critical and the voluntary nature, suggests fewer cost categories are applicable.

We note also that zero net cost is a plausible low cost option. This reflects the voluntary nature of extensions, which means that companies will only proceed if it meets company objectives – primarily profit. This means that new products would only be introduced where it is expected that any additional costs could be passed on to the consumer in the form of higher prices, depending on market share strategies. In the context of a competitive market place and choice of products with/without fortification this means that the consumer must perceive an additional benefit from the product. Based on the economic theory of revealed preference (and as a matter of logic), the benefit to the consumer (which is likely to be additional to benefits captured in reduced incidence of NTDs) can be presumed to be at least equivalent to the additional cost yielding a net zero cost.

Table 3.3 Indicative costs of extending voluntary permissions

	Upfront cost		Ongoing Cost/ year	
	Australia	New Zealand	Australia	New Zealand
	AU$	NZ$	AU$	NZ$
Moderate scenario				
'Base case'	500,000	112,000	50,000	11,000
Upper estimate for sensitivity	1,000,000	225,000	100,000	22,000
Lower estimate for sensitivity	100,000	22,000	10,000	2,200

3.6 Cost effectiveness $/NTD avoided

Assumptions

The following is a list of assumptions adopted in modelling the cost effectiveness of the three extended voluntary fortification scenarios:

- Costs discounted at 5% pa. Outcomes discounted a 0 or 5% pa
- Time horizon 10 years (base case)
- AU$ for Australia, NZ$ for New Zealand
- 85% bioavailability of folic acid when consumed with food
- Folate from natural sources or supplements presumed not to change.
- Costs apply in year 1 and on an ongoing basis to maintain the intervention (as described in Table 3.3
- NTD link to increased folic acid intake calculated using model described by Bower and deKlerk et al 2006. This has been applied to population means, that is without any account of the distribution of folate levels and how that distribution might change
- Other assumptions as outlined in presentation of costs and effectiveness

Base case

The base case refers to the moderate scenario described by FSANZ, with costs and outcomes as described above. The data is drawn together in Table 3.4.

Sensitivity analysis

Sensitivity analysis is reported in chapter 6 (Table 6.2). Results are most sensitive to the estimated cost of implementation and confidence in NTDs estimated. We also do not know which, if any of the specified scenarios are likely to eventuate. Ideally a more detailed and precise costing would be undertaken of all the extended voluntary scenarios. Also, as noted above, if benefits to consumers from an extension in voluntary fortification (in the form of broad health benefit) are presumed to at least offset additional costs, in addition to generated NTD reductions, this is equivalent to a zero net cost for voluntary extensions. This reasoning would make any extension to voluntary fortification dominant relative to the status quo (less costly and more effective).

Table 3.4 Cost per NTD prevented for proposed extensions relating to voluntary folic acid fortification

Scenario	Present value cost	Mean NTDs prevented/ year o' 10 yrs		Cost per NTD prevented	
				Only costs discounted	Costs & NTDs discounted
Australia $AU					
Base case (FSANZ medium scenario) + middle cost estimate	$815,000	7.1	71	$11,500	$14,900
Lower industry estimate (with low NTDs and middle cost)	$815,000	1.8	18	$45,300	$58,600
Optimistic scenario (with high NTDs and middle cost)	$815,000	11.2	112	$7,300	$9,400
New Zealand $NZ					
Base case (FSANZ medium scenario) + middle cost estimate	$183,000	3.01	30	$6,100	$ 7,900
Lower industry estimate (with low NTDs and middle cost)	$183,000	1.89	19	$9,700	$12,500
Optimistic scenario (with high NTDs and middle cost)	$183,000	3.86	39	$4,700	$6,100

3.7 Safety – percent reaching upper limit

Tables 3.5 and 3.6 display the proportion of the Australian and New Zealand population by age group estimated by FSANZ 2007 to exceed the NHMRC defined upper limits (UL) at baseline, and after proposed extensions in take up of voluntary fortification. FSANZ calculations suggest that compared with baseline, the 'moderate' scenario would put an additional 30,000 persons at or above the NHMRC nominated 'upper limit' in Australia and 1200 persons in New Zealand.

Table 3.5 Estimated % of population and persons by age group with folic acid intakes above NHMRC specified Upper Limits (UL) Extended Voluntary Australia

Population Age Group (years)	Australian Population (a)	Estimated number (approx) and percent of the population with folic acid intakes at or above prescribed UL (b)							
		Baseline (c)		Industry proposal		Moderate Scenario		'Optimistic' Scenario	
		N	%	n	%	n	%	n	%
2-3	498,102	10,000	2	10,000	2	10,000	2	19,900	4
4-8	1,310,510	13,100	1	13,100	1	26,200	2	39,300	3
9-13	1,382,715	13,800	1	13,800	1	13,800	1	27,700	2
14-18	1,384,154	6,900	0.5	9,700	0.7	11,100	0.8	11,100	0.8
19-29	3,066,255	6,100	0.2	9,200	0.3	12,300	0.4	12,300	0.4
30-49	5,992,122	12,000	0.2	18,000	0.3	18,000	0.3	24,000	0.4
50-69	4,302,947	8,600	0.2	8,600	0.2	8,600	0.2	13,000	0.3
70+	1,895,986		0		0				0
All persons		70,000		83,400		100,000		109,900	

Source:/Notes

a. ABS 2006. Population by Age and Sex, Australian States and Territories. ABS cat no. 3201.0
b. FSANZ. *First Review*. Proposal P295: Consideration of Mandatory Fortification with Folic Acid, March 2007. The UL is based on folic acid from fortified foods, not natural folate. Supplement use by women is also not included in the model.
c. Baseline mean intake of folic acid from voluntarily fortified foods estimated at 108ug.

Table 3.6 Per cent of New Zealand population with folic acid intakes above the Upper Level (UL): Increased Voluntary Proposals

Population Group (years)	New-Zealand Population (a)	% of respondents with folic acid intakes > UL (b)			
		Baseline (c) %	Industry proposal increase n %	Moderate proposed increase n %	Higher proposed increase n %
15-18	249,750	0	0	0	0
19-29	607,830	0	0	0	0
30-49	1,204,020	0.1	1,204 0.1	1,204 0.1	1,204 0.1
50-69	827,440	0	0	0	0
70+	355,110	0	0	0	0

Source/Notes:

a. Statistics New Zealand. Demographic Trends (2006) – Reference Report. Chapter 1 Population change and structure. 2007
b. FSANZ. *First Review*. Proposal P295: Consideration of Mandatory Fortification with Folic Acid, March 2007. The UL is based only on folic acid that is from fortified foods, not intake of natural folate, nor supplement use by women.
c. At baseline mean intake of folic acid from voluntarily fortified foods in New Zealand is 58ug.

3.8 Overview

Voluntary permissions to fortify foods with folic acid have been widely used in Australia and New Zealand and are calculated to be responsible for a considerable increase in mean folate levels in the population. This has been estimated to account for 60 to 160 fewer NTDs in Australia. The possible impact of extending permissions or uptake is limited by the success to date.

Under a moderate extensions scenario, it is estimated that mean folate levels could be further increased by 18ug/day in Australia and 57ug/day in New Zealand (where they are not currently as high) resulting in an estimated 7/year fewer NTDs in Australia and 3/year fewer in NZ respectively.

Costs are difficult to estimate, due to a combination of conceptual and technical challenges, However it is likely that the cost/NTD avoided will be AU$20,000 for Australia and NZ$10,000 for NZ. A comparison with the other intervention options modelled is provided in Chapter 6, and a discussion of the key limitations of the research and suggested research directions is provided in Chapter 7.

Chapter 4 Mandatory fortification

4.1 Background – History of fortification in selected countries

Much of the information for this chapter comes from FSANZ. *Final Assessment Report. Proposal P295. Consideration of Mandatory Fortification with Folic Acid,* July 2006 and October 2006 and revised costing data and scenario specification communicated during March 2007.

A number of countries have introduced mandatory fortification of foods with folic acid in an effort to reduce the incidence of NTDs. These countries include Canada, the United States of America, Indonesia and a number of African and South American countries. Within these countries, wheat flour is the most common food fortified with folic acid.

The US Food and Drug Administration (FDA) in 1998 mandated that all enriched grain products be fortified with folic acid. The study by Bentley et al. (2006) used data from the National Health and Nutrition Examination Surveys to examine the effect of the FDA folic acid fortification policy. The analysis demonstrated an increase of total folate intake levels after fortification among US adults, but there were considerable variations in intake by age, gender, and race. Within the target population - women of childbearing age - the median folate intake increased by at least 100ug/day following fortification, and the percentage of women of childbearing age consuming more than 400ug/day of total folate increased from an estimated 26% to 38%. The study also found that within all racial groups, fewer women of childbearing age were taking folic acid supplements compared to pre-mandatory fortification rates. Among persons aged 65 years and older, the percentage who consume more than 1000ug/day (UL) has at least doubled among whites and black men. It is important to note that in the USA voluntary fortification had not been in place prior to the introduction of mandatory fortification. This limits the relevance of these outcomes for Australia and NZ.

4.2 Proposed fortification and Effect on mean intake of folic acid

The proposed level of mandatory fortification is 200 ug of folic acid per 100g of bread, which in Australia is presumed to be achieved through the fortification of bread making flour and in New Zealand of bread. If intake from voluntary fortification remains unchanged (baseline) then mandatory fortification of all bread-making flour at levels of 200ug/100g is estimated to result in a mean total intake of folic acid from fortified foods of 195ug/day in Australia and 189ug per day in New Zealand among women aged of child bearing age (16-44years). This represents an increase of 100ug/day and 140ug/day respectively. (Table 4.1)

Table 4.1 Estimated mean folic acid intake for women of child-bearing age due to mandatory folic acid fortification of all bread-making flour

Scenario (ug/100g)	Mean folic acid intake (ug/day)	
	Australia	***New Zealand***
Baseline (current voluntary)	108	62
All bread-making flour 200ug	208	-
Bread 135ug	-	202

4.3 Effectiveness: Impact on mean folate levels and NTDs

In Table 4.2 we summarise the estimated impact of the two fortification scenarios on:

- incremental folic acid intake, adjusted for bioavailability and
- annual reduction in NTDS.

Table 4.2 Estimated folic acid intake and NTDs prevented by mandatory fortification (a)

	Australia		New Zealand	
Estimated mean folic acid intake		@85%(b)		@85%(b)
▪ *Baseline* current (c)	108	92	62	53
▪ *With mandatory fortification*				
o Fortified breadmaking flour- 200ug/100g	208	177		
o Fortified bread- 135ug/ 100g			202	171
Additional folic acid from fortification				
o Fortified breadmaking flour- 200ug/100g		85		
o Fortified bread- 135ug/ 100g				119
Estimated number of NTDs prevented				
o Fortified breadmaking flour- 200ug/100g		24		
o Fortified bread- 135ug/ 100g				7

Source/notes

a. FSANZ. *First Review*. Proposal P295: Consideration of Mandatory Fortification with Folic Acid, March 2007

b. Folic acid consumed within fortified bread is 85% bioavailable.

c. No change in levels of folic acid from voluntary fortifications or supplement use.

4.4 Cost ($)

Cost of mandatory fortification

We have been provided with two very different estimates of costs on industry for mandatory fortification. One cost estimate is based on the report of a consultant commissioned by FSANZ, and the other on a report of a consultant commissioned by industry. Both incorporate very detailed costing analyses. The costs from these sources are summarised in Table 4.3. In addition there are costs to government for enforcement, provided by FSANZ. These are also reported in Table 4.3.

A cost estimate for monitoring the effect of mandatory fortification has also been developed and is reported. The primary aim would be to ascertain the effect on folate levels, to establish whether the intended impact is being achieved, but also to assess numbers exceeding the ULs and whether the expected reduction in NTDs is being observed. Monitoring of this or any other intervention would require the establishment of sound baseline data prior to implementation as well as an on-going data collection activity, probably involving the taking blood samples from the population – overall and within selected target groups. FSANZ has estimated the cost of monitoring to government at AU$435,000 and NZ$67,200 up-front plus AU$205,000 and NZ$50,400 per year ongoing. For this exercise, whilst monitoring of mandatory fortification and other interventions is highly desirable, it is rarely include in cost-effectiveness analyses. Therefore it does not appear in our base case analysis (for this or any other intervention). We have modelled it in sensitivity analysis in this case, as the mandatory nature of this intervention, may be thought to create a greater obligation for monitoring and evaluation. We note however, that it does not form part of the highest cost scenario.

We also note that members of the public health and clinical community have identified the need for a complementary public health campaign to support mandatory fortification[6], as a means to reduce the risk of a negative impact on supplement use by pregnant women or on the production and sale of voluntarily fortified products. The cost of such a campaign could be substantial and similar to that estimated in chapter 2 for a public health campaign to promote supplement use, that is, in the order of $5 million up front plus $1million annually. The cost of a complementary public health campaign has not at this stage been included in the modelled cost of mandatory fortification.

[6] as enunciated at the public health interest group workshop

Costs may also be incurred if companies choose to withdraw existing voluntarily fortified products from the market. One cereal company has estimated that this would cost a minim of $120,000 in labelling changes and some further costs associated with removing folate from product lines. These costs have been conservatively omitted from our estimates of the cost of mandatory fortification.

Table 4.3 Estimated costs associated with Mandatory folic acid fortification in Australia and New Zealand

	Australia				New Zealand	
	Lower (FSANZ) (a) AU$		Higher (Industry) (b) AU$		Mid estimate NZ$	
Industry Compliance- Upfront costs						
Labelling	2,486,400		2,486,400		436,063	
Packaging write off	4,000,000		4,000,000		500,000	
Equipment	1,400,000		22,100,000		80,000	
Total	*7,886,400*		*28,586,400*		*1,016,063*	
Industry Compliance- Ongoing costs						
Folic acid	112,000		-		-	
Premix	51,893		-		1,786,818	
Analytical testing	673,077		12,400,000		2,253,497	
Administration	186,883		186,883		109,278	
Clean out mill	34,739		34,739		-	
Total	*1,058,592*		*12,621,622*		*4,149,593*	
Government Enforcement- upfront costs						
Training and awareness	*27,169*		*27,169*		*7,920*	
Government Enforcement- ongoing costs						
Training and awareness					2,400	
Auditing content	74,390		74,390			
Auditing labels	19,017		19,017		80,000	
Administration	13,604		13,604		1,320	
Complaints	14,324		14,324			
Enforcement					4,780	
Total	*121,336*		*121,336*		*88,500*	
	Up front	*On-going*	*Up front*	*On-going*	*Up front*	*On-going*
Total Industry & government	7,913,569	1,179,928	28,613,569	12,742,958	1,023,983	4,238,093
OTHER COSTS						
Monitoring/evaluation (c)	435,000	205,000	ditto		67,200	50,400
Pubic health campaign d)	$3-5 million	$1 million	ditto			(d)

Source/notes:

FSANZ *First Review*. Proposal P295: Consideration of Mandatory Fortification with Folic Acid, March 2007.

a. Low estimates based on report by Gerard Mc Mullen prepared for FSANZ,
b. High estimate based on report prepared for industry, as summarised by FSANZ
c. The cost of a monitoring program has been estimated by FSANZ
d. A complementary public health campaign may be deemed necessary to gain public support and ensure supplement use by pregnant women does not fall and the consumption of voluntarily fortified products is not negatively affected. For costs see discussion in chapter 2.

Value assigned to loss of consumer choice/Principles pertaining to mandatory fortification of foods

One of the issues to be considered with mandatory fortification is the loss of consumer choice. This can be argued in several ways.

On the one hand it can be argued that fortification of flour or bread, as staples (and why they are the chosen vehicle) cannot readily be substituted, thus restricting people's ability to avoid fortified food should they wish to. Taking that view, the loss in consumer choice is real. Whilst it has been decided that 'organic flour' is to be exempt, this constitutes only a small proportion of the market and consumer choice will remain severely restricted. A standard way of incorporating loss of consumer choice, which results in a loss of consumer surplus (the difference between what is paid a good or service and the benefit derived), is to place a dollar figure on this loss. This could be applied to the consumption of fortified foods as much as to any other product for which choice is restricted. Whilst we have not been able to pursue this in detail, the implication of applying this concept can be simply illustrated. Consider allocating a $ figure to the loss of choice for each person who falls outside the target group for folic acid fortification, for the purpose of reducing NTDs. Taking the target as all women between the ages of 18 and 45, this leaves some 16.4 million persons outside the target in Australia and 3.3 million in New Zealand. If even $1 per person per year were assigned to this loss, the cost of mandatory fortification would be considerably increased.

The seriousness of curtailing consumer choice is recognised in the set of five high level policy principles developed by government relating to the mandatory fortification of food (Department of Health). These principles state, to paraphrase, that mandatory fortification of the food supply should only be introduced:

1. In response to a demonstrated significant population health need, and

Where

2. It is the most effective public health strategy to address the problem
3. It is consistent with the nutrition policies and guidelines of Australia and New Zealand
4. It will not result in detrimental excesses or imbalances
5. It will deliver effective vitamins to the target population to meet the health objectives

The current research will assist in determining whether mandatory fortification of bread with folic acid to reduce the incidence of NTDs meets these principles. Specifically it will contribute to an understanding of the level of effectiveness in terms of estimated prevention of NTDs and cost-effectiveness relative to other potential options. (See Chapters 6 and 7).

The issue of consumer choice is however complex. It could also be argued that consumers currently have little choice in relation to the nutrient quality of the foods that they consume. For example flour, rice and other staples are stripped of much of their nutrient value in the refinement processes, a factor over which consumers have no effective control. In that vein, it could be argued that fortification with folic acid and other essential nutrients is simply designed to put nutrients back into the food supply that have been taken out, without explicit consent of consumers and to the detriment of the public health.

A preferred approach may rather be to seek to reintroduce nutrients into food staples in as natural a form as possible and in a way that incorporates a range of 'missing' nutrients. This approach may achieve greater health benefits by potentially addressing several nutrient deficits simultaneously. A broader expression of the research question may have identified other options for consideration. Various products may fit that description. One product that is high in natural folate as well as other nutrients, wheat aleurone flour illustrates the principle and is briefly described in an Appendix.

4.5 Cost effectiveness: $/NTD avoided

Assumptions
The following is a list of assumptions used to model the cost effectiveness of mandatory fortification with folic acid:

- Costs discounted at 5%, outcomes at 0 and 5%
- Time horizon 10 years
- AU$ for Australian NZ$ for New Zealand
- 85% bioavailability of folic acid when consumed with food
- No impact of folate from natural sources or supplements
- NTDs link to increased folic acid intake according to Bower and deKlerk et al 2006,
- Other assumptions as outlined below.

Base case
We have presented a number of scenarios in the 'base case' specifically high cost (industry) and low cost (FSANZ) for the 200ug/100g concentration. See Table 4.4. Net present value cost for Australia is estimated at $15.5 million based on the FSANZ estimate of up front and on-going costs or $113.5 million based on the industry costs and for New Zealand at $29.7 million. These cost estimates include direct costs on industry plus government costs for enforcement. They do not include costs for the development and implementation of a monitoring program to evaluate the effect of mandatory fortification, nor do they include the costs of a population wide publicity campaign to explain the policy and promote continued uptake of complementary elements (such as taking of folate supplements by women planning a pregnancy).

Relative to an estimated 238 NTDs prevented this means for Australia $78,000 or $602,000/NTD prevented depending on which cost estimate is used, and $572,000/NTD prevented for New Zealand. This is with costs but not NTDs discounted. If NTDs are also discounted cost/NTD is somewhat higher. See Table 4.4.

Table 4.4 Cost per NTD averted mandatory fortification with folic acid – 'Base case'

Intervention	Net Present Value cost $ '000 (a)		Estimated NTDs averted			Cost per NTD prevented $	
	Low cost	High cost	per yr	10 yrs	@5% disc	NTDs 0% disc	NTDs disc @5%
Australia $AU							
200ug	15,500		23.81	238	184	77,800	84,000
		113,500				601,800	617,000
New Zealand $NZ							
135ug bread	3,916,700		6.94	69	54	571,900	554,000

a) NPV cost = cost per year over 10 years discounted and summed.

Sensitivity analysis
For mandatory folic acid fortification, a number of cost and implementation scenarios are reported in the 'base case'. Sensitivity analyses were performed for i) the confidence intervals derived when translating folic acid increase into NTDs prevented, ii) inclusion of the cost of monitoring/evaluation and iii) loss of consumer choice. The results are highly sensitive to the NTD confidence interval - with most estimates near halving or doubling, as well as costing loss of consumer choice. (See Table 6.2 in Chapter 6 for sensitivity results).

4.6 Safety (% reaching upper limit)

Tables 4.5 and 4.6 present the proportion of each population group in Australia and New Zealand exceeding the upper level (UL) assuming the introduction of mandatory folic acid fortification of all bread-making flour/bread.

Table 4.5 Number, % Australians folic acid intakes above UL: Mandatory Proposals

Population Group (years)	Australian Population (n)	% of respondents with folic acid intakes > UL		
		Baseline* %	Mandatory 200ug/100g flour n	%
2-3	498,102	2	44,800	9
4-8	1,310,510	1	52,400	4
9-13	1,382,715	1	27,700	2
14-18	1,384,154	0.5	27,700	2
19-29	3,066,255	0.2	21,500	0.7
30-49	5,992,122	0.2	24,000	0.4
50-69	4,302,947	0.2	8,600	0.2
70+	1,895,986	0		0
Total persons			**206,700**	

Source: FSANZ. *First Review*. Proposal P295: Consideration of Mandatory Fortification with Folic Acid, March 2007

* Baseline: Mean intake of folic acid from voluntarily fortified foods 108ug. (see also chapter 3)

Table 4.6 Number and per cent of New Zealand population with folic acid intakes above the UL: Mandatory Proposal

Population Group (years)	New Zealand Population (n)	N and % with folic acid intakes > UL		
		Baseline* %	Mandatory Proposal 135ug/100g bread n	%
15-18	249,750	0	2,000	0.8
19-29	607,830	0	600	0.1
30-49	1,204,020	0.1	1,200	0.1
50-69	827,440	0	800	0.1
70+	355,110	0	0	
Total			**4,600**	

*Baseline: The mean intake of folic acid from voluntarily fortified foods in New Zealand is 58ug/day.

Chapter 5 DIETARY FOLATE

5.1 Introduction

The NHMRC recommends that women capable of or planning a pregnancy consume additional folic acid as a supplement or in the form of fortified foods at a level of 400ug/day for at least one month before and three months after conception, in addition to consuming food folate from a varied diet. (NHMRC, 2006) There is however a lack of information regarding intake of dietary folate during pregnancy and the effect on folate status and NTDs. In this chapter we report on the cost-effectiveness of dietary interventions to promote foods rich in natural folate and fortified foods as part of a multi-component strategy to reduce the incidence of NTDs. We briefly present some of the evidence on the relationship between natural dietary folate and NTDs and on the ability to increase natural folate intake at an individual and population level. Limited evidence concerning the possible success of dietary campaigns is also used to inform the cost-effectiveness model of dietary interventions.

5.2 Introduction to evidence on natural folate and NTDs

Natural Sources of folate

Foods naturally high in folate include asparagus, spinach, brussell sprouts, oranges, bananas and legumes. The folate content of selected foods is presented in Table 5.1.

Table 5.1 Natural folate content of foods

Food	Status	Quantity	Folate (ug)
Blackeye beans	Cooked, boiled	½ cup	105
Spinach	Frozen, cooked, boiled	½ cup	100
Asparagus	Boiled	4 spears	85
Baked beans	Canned	1 cup	60
Spinach	Raw	1 cup	60
Green peas	Frozen, boiled	½ cup	50
Broccoli	Frozen, cooked	½ cup	50
Avocado	Raw	½ cup	45
Peanuts	Dry roasted	1 ounce	40
Orange Juice	(includes concentrate)	¾ cup	35
Orange	Fresh	1 small	30
Banana	raw	1 medium	20

Source: U.S. Department of Agriculture, Agricultural Research Service. 2003. USDA National Nutrient Database for Standard Reference, Release 16.

Literature search

A literature search was conducted in January 2007 using the search engines; Ovid, Medline, ScienceDirect and ProQuest 5000 International. Key terms included Folate, Dietary Folate, and Neural Tube Defects, yielding over 600 citations. Of these articles, only a small number concern natural dietary folate. Eleven articles were examined in detail and are summarised in this chapter.

Relationship between red cell folate levels and NTDs

A case control study by Daly et al. (1995) investigated the relationship between red cell folate levels and NTDs. The study involved the collection of blood from all women attending their first antenatal clinic in one of the three Dublin, Ireland, maternity hospitals from 1986-90. From the samples (taken at median gestational age of 15 weeks) blood was retrieved for 84 NTD cases and 266 controls. Given an overall NTD rate of 1.9/1000 births in the study hospital, Daly LE et al. estimated NTD risks in different groupings of plasma or red cell folate levels.

Table 5.2 illustrates the distribution of red cell folate in cases and controls and NTD risk in each category. A dose-response relationship is seen. There is a more than eightfold difference in risk between those with red cell folate levels less than 340nmol/L compared with those with levels of 906nmol/L or higher. The differences in red cell folate will primarily reflect varying consumption of foods rich in natural folate, as in the study population only 5% used folic acid supplements and folic acid fortified foods were not available.

Table 5.2 Distribution of cases and controls and risk of NTD by red cell folate level

Red Cell Folate nmol/L	NTD cases N	%	Controls N	%	Risk of NTD per 1000 Births	NTD Relative Risk	95% CI
0-339	11	13.1	13	3.8	6.6	8.3	3.3 – 11.7
340-452	13	15.5	24	9.0	3.2	4.0	1.7 – 5.5
453-679	29	34.5	75	28.2	2.3	2.9	1.6 – 3.3
680-905	20	23.8	77	29.0	1.6	2.0	1.0 – 2.4
≥ 906	11	13.1	80	30.0	0.8	1.0	0.4 – 1.5
Total	84	100.0	266	100.0	1.9		1.5 -2.3

Evidence of relationship between natural folate and NTDs from observational studies

Only a small number of studies have investigated the relationship between natural dietary folate and NTD's. Four observational studies have been examined in detail and are summarised in Table 5.3. A population based case control study by Thompson et al. conducted between 1992 and 1997, included 179 first occurrence NTD-affected pregnancies and 288 control mothers from South Carolina. Dietary folate intake from natural sources was assessed using the Harvard Food Frequency Questionnaire for the period three months prior to conception through the first three months of pregnancy. The study displayed a considerable protective effect from NTD's at the highest quartile of dietary folate. (Thompson SJ *et al,* 2003)

A US prospective study in the mid 1980's by Moore et al. (2003) interviewed 23,228 women in the early second trimester of pregnancy. During the first 8 weeks of pregnancy dietary folate intake was assessed using a food frequency questionnaire. Women with the lowest intakes of dietary folate from foods (<100 DFEs per day) had the highest risk of an NTD birth, suggesting a protective effect from higher food folate.

Bower C and Stanley FJ (1989) conducted a case-control study in WA drawing on information from 77 mothers giving birth to a child with an NTD born between1982-1984, matched against a control group of subjects with no birth defects (n=154). With respect to the occurrence of neural tube defects, the crude odds ratios were less than one in all quartiles above the first with a trend towards decreasing odds ratios with increasing quartiles of total folate intake. The analysis of total dietary folate (without the addition of folate supplements) showed a protective effect with increasing folate intake, (Bower C and Stanley FJ, 1989).

A more recent case control study by Bower C et al. (2004) was conducted between 1997 and 2000 to investigate the effect of the health promotion activities undertaken in WA in 1992, in terms of consumption of folic acid supplements and periconceptional dietary intake of folate in preventing NTDs. The study included 36 cases and 578 control mothers. Cases with NTDs were identified from the WA birth defects registry and a random sample of all live born infants in WA was selected to form the control group. The mothers completed a pregnancy questionnaire and a semi-quantified food frequency questionnaire. For women not taking ≥ 200ug folic acid supplements daily in the periconceptional period, there was a non-significant reduction in risk of NTD with increasing amount of dietary folate intake. There was a reduced odds ratio for the highest two tertiles of natural folate daily compared with the lowest tertile. (Bower C *et al,* 2004).

The results are summarised in table A5.1 (Annex to this chapter)

Quality of studies

Food frequency questionnaires were the method used to determine dietary folate intake in all 4 studies. This method can be prone to error. There is also potential for inaccurate recall in reporting dietary patterns prior to and after conception. Natural dietary folate was separated from folic acid fortified foods in all studies, except the study by Thompson SJ *et al,* 2003. In this case although fortification of grain products was not mandated until January 1998, it is possible that foods were fortified prior to then and could be part of dietary intake. The study by Moore et al. assessed dietary folate intake only during the first 8 weeks of pregnancy, which may or may not be representative of their diet prior to pregnancy. In other ways, eg in relation to control group matching, the studies appear sound.

Relationship between natural dietary folate and folate status

There is little data on natural dietary folate intake during pregnancy and the effect on folate status. Often studies compare food-derived folate with supplemental folate, rather than the effect of different levels of consumption of natural folate on folate status. (Koebnick *et al,* 2001) In addition, uncertainties remain in regard to the efficiency of the use of folate in food, its absorption and the actual content of folate in the diet. (Bower & Stanley 1989). Three intervention studies which have examined the relationship between natural folate and folate status are described in detail and summarised in Table A5.2.

A three month intervention study by Cuskelly et al. (1996) explored the effects of dietary folate and folic acid enriched foods on folate status. Forty-one women from Northern Ireland were randomly assigned to either i) folic acid supplement (400ug/day); ii) Folic acid fortified foods (+l 400ug/day); iii) Natural food folate (+ 400ug/day); iv) Dietary advice and v) Control. All four interventions increased folate/folic acid intakes. However, folate status (as assessed by red-cell folate concentrations) improved significantly only in the groups taking folic acid supplements or folic acid fortified food. There was no increase in the group consuming extra food folate or given dietary advice. Only Groups i and ii achieve red cell folate above 400ug/L. In the groups taking supplements or fortified foods, serum folate doubled in both instances, whereas in the groups assigned to dietary folate and dietary advice, moderate increases were observed. This study is however compromised by very small sample sizes, with only 6 to10 persons per arm, resulting in very wide confidence intervals around observed values.

Conversely, an intervention study by Brouwer et al. (1999) which investigated the effects of natural dietary folate from vegetables and citrus fruits on folate status, found a positive effect on folate status. 67 healthy men and women (not pregnant) aged 18 – 45 years participated in the study. The treatments for each group were: i) dietary folate group (a diet high in natural folate plus a placebo tablet) (n = 23); ii) a folic acid group (a diet low in folate plus supplemental folic acid) (n = 22); and iii) a placebo group (low folate diet plus a placebo tablet) (n = 22). After the 4 week intervention, the plasma folate and red blood cell folate concentrations increased in both the dietary folate and the folic acid group. This study found that a diet rich in folate-dense vegetables and citrus fruits significantly enhanced the folate status in healthy volunteers.

Ashfield-Watt et al. (2003) undertook a 4 month intervention study of 135 healthy men and women of the ‘wild-type’ CC genotype for the MTHFR C677T polymorphism. This study investigated the relative efficacy of 100ug/day folate from natural sources (fruit and vegetables) compared with 100ug/day folic acid from fortified foods in terms of changes in folate status. Subjects were randomly allocated to: i) Control diet (normal diet, including usual intake of folic acid fortified products); ii) Fortified diet (+100ug/day folic acid from fortified foods); iii) Natural folate diet (+100ug/day folate from natural sources and usual intake of folate fortified products). Folate intake was assessed using a semi-quantitative food frequency questionnaire.

Dietary folate intake increased significantly in both intervention groups, compared with controls, yet the increase in total folate in the fortified groups was significantly greater than in the natural folate group (difference 54ug/day). Both intervention groups in this study significantly raised plasma folate concentrations compared with controls. The change in plasma folate was similar in both intervention groups, despite the greater total folate intake in the fortified folate group.

Bioavailability of natural folate

Although there have been advances in understanding folate bioavailability there are still areas of uncertainty, especially with respect to naturally occurring dietary folate. (Gregory JF, 2001) The term dietary folate equivalents (DFE) was introduced to accommodate the varying bioavailabilities. Dietary folate equivalents are defined as:

Naturally occurring food folate (ug) + 1.7 x synthetic folate (ug).

This equation adjusts for a a greater bioavailability of folic acid, although there is some debate about the validity of the multiplicand, especially in view of the small sample n=10 in the original study (Sauberlich *et al,* 1987, Gregory 2001). A more recent study by Brouwer IA et al. (1999) suggests the relative bioavailability of natural folate compared to folic acid is much higher, depending on the selected end point; at 60% based on homocysteine concentration, 78% based on plasma folate concentration and 98% based on red blood cell folate concentration. The Ashfield-Watt study also suggests higher bioavailability of natural folate. In this study change in plasma folate was similar in both intervention groups, despite the greater total folate intake in the fortified folate group, which does not suggest a poorer bioavailability of natural sources of folate compared with folic acid.

5.3 Evidence of potential to increase natural folate intake

Range in natural folate intake – across countries, time, populations

The National Nutrition Survey estimates folate intake from the natural folate content of foods and beverages, that is excluding folate form fortified foods. (ABS, 1998). The mean daily folate intake in Australia for females aged 19-44 years was 230ug in 1995, and in New Zealand, 211ug. Cereal products, vegetables and milk products provided approximately 55% of folate intake for all ages in Australia. Tea and beer also made a moderate contribution to women and men's folate intake respectively. (ABS, 1998) In the New Zealand population, the principle dietary sources of folate were vegetables (18%), bread (13%) and breakfast cereals (11%). Additional sources included fruits, potatoes and kumara. (NZ Food: NZ People, 1999)

The percentile distribution of daily folate intake for females aged 19-44 years in Australia and New Zealand is reported in Table 5.5. (ABS, 1998, NZ Food: NZ People, 1999). This shows considerable variation with highest decile consuming more than 300ug, while the bottom decile is consuming less than 165ug in Australia and 140 in NZ (or 125 in persons 19 to 24). This indicates obtaining reasonably high levels of folate intake from natural sources is possible, but also that many people currently consume very low levels of natural folate.

Table 5.3 Percentile distribution of daily folate intake (ug)

AUSTRALIA	**Percentile**				
Age group (years)	**10**	**25**	**50**	**75**	**90**
19-24	164.1	188.2	224.3	260.1	311.1
25-44	166.1	188.9	218.4	253.8	295.9
NEW ZEALAND	**Percentile**				
Age group (years)	**10**		**50**		**90**
19-24	125		195		290
25-44	141		213		307

Observational studies

A number of observational studies report the consumption of dietary folate from natural sources by pregnant women or mothers. The results of these studies are summarised in Table A5.3.

A prospective study by Koebnick C et al. recruited 109 pregnant women from 1995-1997. Information on dietary intake and blood samples were collected in each trimester of pregnancy. The study group included 'vegetarians', who were divided into low meat eaters and ovo-lacto vegetarians. Women eating a typical Western diet were the control group. Folate intake was highest in ovo-lacto vegetarians and lowest in the Western diet group. The estimated average requirements (EAR) of 520ug DFE was met by 13% of ovo-lacto vegetarians, 9% of low meat eaters and 5% of the Western diet group throughout pregnancy. (Koebnick C *et al,* 2001)

In the population based case control study by Thompson SJ et al., of the 35 cases and 42 control mothers who reported no use of multivitamins, 34.3% and 47.9% respectively, had dietary folate levels of 322ug or greater. (Thompson SJ *et al,* 2003)

Werler MW et al. interviewed 1136 mothers of infants with major malformations from the Boston and Philadelphia areas, whose pregnancies began from 1993 to 1995. The estimated daily intake of folate from natural sources was 250ug.

The Western Australian case control study by Bower C et al. (2004) found that 34% of non-supplementing control mothers (n = 105), and 25% of case mothers (n = 5), obtained 400ug of folate daily from natural sources. (Bower C *et al,* 2004). (We note this is higher than that suggested by the ABS nutrition survey)

Food frequency questionnaires were the method used to determine dietary folate intake in all studies therefore there is potential for recall bias. The results did not include folic acid supplement users, and all studies (except the study by Thompson SJ *et al,* 2003*)* separated natural folate from folic acid fortified foods.

Intervention studies

The NHMRC recommends that women capable of, or planning a pregnancy should consume additional folic acid at a level of 400ug/day for at least one month before and three months after conception, in addition to consuming food folate from a varied diet. Compliance with the recommendation for folate supplements remains incomplete and high consumption of folate rich foods such as vegetables and fruits is then important, (Conlin ML *et al,* 2006).

There are few reported studies designed to promote increased consumption of folate from natural dietary sources that could be used to evaluate the effect of this type of intervention. Our choice of studies from which to draw evidence is thus limited and far from ideal.

As described above, the intervention study by Ashfield Watt et al. sought to investigate the relative efficacy of 100ug/day folate from natural sources (fruit and vegetables) compared with 100ug/day folic acid from fortified foods. Dietary folate intake increased significantly in the intervention groups compared with controls, and the increase in total folate in the fortified groups was significantly greater than in the natural folate group (difference 54ug/day). Folate consumption increased by 50ug in the natural folate group (not including folic acid fortified foods) and 104ug in the fortified folate group (from fortified foods and natural folate). Subjects in the natural folate group reported more difficulty in attaining the target increase in folate, although, some were unable to reach the target due to an already high intake of fruit and vegetables. The study demonstrates that a significant increase in natural folate is achievable, which is associated with increased plasma folate. (Key results are reported in Table A5.4)

The NHMRC recommended in 1993 that 'all women planning a pregnancy or likely to become pregnant should be offered advice about folate in the diet and encouraged to increase their dietary intake of folate rich foods'. The South Australian 'Folate before Pregnancy' campaign targeted health professionals and women of reproductive age with three key messages:

- An adequate folate/folic acid intake by women of reproductive age may reduce the risk of NTD such as spina bifida
- Green leafy vegetables, fruit and cereals are the food groups with the most folate
- Adequate folate/folic acid needs to be taken in the periconceptional period – before pregnancy and in the first three months of pregnancy

Chan A et al. evaluated the impact of the campaign in South Australia on women of reproductive age and on health professionals. (Chan A *et al,* 2001). A random sample of 400 women 15-44 years was interviewed in July 1994 early in the campaign and in October 1995. Other surveys were also drawn on, a December 1996 survey of 400 (15-44years) women (part of a disability survey), a 1995 and 1996 survey of women who delivered a baby at the Women's & Children's Hospital and a survey in 1998 of 2079 women of reproductive age. The proportion of women reporting that they increased their consumption of folate-rich foods, before conception and in the first three months of pregnancy, rose from 12.0% to 18.2% between 1995 and 1996, with a further increase to 43.7% in 1998. In 1995 and 1996 14.5% said they did not increase their folate consumption presuming they were consuming enough. Of three specified approaches to the prevention of NTDs, increased consumption of folate-rich foods was the first preference of 76.1% women. It should be noted that by 1997-1998, voluntary fortification had been introduced and several promotional factors may have contributed to the higher knowledge and consumption of folate rich foods.

Other dietary campaigns

Given the dearth of studies to promote folate rich foods we have also drawn on other evidence that explores the possibility of changing dietary behaviour in either the population or a high risk target.

The *Go for 2&5* campaign is an example of a population based campaign, aimed at achieving dietary changes consistent with a folate rich diet. This fruit and vegetable information campaign – ran from April to July 2005. The primary target was parents and carers of children and youth (0-17 years), with children aged 5-12 and youth a secondary target. The *Go for 2&5* campaign was evaluated through comparison between a Baseline survey (prior to the campaign launch) with the results from two Follow up surveys (one after on-air television commercials and one at the end of the campaign). (Woolcott Research. 2006)

In the baseline survey 60% of parents claimed to eat the recommended two+ serves of fruit per day. Levels of individual fruit consumption remained fairly consistent across the three surveys. Only 10% of persons surveyed consumed the recommended intake of vegetables. At Baseline and 1st Follow up survey ~ a quarter of parents were eating only one or 2 serve of vegetables per day. In the 2nd Follow up survey, there was a significant decrease in the proportion of persons eating only one serve of vegetables per day and a corresponding increase in those consuming four or more serves per day. These changes resulted in a small increase in mean serves per day. (Table 5.4)

Table 5.4 Individual Fruit & Vegetable Consumption - % in each category

Serves per day (per day)	**Baseline** n = 1200		**Follow up 1** n = 591		**Follow up 2** n = 1001	
	Fruit	Vegetables(%)	Fruit	Vegetables (%)	Fruit	Vegetables (%)
Less than one serve	6	1	4	1	6	2
One serve	33	23	26	27	30	16
Two serves	32	27	35	26	33	24
2 + serves	60		63		61	
Three serves	18	24	21	23	19	25
Four serves		15		12		19
5 + serves		10		8		12
Mean serves	2.0	2.6	2.2	2.5	2.1	2.9

A comparison of the behaviours reported in the 2001 National Health Survey with the 1995 National Nutrition Survey demonstrates an increase in the mean number of serves of vegetables consumed per day, and particularly in person consuming 4+ serves. This may well reflect the effect of a number of inter-related health messages. (Table 5.5) (ABS, 2003)

Table 5.5 Usual daily serves of vegetables: Comparison between 1995 and 2001.

	1995	2001
Doesn't eat vegetables	0.5	0.5
1 serve or less	23.2	18.4
2-3 serves	55.3	48.2
4-5 serves	18.5	27.6
6 serves or more	2.0	5.2
> 4 serves (%)	20.5	32.8
Estimated mean serves per day (n)	2.42	2.90

The Women's Health Initiative Randomised Controlled Dietary Modification Trial was a very large n= 48 835 randomised control dietary intervention trial in post menopausal women. The trial had a long follow up of a mean 8.1 years. (Prentice et al 2006). The primary dietary aim in the experimental group was to reduce fat as a proportion of the diet and increase consumption of fruit and vegetables and grains. The experimental group was asked to participate in 18 group sessions run by a dietitian in year 1 plus quarterly sessions after that. The clinical aim was to reduce breast cancer incidence.

Whilst the clinical aim was not achieved, the study found considerable and significant changes in diet, that conformed with the dietary advice. Key results in terms of changes in consumption of target foods/nutrients at 1 year and the difference between groups at 6 years is summarised in table 5.6. There was a mean increase of 1.5 serves of fruit and vegetables. Relative to the control group, at 6 years, fruit and vegetables intake was 1 serve greater per day and grains 0.4 of a serve per day .

This study demonstrates that large and significant changes in diet resulting in important differences in nutrient intake is possible on a wide scale, from an intensive clinical intervention. The study also found a large increase in mean folate levels, from baseline of 140ug/day and a significant difference from control of 62ug/day at year 1 and 45ug/day at year 6. (See Table 5.6.)

Table 5.6 Mean intake of target foods/nutrients baseline and 1 year Women's Health Initiative

	Intervention (Diet) group		Control Group		Mean diff in change b/w groups	
	Base line	Year 1	Base line	Year 1	Year 1	Year 6
Fat % of energy	37.8	24.3	37.8	36.1	-10.7 *	-8.1*
total gram	75.7	40.9	75.7	63.0	-22.4*	-18.4*
Vegetables & fruit serves per day	3.6	5.1	3.6	3.9	1.2*	1.1*
Grains servings	4.7	4.8	4.8	4.2	0.7*	0.4*
Folate ug per day	259	398.5	259.3	346.1	62.1*	45.6*

Source: Prentice et al 2006, Table 2 p 632

* Difference significant at $p<0.001$ from a 2-sample t test

The *Lyon Diet Heart Study* is an example of a low cost targeted dietary intervention, which demonstrates the possibility of significant strategic changes to peoples' diet, which results in very considerable health gain. Key data about this trial are summarised in Annex A5.

5.4 Effectiveness of interventions for cost effectiveness

Search and selection

The search strategy and studies identified regarding increasing naturally occurring dietary folate have been described in detail above. The most appropriate study design to determine the effectiveness of interventions aimed at reducing NTDs through the increase of naturally occurring folate would be a randomised trial comparing alternative options to the status quo, supplement use or fortification with long follow up and a sufficient sample size to detect the resulting difference in NTDs. No such studies were identified, so we have chosen to model the following interventions that cover a range of settings and target groups:

A National folate health promotion campaign- with campaign design similar to those conducted in WA and SA and results similar to "Go for 2&5"

B Targeted natural dietary folate education campaign- based on Ashfield-Watt et al (2003).

It is likely that interventions aimed at increasing naturally occurring dietary folate when applied in a real life setting would also include a component to increase voluntarily fortified foods. It is however important that the individual effectiveness of the naturally occurring dietary folate is also established alone. We provide two scenarios for each intervention 1) naturally occurring dietary folate alone 2) naturally occurring dietary folate plus voluntarily fortified foods. The identified studies are all subject to limitations and potentials for bias and the resulting cost effectiveness can be seen as scenario development and analysis due to the need for a number of assumptions which will be explicitly outlined.

Intervention details

The Ashfield-Watt intervention has been chosen as an example of a targeted, specific campaign with possible application in a general practice or obstetric setting. The second option is a National folate health promotion campaign which would be based on the SA and WA campaign with estimated results for natural folate similar to the Go for 2&5 intervention. Specific details of each intervention and participants have been outlined above and described further in Table A5.11.

Assessment of Trial Quality

The design of a National folate health promotion campaign is assumed to be similar to and based on the WA and SA studies. It is only the design of the intervention that is therefore relevant to this work. The results of the national campaign are based on the results of the Go for 2&5 campaign. This has a number of limitations. The Go for 2& 5 campaign is a pre-post evaluation where a different group of participants were assessed before and after the campaign. It is possible that they differed in important ways that were unmeasured. It is also difficult without a control group to conclude that any changes were solely due to the intervention as there may have been other background contributors. The evaluation also relies on self-reported data which may be subject to bias. The evaluation also provides no insight into the types and quantities of food consumed.

The Ashfield-Watt study was a randomised trial of participants who had been previously screened for, but not recruited to another study. All subjects were non supplements takers. There were 16 males and 29 females in each of the 3 group, so it is unclear if these participants were representative of the target group and if there was sufficient study power to detect significant differences between groups. The study involves detailed completion of food diaries which gave some immediate feedback on folate intake, so this exercise should be viewed as part of the intervention. This study was conducted under controlled experimental conditions with effort given to assist compliance such as telephone calls to those who did not return diaries. The greatest limitation of this study is therefore the generalisability of results to a real life setting. It does however provide an indication of what it is possible. It can also be noted that the fortified folate consumed at baseline in this study is similar to the consumption of fortified foods in Australia (Ashfield-Watt 98ug/day compared to 108ug/day current voluntary use in Australia).

Results and scenarios

The original results for the Ashfield Watt study were summarised previoulsy. We will use the results to inform two scenarios 1) naturally occurring dietary folate alone 2) naturally occurring dietary folate plus folate from voluntarily fortified foods. From the Ashfield-Watt study the base case for the first scenario of is taken from the increase in natural folate for the natural dietary group. The 50ug/day increase is converted into folic acid equivalents by dividing by 1.7. In sensitivity analyses we also consider the increase in plasma folate for the natural diet group from 26.1 to 27.8 nmol/l which we convert back to ng/ml(ug/L) by dividing by 2.265.

The base case for scenario 2 is taken by adding the 'fortified folate' increase in the fortified group to the midpoint of the increase in 'natural folate' from the natural group and the fortified group. This figure is then also converted to a folic acid equivalent by dividing by 1.7. For sensitivity analysis two estimates are used, first the plasma folate converted back to ng/ml or ug/l by dividing by 2.265 for the fortified group alone and second for the fortified group added to the natural group.

Table 5.7 Targeted campaign baseline and follow-up folate- figures used in two scenarios and sensitivity analysis

Scenario	Folate	Baseline	Follow-up	Change ug/day
Targeted campaign Scenario 1 –intervention to increase natural folate alone				
Base case	Natural folate ug/day (Folic acid equiv.)	200	251	50 (29.4)
Sensitivity analysis	Plasma folate nmol/l	26.1	27.8	1.7
	(Converted to ug/l or ng/ml)	11.5	12.3	(0.77)
Targeted campaign Scenario 2- intervention to increase natural folate and fortified folate from voluntarily fortified foods				
Base case	Fortified folate ug/day	47	144	98
	Natural folate* ug/day			28.5
	Combined folate ug/day (Folic acid equiv.)			126.5 (74.4)
Sensitivity analysis	a) Plasma folate fortified group	25.7	27.6	2.1
	(Converted to ug/l or ng/ml)	11.3	12.2	(0.93)
	b) Plasma folate fortified plus natural	51.8	55.4	3.8
	groups (Converted to ug/l or ng/ml)	22.9	24.5	(1.7)

*estimated by taking the midpoint between the change in natural folate in the fortified group (7ug/day) and the change in natural folate for the natural folate group (50ug/day)

There was no information reported in the SA or WA campaigns regarding the increase in natural folate as a result of the campaign. We therefore model some scenarios as an indication of what may be achieved although acknowledge this is preliminary and not based on trial results. Chan et al evaluated the SA campaign and reported that the proportion of women who increased their 'consumption of folate-rich foods' (before conception and in the first three months of pregnancy) according to self report rose from 12.0% in 1995 to 18.2% in 1996 and 43.7% in 1998. There was however no information provided regarding the actual level or change in natural folate consumption. We thus rely on increases in consumption from the recent National fruit and vegetable campaign 'Go for 2&5' which reported average increases of 0.5 serves of vegetables on average with no significant increase in fruit consumption. This will be used as a base case for our economic modelling although it is possible that larger increases would be achievable for more targeted campaign such as folate promotion for women of childbearing age and we will therefore model other scenarios as summarised in Table 5.7.

In order to model the increase in folate we need to estimate folate intake from a typical diet. We estimate current consumption of folate rich foods leading to the average current folate consumption of 230ug/day (NNS, 1995) as a starting point.

(Note our estimate falls slightly short at 215 in order to allow for a small amount of folate from unlisted sources). We then estimate potential increases in folate through consumption of various scenarios of additional fruit and vegetables. This is based on assumptions rather than empirical work and should be viewed and interpreted as such. Table 5.7 and 5.8 outlines 4 scenarios- baseline current consumption, base case for modelling, upper estimate and lower estimate for sensitivity analysis.

In order to inform scenario 2 (increase natural and fortified folate) for the economic modelling, we have assumed consumption of fortified folate in addition to increased folate intake from natural sources. As there is no evidence available for promotion of additional fortified food, we make some assumptions about what may be possible and assumed that the New Zealand current average of 62ug/day increases to the Australian average of 108ug/day and that the Australian average increases by 20%. We assume that fortified folic acid has bioavailability of 85% as it is consumed with food. See Table A5.8.

NTDs prevented

Using the above scenarios it is possible to calculate the number of NTDs prevented. Bower, DeKlerk et al (2006) provide NTDs prevented for incremental increases in folic acid intake or alternatively for increases in serum folate both for the general Australian and New Zealand populations at risk. It must be noted that this model is limited in that it applies mean increases in folic acid with no differentiation according to the baseline level of folic acid intake or baseline serum level. Note that scenario 1 refers to an intervention or campaign to increase natural folate alone and scenario 2 refers to increasing natural folate and folic acid from fortified foods. For the Ashfield-Watt intervention we have assumed that the intervention will only reach 25% of births, ie it will have a scope of 25% and the NTDs have been adjusted accordingly.

Table 5.8 Estimated NTDs prevented- Australia and New Zealand

Scenario	Increase in folic acid µg	Increase in serum folate ug/l or ng/ml	Estimated NTDs prevented/year AUS	Estimated NTDs prevented/year NZ
Ashfield-Watt education intervention				
Scenario 1: Base case	29.4		2.2	0.5
Scenario 1: Sensitivity		0.77	5.8	1.2
Scenario 2: Base case	74.4		5.3	1.1
Scenario 2: Sensitivity a)		0.93	6.9	1.5
Scenario 2: Sensitivity b)		1.7	11.7	2.5
National health promotion campaign				
Scenario 1: Base case	14.7		4.4	1.0
Scenario 1: Sensitivity a)	32.4		9.5	2.0
Scenario 1: Sensitivity b)	44.1		12.8	2.7
Scenario 2: Base case	33.1 (53.8 NZ)		9.7	3.3
Scenario 2: Sensitivity a)	124.2 (85.1 NZ)		33.6	5.1
Scenario 2: Sensitivity b)	135.9 (96.8 NZ)		36.4	5.8

Assumptions

- 30% supplement use
- Increase in natural folate applies equally to those who do and do not take folic acid supplements
- Baseline serum of 7.9 (non supplement users) and 12.6 (supplement users)
- The scope of the targeted intervention will reach 25% of births

- Current folic acid intake from voluntarily fortified foods is 108 in Australia and 62 in New Zealand and is associated with 85% bioavailability as it is taken with food

5.5 Cost of interventions ($)

The National folate health promotion campaign is assumed to cost the same as the health promotion campaign described in the supplement chapter with a cost of AU$5 million in year 1 and AU$1 million per year ongoing. If the population of Australia is assumed to be 20 million and the population of New Zealand 4 million then we assume that this campaign will cost one fifth when applied to New Zealand or AU$1 million upfront and AU$200,000 per year (NZ$1,120,000 and NZ$224,000 respectively) ongoing for the National campaign.

The cost of the Ashfield-Watt education intervention is calculated based on estimated resource use to conduct the intervention via general practitioners and is described in Table 5.8.

Table 5.8 Estimated costs of the Ashfield-Watt intervention

Description	Units	Cost inputs $AU	Total cost $AU	
			Year 1	ongoing
Program manager and administration	1 manager and 1 administration staff full time in year 1 and 0.20 FTE ongoing	$74,703 + 20% oncosts manager* $50,077 + 20% oncosts administration*	$149,736	$29,947
Information pack materials	1 information pack per GP, assumes 5% new GPs each year who receive info pack	36,300 GPs in Australia @ $5 per pack	$181,500	$9,075
GP advice	Target 500,000** women 25% of GPs advise patients for an average of 5 minutes	Hourly rate for GPs $121.90†	$1,269,792	$1,269,792
Total Australia			$1,601,028	$1,308,814
Total New Zealand‡			NZ$358,983	NZ$293,462

*A manager is costed as General Staff salary HEO10 and an administrator at HEO5-6 based on current 2007 University of South Australia pay scales **Approximately double the number of births per year in Australia † Double MBS item number 36 surgery consultation level C assumes average of 30 minute consultation ‡ New Zealand cost assumed to be one fifth of the Australian cost currency converted at a rate of 1.12 (Jan 2007)

5.6 Cost-effectiveness ($/NTD avoided)

Assumptions

The following assumptions were applied when modelling the cost effectiveness of these interventions:

- Costs discounted at 5% and outcomes disocutned at 0% or 5%
- Time horizon 10 years base case (5 and 20 modelled in sensitivity)
- AU$ for Australian NZ$ for New Zealand
- 85% bioavailability of fortified folic acid, ratio of 1 to 0.6 for natural folate to folic acid
- 30% of target group currently take supplements
- Average dose of folic acid when taken 500mg Australia, 800mg New Zealand
- NTDs link to increased folic acid intake according to Bower and deKlerk without regard for the absolute initial intake of folic acid

Base case: The base case refers to a time horizon of 10 years, discounted at 5%.

Table 5.9 Cost per NTD prevented natural folate only (scenario 1)

Intervention	Average costs/ year	mean NTDs prevented/ yr	Cost/NTD prevented	Discounted cost per NTD prevented
Australia $AU				
Ashfield-Watt education intervention	$1,338,035	2.17	$616,606	$619,749
National folate promotion campaign	$1,400,000	4.41	$317,460	$338,628
New Zealand $NZ				
Ashfield-Watt education intervention	$300,014	0.47	$638,328	$641,582
National folate promotion campaign	$313,908	0.95	$330,429	$352,462

Table 5.10 Cost per NTD prevented for interventions targeting natural folate and voluntarily fortified folate consumption (scenario 2)

Intervention	Average costs/ year	Mean NTDs prevented/ yr	Cost/NTD prevented	Discounted cost per NTD prevented
Australia $AU				
Ashfield-Watt education intervention	$1,338,035	5.26	$254,379	$255,676
National folate promotion campaign	$1,400,000	9.74	$143,737	$153,321
New Zealand $NZ				
Ashfield-Watt education intervention	$300,014	1.13	$265,499	$266,853
National folate promotion campaign	$313,908	3.33	$94,267	$100,552

Sensitivity analyses

Once again results are presented for the two scenarios (1= natural folate intake only and 2= all dietary folate intake both natural and voluntarily fortified).

Scenario 1: Natural folate: For the National health promotion of dietary folate cost/NTD prevented ranged from $116,000 to $747,000 for Australia and $112,000 to $1.7 million for New Zealand with results most sensitive to the confidence intervals around the translation of folic acid into NTDs. For the Targeted intervention results ranged from $255,000 to $1.3 million for Australia and $267,000 to $3 million for New Zealand, with results most sensitive to the alternative estimate of the increase in folate and the confidence intervals around the translation of folic acid into NTDs.

Scenario 2: All dietary folate;For the National health promotion of dietary folate intervention (including effects of voluntarily fortified food) costs/NTD prevented ranged from $83,500 to AU$298,700 for Australia and $55,800 to $334,800 for New Zealand, with results most sensitive to the confidence intervals around the translation of folic acid into NTDs. For the Targeted intervention results ranged from $116,000 to $448,000 for Australia and $121,000 to $603,000 for New Zealand, with results most sensitive to the alternative estimate of the increase in folate and the confidence intervals around the translation of folic acid into NTDs.

5.7 Safety

There have been no adverse effects reported for consumption of high levels of natural folate. Rather, studies show that high natural folate levels may be protective for some diseases or conditions.

Annex to Chapter 5. Selected Tables

Table A5.1 Summary of 4 studies: Relative Risk of NTD's according to natural dietary folate intake

Study	Folate (ug)	n		OR		95% CI
Thompson JS *et al,* 2003		**Cases**	**Controls**			
	15 – 235	68	68	1.00		
	236 – 321	35	66	0.62		0.36 - 1.09
	322 – 456	42	68	0.70		0.40 - 1.22
	457 – 3125	25	67	0.40		0.19 - 0.84
Moore LL *et al,* 2003				**Prevalence /1,000**	**RR**	
	0-99	744		4.0	1.00	
	100-199	6,011		2.0	0.52	0.14 – 1.8
	200-299	8,095		1.7	0.45	0.13 – 1.6
	300-399	4,709		2.3	0.61	0.17 – 2.2
	≥400	3,669		2.5	0.64	0.17 – 2.4
Bower C and Stanley FJ, 1989 (control group2)		**Cases**	**Controls**			
	20 - 178.4	25	39	1.00		
	178.5 - 239.6	20	32	0.94		0.38 – 2.31
	239.7 - 350.1	17	42	0.61		0.25 – 1.47
	350.2 - 1787	13	37	0.38		0.14 – 1.02
Bower C *et al,* 2004	<326	12	111	1.00		
	≥326	8	198	0.37		0.15 – 0.94

Table A5.2 Effect of dietary folate and folic acid on folate status

Study	Group	Baseline folate intake (ug)	Follow up folate intake (ug)	Actual change in folate intake ug	Plasma folate change (nmol/L)	RBC folate Change (nmol/L)
(Cuskelly GJ *et al,* 1996) Three month intervention study. 41 women from Northern Ireland	Dietary Folate (n = 10)	209	410 0 folic acid	201		28
	Supplement (n = 9)	209	601 400 folic acid	392		141
	Fortified Foods (n = 6)	186	407 269 folic acid	221		173
(Brouwer IA *et al,* 1999) 4 week intervention study. 67 healthy men and women (not pregnant) aged 18 – 45 years	Dietary Folate Group (+ folate 350ug/d) (n = 23)		594 ± 27		6.5 ± 3.0	59.3 ± 55.5
	Folic Acid Group (+ folic acid 500ug/2d) (n = 22)		226 ± 9 250^2 folic acid		5.8 ± 3.1	42.9 ± 50.5
(Ashfield-Watt PAL *et al,* 2003) 4 month intervention study. 135 healthy men/ women of the 'wild-type' CC genotype for the MTHFR C677T polymorphism.	Natural folate	200	251	50	1.7	
	Fortified folate (natural and folic acid fortified food)	242	347	104	2.1	

Table 5.3 Summary of 4 observational studies: folate intake from natural food sources

Method	Reference	Subjects Groups		Folate Intake (ug)
(1992 – 1997) 179 first occurrence NTD - affected pregnancies 288 control mothers from South Carolina	S J Thompson *et al.* 2003	Cases (%)	Controls (%)	
		40	25.3	15 – 235
		20.6	24.5	236 – 321
		24.7	25.3	322 – 456
		14.7	24.9	457 – 3125
(1993 – 1995) 1136 mothers of infants with major malformations from the Boston and Philadelphia areas	Werler MW *et al.* 1999	n = 807 (not taking folic acid supplements)		250 (average intake)
(1995 – 1997) Prospective study. 109 pregnant women.	Koebnick C *et al.* 2001	Ovo-lacto vegetarians (n = 27)		217 (192/246)
		Low meat eaters (n = 43)		193 (168/229)
		Average Western Diet (n = 39)		149 (134/181)
(1997 – 2000) 36 cases (NTDs) and 578 control mothers.	Bower C *et al.* 2004	Cases %	Controls %	
		60	35.9	<326
		40	64.1	≥326

Table A5.4 Baseline and follow-up dietary and biochemical parameters

	Dietary Group	Baseline	Follow-up	Change	Percentage Change
Natural folate ug/day	Control	197	186	-11	-5.6
	Fortified	195	203	7	4.3
	Natural	200	251	50	25.2
Fortified folate ug/day	Control	43	50	5	15.0
	Fortified	47	144	98	203.7
	Natural	43	55	11	28.8
Total folate ug/day	Control	241	236	-7	-1.8
	Fortified	242	347	104	43.3
	Natural	243	306	62	25.9
Plasma folate nmol/l	Control	25.9	25.2	-0.9	-2.6
	Fortified	25.7	27.6	2.1	7.1
	Natural	26.1	27.8	1.7	6.8

Source: Ashfield-Watt PAL *et al,* 2003

Table A5.5 Details of intervention and participants

	SA Health promotion campaign (1994-1995)	WA health promotion campaign (1992-1995)	Ashfield-Watt education intervention
Participant characteristics	No information reported regarding age, marital status, ethnicity, education, previous or planned pregnancies	Age 17-43 years (mean 28.7), 86% married or de facto, 83% born in Australia, New Zealand or UK, 58% high school education only, 61% planned pregnancies	Healthy men and women living in South Wales, UK. Mean age 41 years, Not currently taking supplements
Intervention details	Key message: folate/folic acid reduce risk of NTD, green leafy vegetables, fruit and cereals are good source of folate, adequate folate/folic acid needs to be taken periconceptionally and in first 3 months of pregnancy. Health professionals (including pharmacists, GPs, dieticians, nursing and medical staff)- posters, information leaflets, NHMRC guidelines, information in professional newsletters and presentations. Wider community- posters/pamphlets to high school librarians, health education teachers, women's community groups and fruit and vegetable vendors, health food shops, libraries, shopping centres, childcare centres and preschools. Newspaper, magazine, TV and radio advertising.	Key message: raise awareness about folate and NTDs, increase women's folate intake Physicians, pharmacists, dieticians, community and child health workers- information sheets, pamphlets, posters, information sheets on genetic counselling and high risk women, articles in journals, newsletters and bulletins, presentations, training and continuing education, stickers for folic acid bottles, printed paper bags, consumer newsletter articles General community- seminars, message on Medicare cheques, magazine articles, newspaper, radio and television ads and editorials, taxi back ads, information sheet to public libraries, displays and food demonstrations, cooking program and education package, information to education department and schools, incorporation of material into curriculum, public launch, stamp, stickers and price tags.	Three dietary interventions: Control diet: subjects were advised to eat their normal diet Fortified diet: subjects were advised to eat an extra 100µg/day folic acid from fortified food products including cereals and breads Natural folate diet: subjects were advised to eat an extra 100µg/day folate from natural sources, particularly fruit and vegetables, and to maintain normal consumption of fortified products All subjects completed 2 week folate diary at baseline, 2 months and 4 months
Potential target group	All Australian women of childbearing age	All Australian women of childbearing age	Women of childbearing age attending GP or gynaecologist. This could also include women planning a pregnancy
Potential settings	Media, pharmacists, supermarkets, professional seminars/workshops, general practitioners, paediatricians, obstetricians and gynaecologists, child health nurses, schools, child care centres, libraries, family planning clinics	Media, pharmacists, supermarkets, professional seminars/workshops, general practitioners, paediatricians, obstetricians and gynaecologists, child health nurses, schools, child care centres, libraries, family planning clinics	Health centres such as general practice, gynaecologists.

Lyon Diet Heart Study – Example of a targeted diet intervention

The Lyon Diet Heart Study is an example of a dietary intervention which has been successful in achieving sustained dietary changes and associated health benefits. (DeLorgeril et al, 1994 & 1999. The Lyon Diet Heart Study is a prospective, randomised, secondary prevention trial aimed at reducing the risk of cardiovascular deaths by diet modification and recurrent myocardial infarction in survivors of a first myocardial infarction. Patients who survived a first myocardial infarction were randomised between 1988 and 1992. Eligible patients were less than 70 years old and clinically stable.

Patients in the experimental group were advised by the research cardiologist and dietitian to adopt a Mediterranean-type diet including more bread, root and green vegetables and fruit and fish, but less meat and cream and butter to be replaced with rapeseed oil margarine supplied by the Trial. Patients of the control group were advised to follow the American Heart Association diet. Cardiovascular morbidity and mortality was recorded on 289 experimental and 295 control group patients. Primary end points were death from cardiovascular causes and non-fatal acute myocardial infarction.

At baseline, the diet of the experimental group was similar to that of the controls. After 52 weeks, the experimental group had higher concentrations of oleic, alpha-linolenic (68% higher) and eicosapentaenoic acids and reduced concentrations of stearic, linoleic and arachidonic acids. The experimental group had a significantly higher intake of bread, fruit, and margarine and a lower intake of butter, cream, meat, and delicatessen items. (Table A5.6)

Table A5.6 Intake of the main foodstuffs after 1 to 4 years follow-up (g/day).

Foods	Control (n = 192)	Experimental (n = 219)	P
Bread	145	167	0.01
Cereals	99.4	94.0	0.22
Legumes	9.9	19.9	0.07
Vegetables	288	316	0.07
Fruits	203	251	0.007
Delicatessen	13.4	6.4	0.01
Meat	60.4	40.8	0.009
Poultry	52.8	57.8	0.42
Cheese	35.0	32.2	0.25
Butter and Cream	16.6	2.8	<0.001
Margarine	5.1	19.0	<0.001
Oil	16.5	15.7	0.65
Fish	39.5	46.5	0.16

The survivors of a first myocardial infarction, assigned to a Mediterranean alpha-linolenic acid-rich diet, had a markedly reduced rate of recurrence cardiac events and overall mortality. A reduction in coronary events and cardiac deaths of ~70% was achieved in the Mediterranean diet group, despite no difference in serum cholesterol, triglycerides, or HDL compared to controls. The protective effect observed by this study was primarily attributed to the higher intake of alpha-linolenic acid. The rate of cardiac death and nonfatal infarction in the experimental group after 46 months was 1.24 per hundred patient years, significantly lower than the control group rate of 4.07 after 46 months See Table A5.7. De Lorgeril *et al* (1999)

The study also found that several years after randomisation, the majority of experimental patients were still closely following the Mediterranean diet recommended. This suggests the adoption of and compliance with new dietary habits is achievable, provided that the instructions to patients are appropriate. It is also important that new dietary habits are palatable and feasible for patients.

Table A5.7 Total primary end points at 27 months & 46 months follow-up.

	27 months			46 months		
	Control (n = 303)	Experimental (n = 302)		Control	Experimental	
	Rate	Rate	Risk Ratio (95% CI)	Rate	Rate	Risk Ratio (95%CI)
Total Primary End Points	5.55	1.32	0.27 (0.12 – 0.59)	4.07	1.24	0.28 (0.15 – 0.53)

Table A5.8 National health promotion campaign- estimates of folate consumption at baseline and extra folate consumption for economic modelling

Types of food	Natural folate content	Baseline	Base case	Mid estimate (a)	Higher estimate (b)
		Number of serves			
Blackeye beans, cooked or boiled ½ cup	105				
Spinach frozen, cooked or boiled ½ cup	100				
Asparagus boiled, 4 spears	85	1			
Baked beans canned, 1 cup	60	½			
Spinach raw, 1 cup	60			½	
Green peas frozen, boiled ½ cup	50		½		1
Broccoli frozen cooked	50	1			
Avocado raw ½ cup	45				
Peanuts dry roasted 1 ounce	40				
Orange Juice (incl. concentrate), ¾ cup	35	1			
Orange fresh 1 small	30			1 average	1 average
Banana raw 1 medium	20	1			
Total serves fruit and veg		4.5	5.0	6.0	6.5
Total serves fruit and veg in addition to baseline		0	0.5	1.0	1.5
Total natural folate		215	240	270	290
Natural folate in addition to baseline		0	25	55	75
Total DFE		126.5	141.2	158.8	170.6
DFE in addition to baseline *(Scenario 1)*		**0**	**14.7**	**32.4**	**44.1**
Additional folic acid from intake of fortified foods		21.6 (46 NZ)	21.6 (46 NZ)	21.6 (46 NZ)	21.6 (46 NZ)
Fortified folic acid (85% bioavailability)		18.4 (39.1 NZ)	18.4 (39.1 NZ)	18.4 (39.1 NZ)	18.4 (39.1 NZ)
Additional total folic acid intake from baseline *(Scenario 2)*		**0**	**33.1 (53.8 NZ)**	**50.8 (71.5 NZ)**	**62.5 (83.2 NZ)**

DFE- dietary folate equivalents

CHAPTER 6

6.1 Introduction

In this chapter we draw together the results of the economic analyses for the four broad proposals for promoting folate consumption in the population to avoid NTD cases. Each proposal is considered in isolation, although the optimal strategy will almost certainly involve a combination of components. We have not been able to assess the extent to which components might be potentially additive. In this chapter we also describe the results of the sensitivity analysis, which highlights the lack of certainty surrounding all the proposals.

6.2 Comparative effectiveness – NTDs avoided

Estimated effect on number of NTDs associated with the base case for each of the twelve proposals modelled for Australia and eleven for New Zealand is presented in Figures 6.1 and 6.2.

In terms of cases of NTDs avoided, none of the proposals in isolation would make a large impact on total NTD cases. And none of the proposals is expected to achieve the equivalent impact of current voluntary permissions or current promotion of folate supplements for women planning a pregnancy. It is thus critical that whatever is introduced does not deleteriously affect current initiatives, other wise the net effect could potentially be an increase in the number of cases of NTDs. On the other hand it is possible new elements might achieve positive synergies with existing initiatives.

Relative to an estimated 340 NTD cases per year currently (2005), (FSANZ 2006, Figure 1), none of the proposals would reduce the incidence of NTDs by even 10%. This contrasts with the introduction of voluntary permissions which was associated with an estimated reduction in NTDs of between 15% and 30%, (FSANZ 2006, Figure 1).

Based on ‘base case’ assumptions, the largest effect, resulting in an estimated reduction of 23 to 27 NTDs is seen to be achieved by the mandatory fortification of bread, or a national campaign to promote use of folic acid supplements in women who may become pregnant. This reduction is equivalent to around 8% of current NTDs and might see 4 fewer live births per year, 2 -3 fewer still births and 14 fewer terminations due to NTDs. While, it is unlikely the effects would be simply additive, it would be expected that a strategy that combined key components would achieve a greater impact than any taken in isolation.

Results are similar for New Zealand, with mandatory fortification and promotion of supplement use estimated to result in 6 to 7 fewer NTD cases per year.

It is important to note that the proposals modelled do not represent all possible options and do not necessarily include the best. The attributes of aleuron flour as described in an Appendix to this report suggest this as a possibly effective way of promoting folate consumption as well as addressing other nutrient deficits.

Figure 6.1 Estimated NTDs prevented 'Base case' Australia

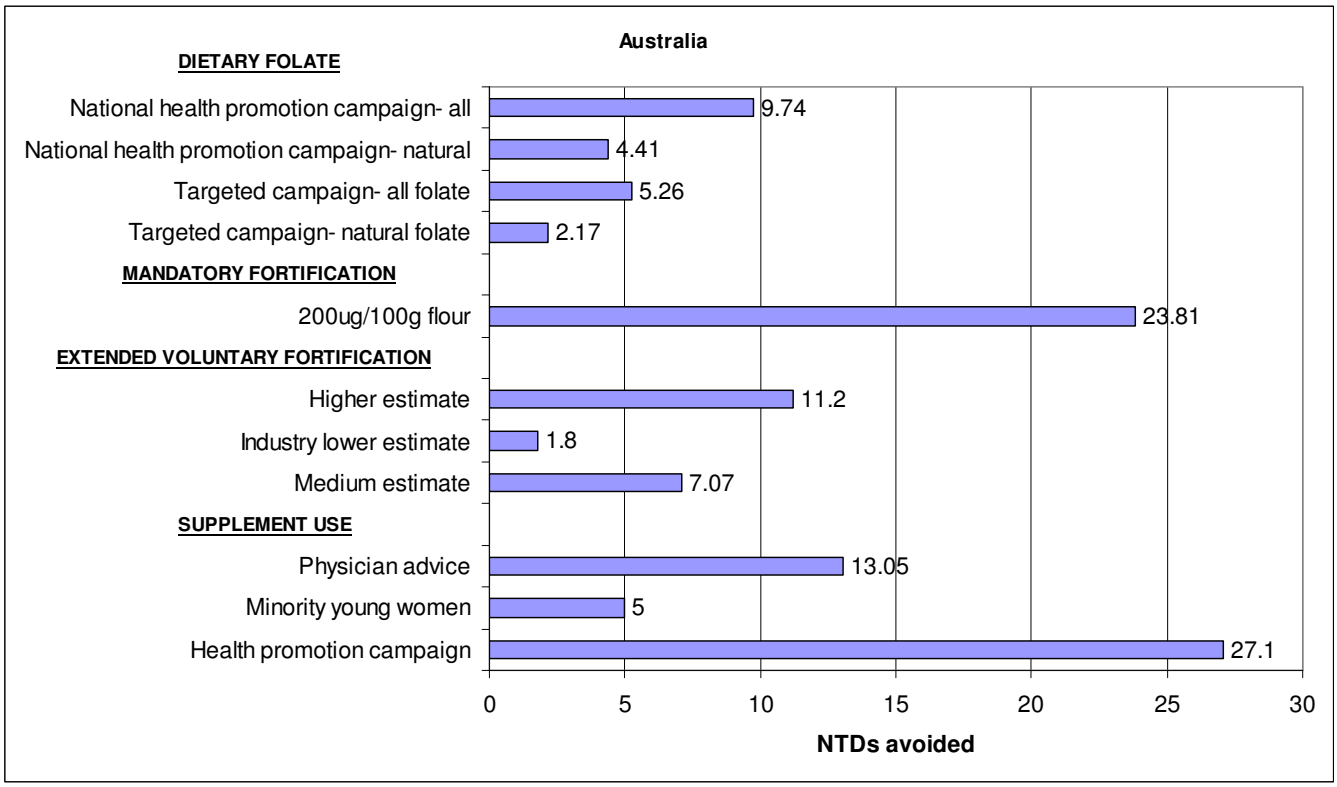
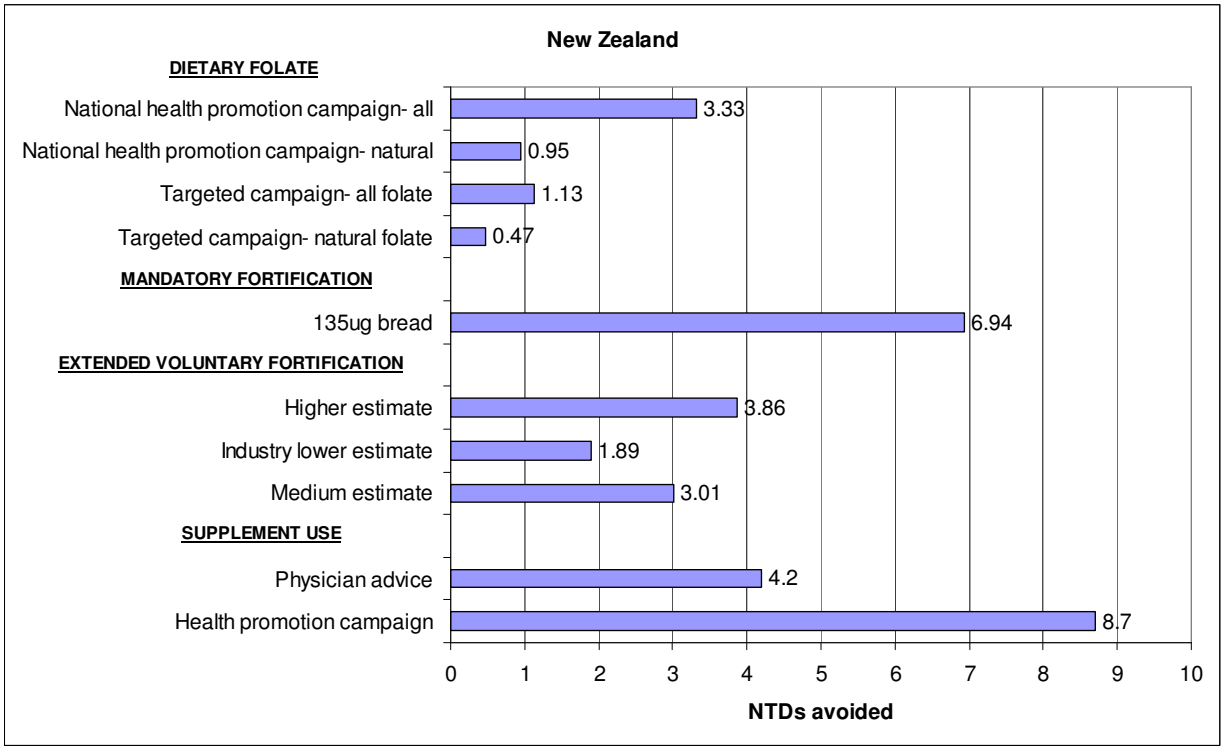


Figure 6.2 Estimated NTDs prevented 'Base case' New Zealand



6.3 Comparative efficiency $/NTD prevented

Cost per NTD prevented is illustrated in Figures 6.2 and 6.3. This reflects the 'base case' assumptions, and incorporates a 5%pa discount on both costs and NTDs. Cost per NTD avoided depends not surprisingly on the costs of each proposal – around which there is considerable uncertainty. See section 6.5 below.

In relation to mandatory fortification of bread making flour, we have modelled cost-effectiveness using both the cost estimate derived from an industry commissioned study and a FSANZ commissioned study. This translates into a very large difference in the cost-effectiveness of mandatory fortification in Australia from $84,000/NTD prevented to nearly $617,000/NTD prevented. Thus, depending on what the actual costs are, mandatory fortification may perform poorly or 'reasonably'in terms of cost-effectiveness. We also note that the base case cost does not include the cost of a monitoring/evaluation campaign nor for an associated public health campaign, nor any value for loss of consumer surplus. The addition of these costs would considerably increase cost and make the cost-effectiveness result poorer. Even at the FSANZ cost estimate it performs more poorly than modelled approaches to extending supplement use or extending voluntary fortification.

We also note that some initiatives that are not highly effective are none-the-less cost effective if associated with relatively low costs. Thus for instance extending voluntary appears highly cost-effective although it is not as effective as other options.

Proposals that perform relatively well in terms of effectiveness and cost effectiveness include physician advice to promote supplement use. Although as will be clear from the sensitivity analysis below there is considerable uncertainty around these estimates
For New Zealand mandatory fortification is not at all a cost-effective option, estimated at over $500,000 per NTD prevented.

Figure 6.3 Comparative cost-effectiveness, $/NTD prevented. Australia

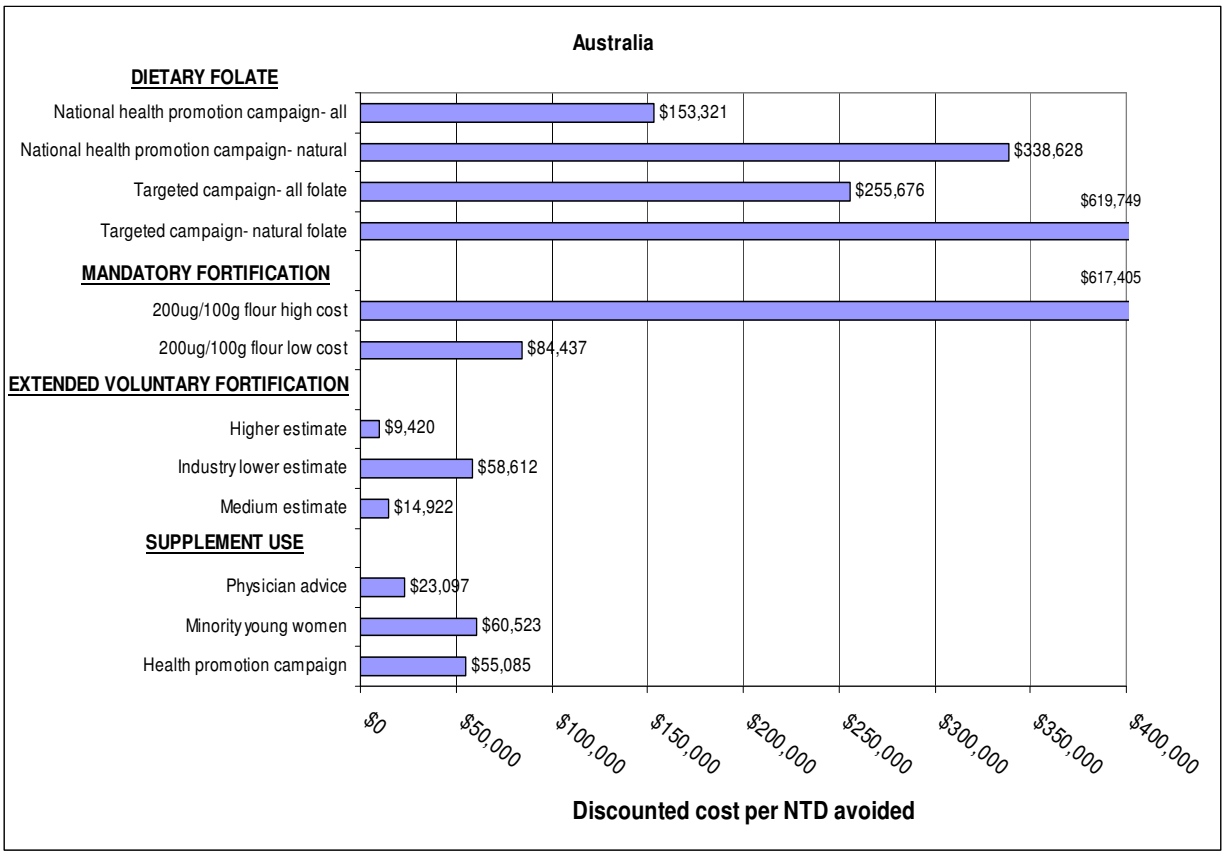
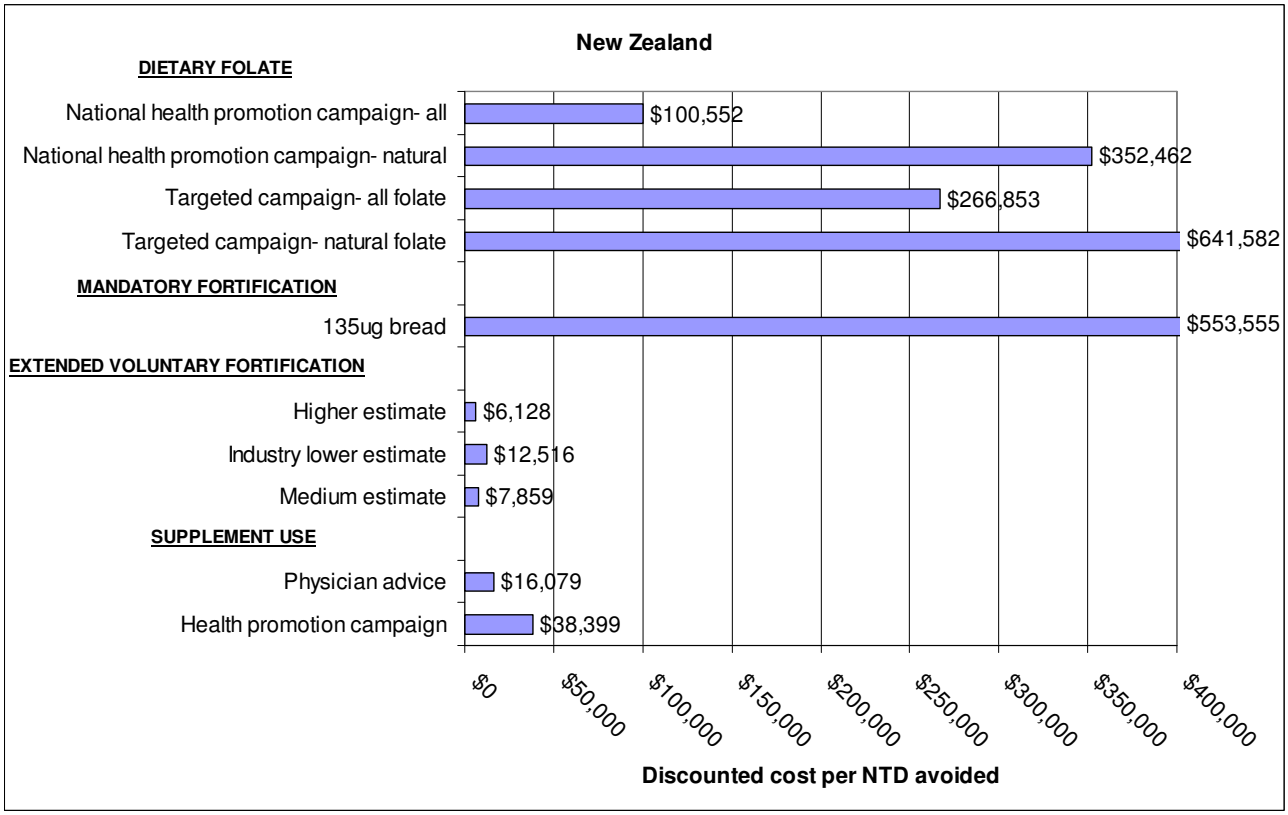


Figure 6.4 Comparative cost-effectiveness, $/NTD prevented. New Zealand



6.4 Comparative efficiency: $/DALYs gained

A standard outcome measure used by health economists to compare performance of alternative health interventions is the quality adjusted life year or the related disability adjusted life year. These outcomes have the attribute of combining quality of life and premature mortality. Qaulity of life is measured on a scale of 0 (or below zero for states worse than death) to 1 perfect health. These quality of life scores are combined with time in health state to calculate a quality adjusted life year. Changes in quality of life can then be captured in a single measure. Quality of life scores are derived in such a way as to have an equivalent with life expectancy, such that of quality of life score of 0.6 is equivalent to loss of 0.4 of a life year, and an intervention that takes someone form a QoL score of 0.6 to 0.8 for a period of two years is equivalent to a gain of 0.4 life years (0.8-0.6 x 2). The DALY is a similar concept, derived by the World Bank and WHO, primarily to measure global health status/disease burden as a combined measure of premature mortality and disability. Disability weights are expressed from 1 to 0 where 1 is total disablement and 0 full health. A series of disability weights have been published and are widely used to measure disease burden (eg DHS 1996). These weights are not without critics.

We have used published disability weights (DHS 1996) and combined with estimated loss of life to derive estimated DALY gain for each of the proposal, and related to cost to estimate $/DALY gain. NTDs and NTDs prevented have been classified into; live births, stillbirths and terminations, which we have presumed occur at a ratio of 19% live births, 11% stillbirths and 70% terminations (ref). The disability weight attached to live births is 0.52 (DHS, 1999). There is no WHO published disability weight for a termination, only for an abortion – which is 0. For this base case we have used a disability weight of 0.01 for terminations, but of course can adjust this. Still births are counted at full loss of life. DALYs gained are discounted at 5% per year as is standard practice with economic evaluations prepared for the Pharmaceutical Benefits Advisory Committee. DALYs gained are summed over the 10 year life of the model.

We present results in Figures 6.5 and 6.6 as $/DALY gain with (gross) and net of the treatment cost offsets. For the net figure, treatment cost savings are estimated in relation to NTD live births averted at $13,500/year for years 1 to 4 and $4,354 for years 5 to 10. These have been adjusted to NZ $ for the NZ scenarios. (Access Economics, 2006, p20).

Results are presented as a discounted cost per disability adjusted life year saved with and without the offsetting treatment costs. Results can be compared with conventional thresholds that are commonly applied to guide decisions within other areas of health such as for listing of pharmacotherapies by the Pharmaceutical Benefits Advisory Committee (PBAC). Threshold of less than AU$40,000 have been viewed as favourable for the decision to fund (ref). Funding through the PBS is however predicated on high quality evidence of effectiveness.

In terms of cost per DALY gained voluntary proposal, promotion of supplement use and promoting the consumption of dietary folate all appear highly cost-effective. Under FSANZ cost estimate, mandatory fortification is close what is acceptable, although this does not include the cost of monitoring or of a related public health campaign. Further NTDs have not been discounted increasing the size of the benefit. See sensitivity analysis.

Once cost offsets are included cost-effectiveness improves considerably across all interventions. We can see that several are now cost saving, that is the expected saving in health service costs is greater than the cost of the intervention.

Table 6.5 Australia: Discounted cost per DALY saved – no cost offsets

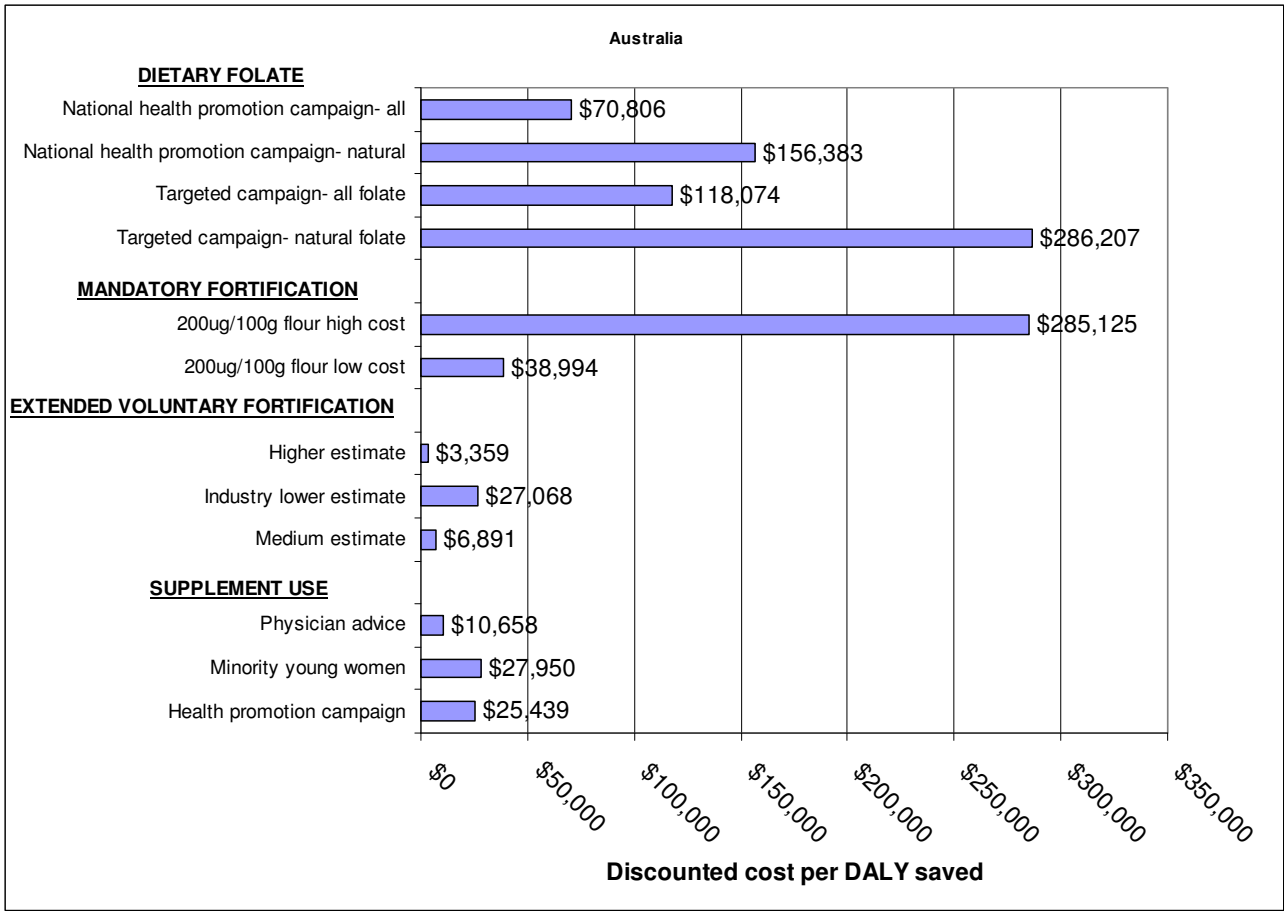


Table 6.6 New Zealand: Discounted cost per DALY saved – no cost offsets

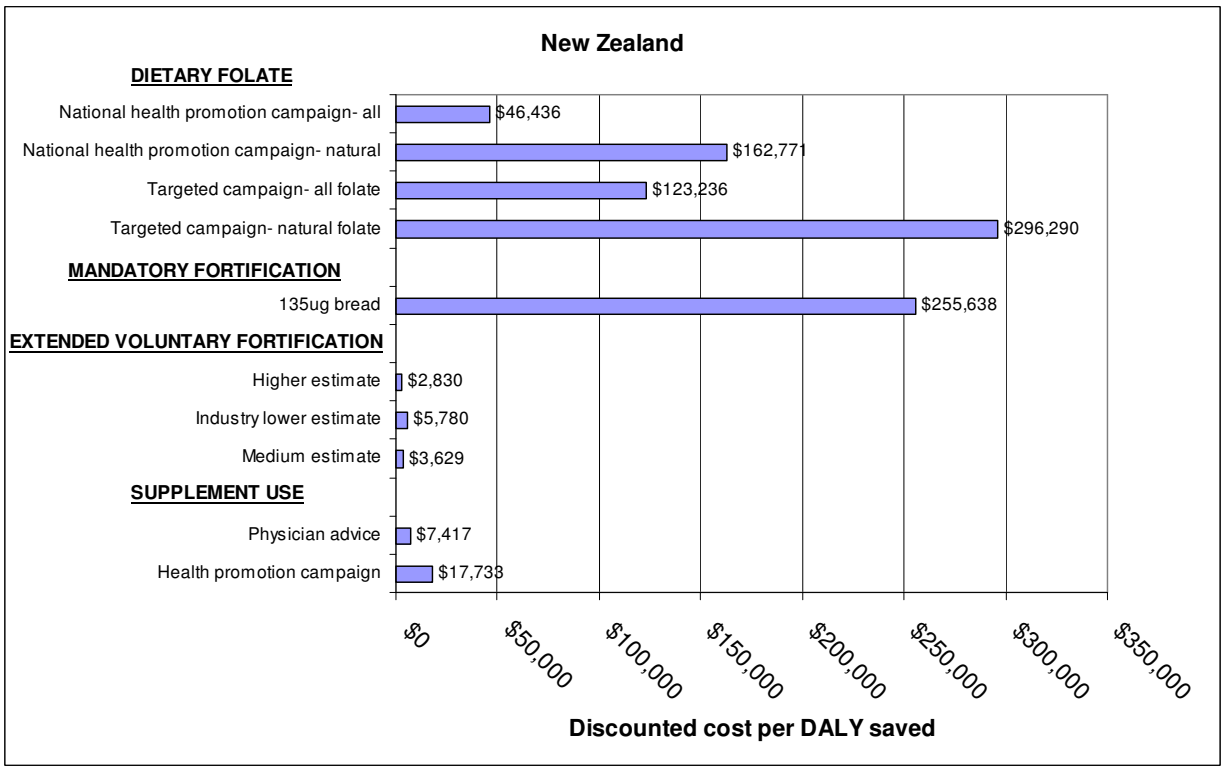


Figure 6.7 Australia: Cost (discounted) per DALY(discounted) saved – cost offsets

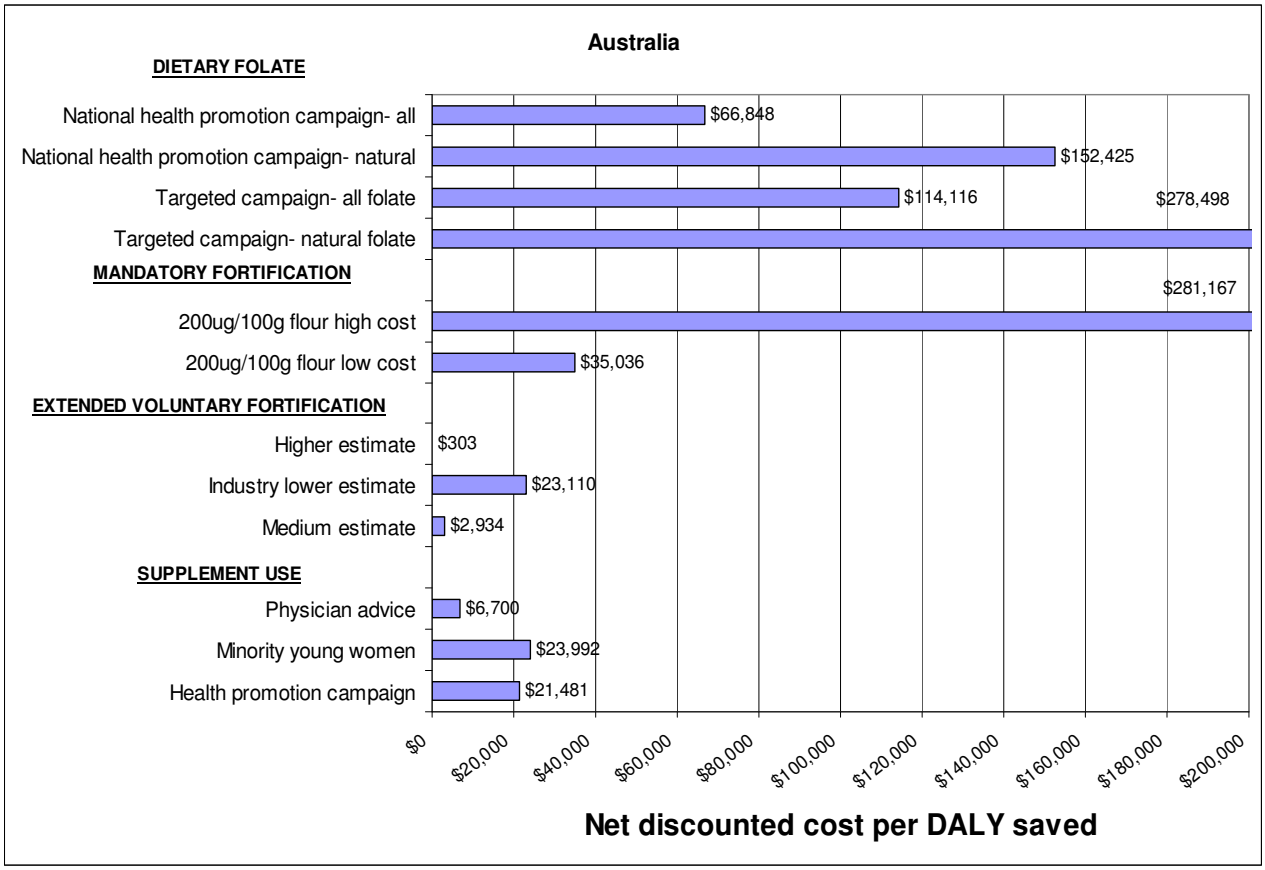
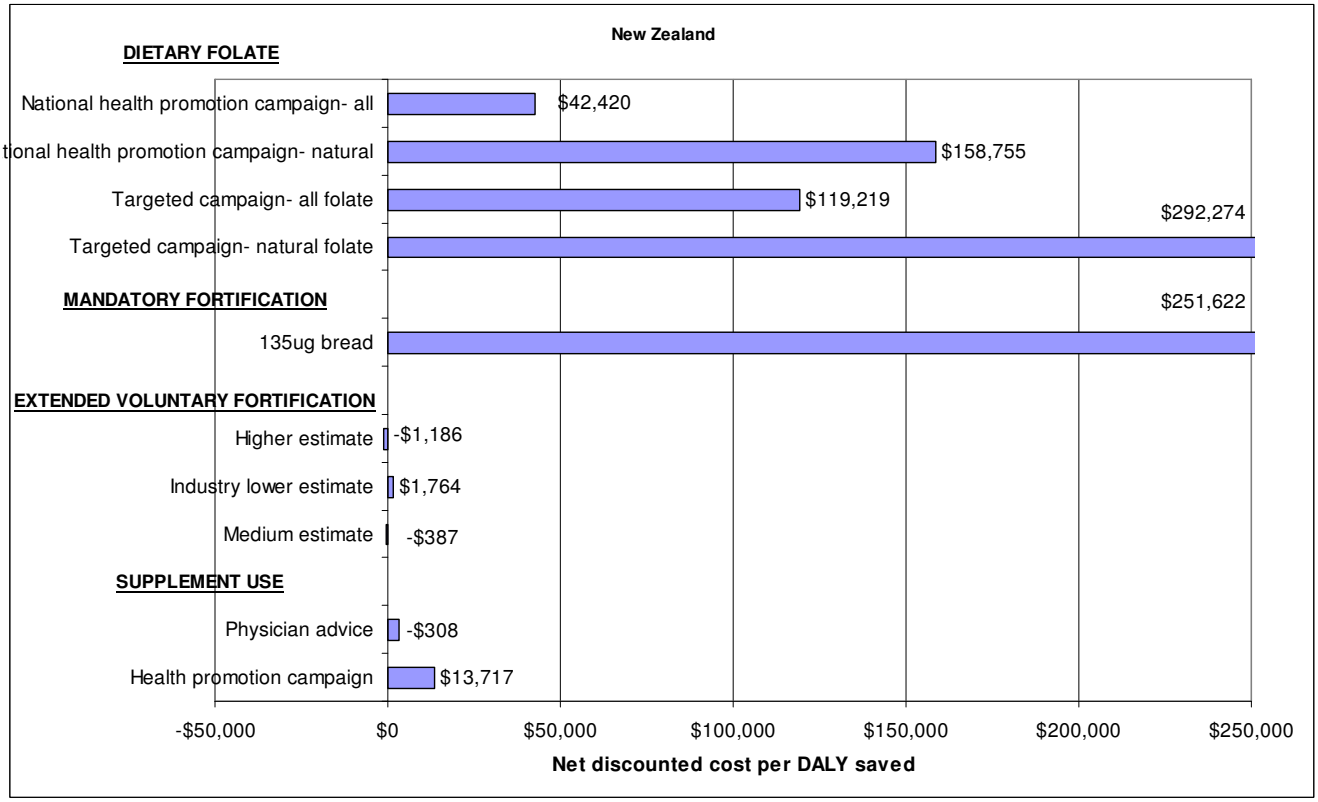


Figure 6.8 New Zealand: Cost (discounted) per DALY(discounted) saved – cost offsets



6.5 Summary of results

Table 6.1 Summary table of base case results- Australia

Intervention	NTDs prevented (per year)	Discounted cost $ per NTD prevented	Cost per DALY $ (Net cost offsets)	Cost per DALY $ Net cost offsets Modelled to life expectancy*
SUPPLEMENT USE				
Health promotion campaign	27.1	55,000	21,500	6,400
Minority young women	5	60,500	24,000	7,200
Physician advice	13.1	23,100	6,700	2,000
EXTENDED VOLUNTARY PERMISSIONS				
Medium estimate	7.07	14,900	2,900	900
Industry lower estimate	1.8	58,600	23,100	6,900
Higher estimate	11.2	9,400	300	100
MANDATORY FORTIFICATION				
200ug/100g flour low cost	23.81	84,400	35,000	10,500
200ug/100g flour high cost	23.81	617,400	281,200	83,900
DIETARY FOLATE				
Targeted campaign- natural folate	2.17	619,700	278,500	83,100
Targeted campaign- all folate	5.26	255,700	114,100	34,000
National health promotion campaign- natural	4.41	338,600	152,400	45,500
National health promotion campaign- all	9.74	153,300	66,800	19,900

*average life expectancy 80 years: average of males 78 year and females 82 years

Table 6.2 Summary table of base case results- New Zealand

Intervention	NTDs prevented (per year)	Discounted cost $ per NTD prevented	Cost per DALY $ (Net cost offsets)	Cost per DALY $ (Net cost offsets) - Modelled to life expectancy*
SUPPLEMENT USE				
Health promotion campaign	8.72	38,400	13,700	4,100
Physician advice	4.21	16,100	3,400	1,000
EXTENDED VOLUNTARY PERMISSIONS				
Medium estimate	3.01	7,900	Cost saving	Cost saving
Industry lower estimate	1.89	12,500	$1,800	$500
Higher estimate	3.86	6,100	Cost saving	Cost saving
MANDATORY FORTIFICATION				
135ug bread	6.94	553,600	251,600	75,000
DIETARY FOLATE				
Targeted campaign- natural folate	0.47	641,600	292,300	87,200
Targeted campaign- all folate	1.13	266,900	119,200	35,600
National health promotion campaign- natural	0.95	352,500	158,800	47,400
National health promotion campaign- all	3.33	100,600	42,400	12,700

*average life expectancy 80 years: average of males 78 year and females 82 year

6.6 Upper Limit Exceedences

FSANZ has prepared estimates of percent by age category at or above the NHMRC age and gender specified upper limits for folic acid for mandatory and voluntary fortification proposals. These have been used to develop the data in Figures 6.9 and 6.10. They show large numbers of young children in Australia, with for instance nearly 100,000 two to eight year olds expected to exceed the specified upper limit. What this means is not clear.

Figure 6.9A Numbers and % exceeding Upper Limits, by age group, Australia (Source FSANZ)

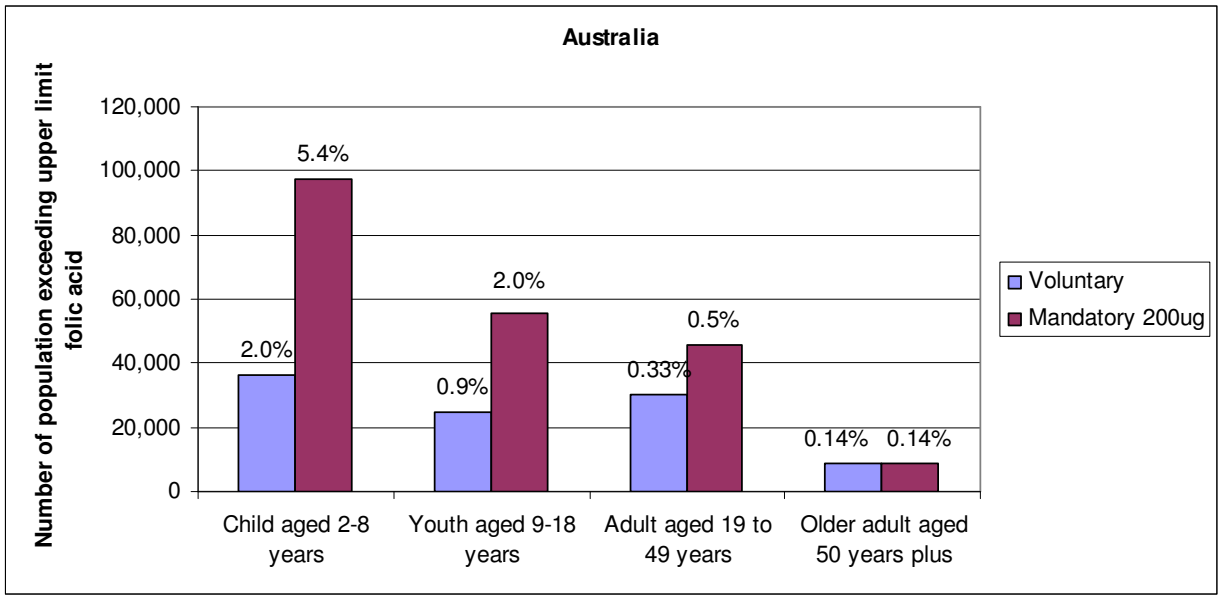
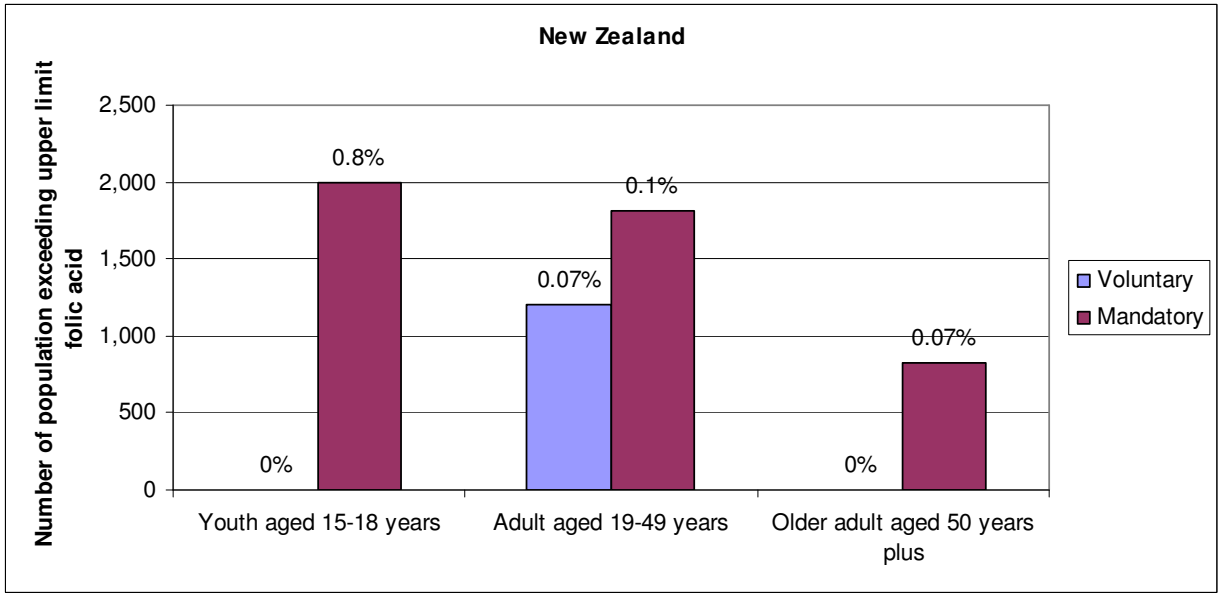


Figure 6.9B Numbers and % exceeding Upper Limits, by age group, Australia (Source FSANZ)



6.7 Sensitivity analysis

For the purpose of this report one way sensitivity analyses have been performed for key parameters for each of the interventions. This involves systematically varying each individual parameter and recording the result on the cost effectiveness estimate. Results can be used as a means of identifying which parameters the economic modelling is most sensitive. A logical progression is then to assess how likely it is that the sensitive parameter would vary, or how certain we are in that piece of evidence or assumption.

Ranges and base cases are illustrated as a summary in Figures 6.10 for Australia and 6.11 for New Zealand. These Figures illustrate the highest and lowest estimate (arrows on either end) of cost effectiveness obtained from all of the one way variations. The base case is presented (middle rectangle) as a reference point but does not indicate a mean value. These figures allow for assessment of which interventions had the greatest range of results but do not indicate which parameters are the upper and lower ones nor how these parameters were varies.

More detailed full sensitivity results are presented in Table 6.2. This table indicates in the left hand column the parameter varied in each one way sensitivity analysis, column two provides the original parameter value used in the economic modelling (New Zealand values in brackets) and column three indicates the parameter value used in the sensitivity analysis. Columns 4 and 5 provide the cost effectiveness result for Australia and New Zealand for each particular sensitivity analysis or one way variation. The final right hand column provides a brief justification for the value chosen in sensitivity analysis or where the parameter estimate was obtained. For each intervention summarised in the table the base case is also presented as the number in italics so that readers can assess the relative variation obtained through each one way sensitivity analysis.

The results for all interventions are highly sensitive to the selected assumptions, especially cost of the intervention and the 95% CIs for translation of folic acid into NTDs.

The tables and figures are self explanatory, and highlight the high level of uncertainty in relation to all the modelled interventions.

Figure 6.10 Summary of sensitivity analyses upper and lower range with base case Australia

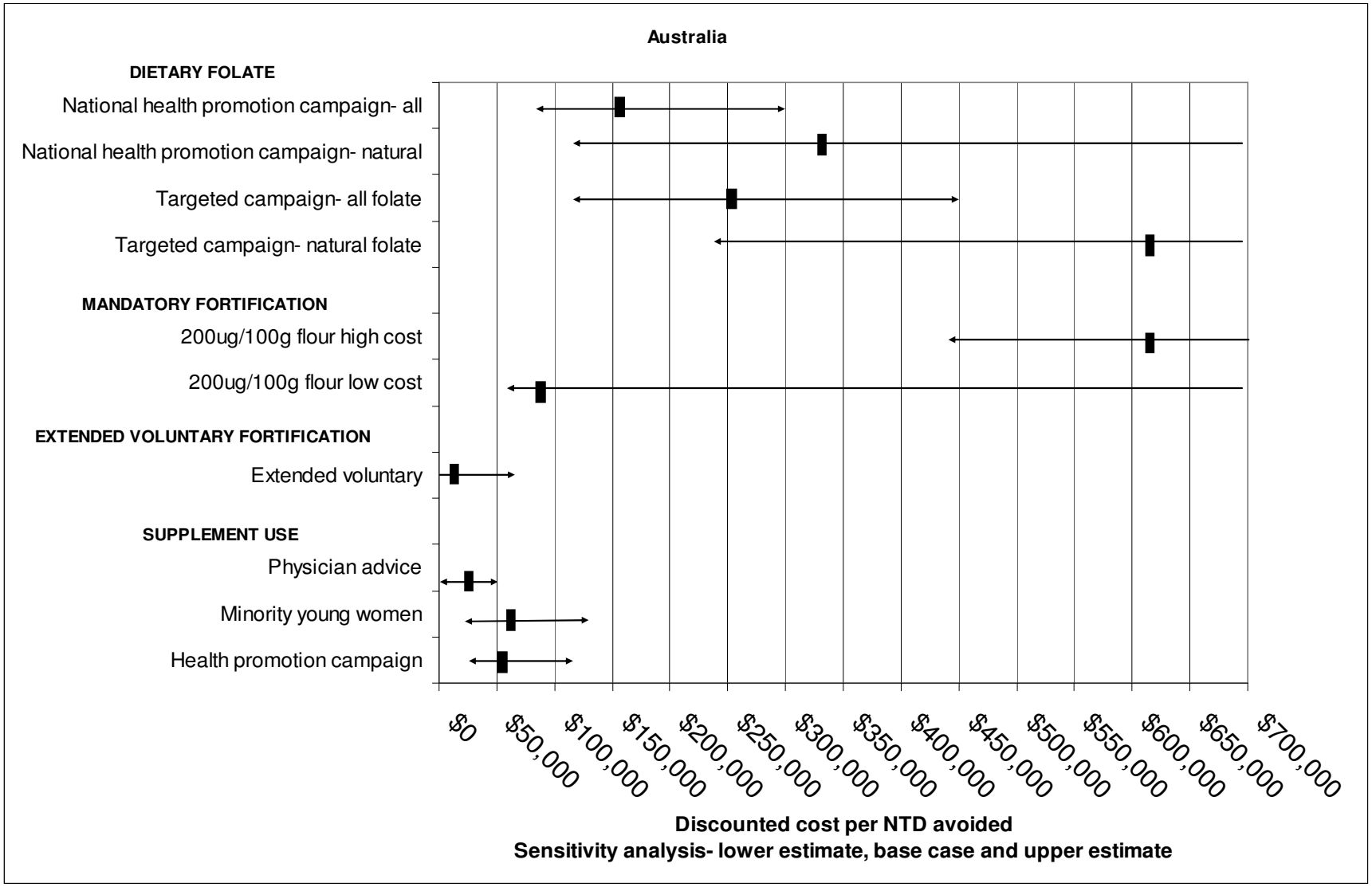


Figure 6.11 Summary of sensitivity analyses upper and lower range with base case- New Zealand

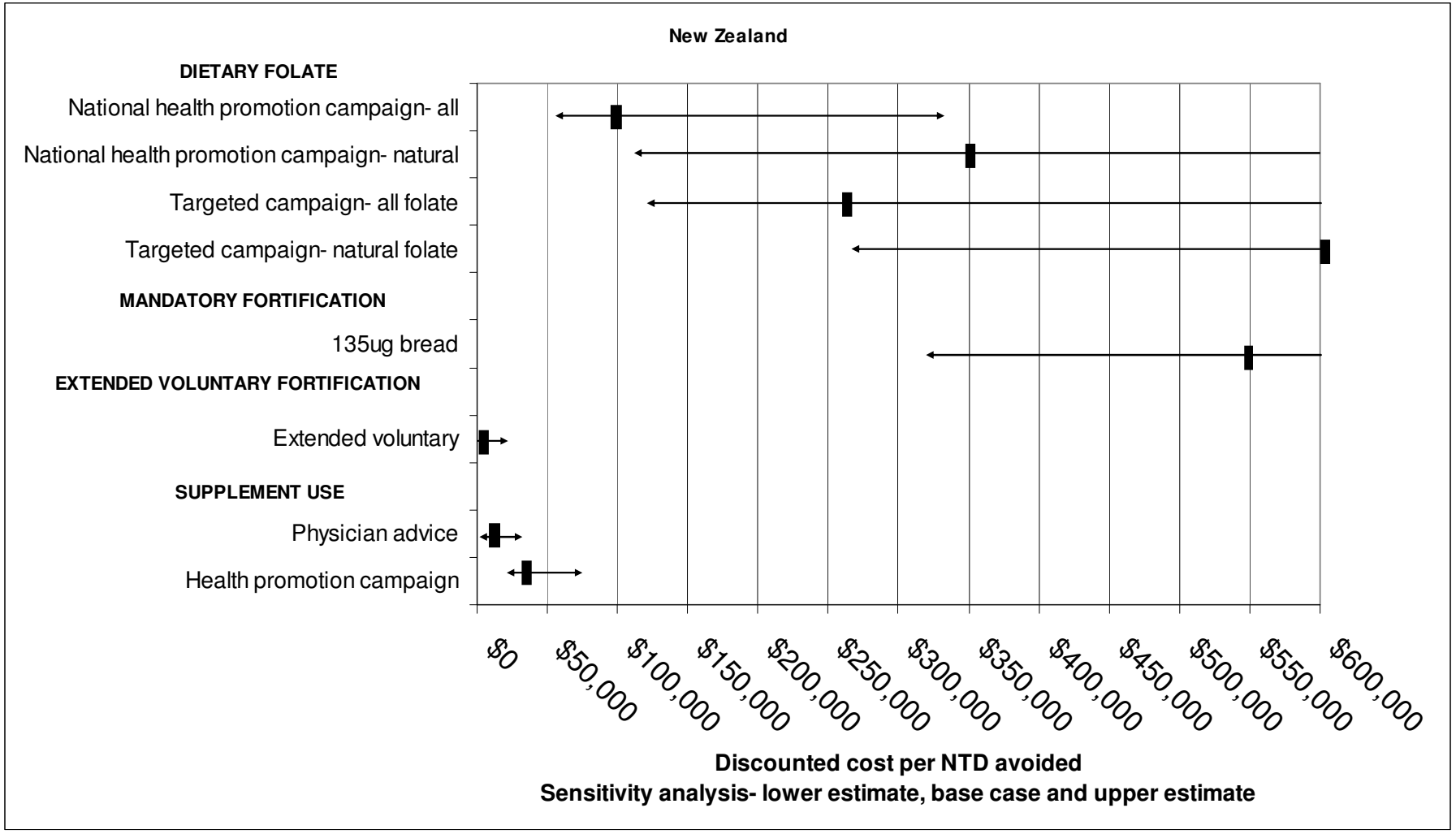


Table 6.2

Table 6.2 Summary of all sensitivity analyses- resulting cost per discounted NTD avoided

			AUS	NZ	
	Base case AU (NZ)	**Sensitivity AU (NZ)**	**dis $/NTD avoided**	**dis $/NTD avoided**	**Source of estimate**
Supplements					
Intervention A- health promotion campaign					
BASE CASE			*$55,085*	*$38,399*	
Effectiveness (% increase supplements)	16.6	10.1%	$86,621	$58,951	WA figure adjusted by taking out effect for tho planned pregnancies (proxy for more motivate
Effectiveness alternative (% increase in supplements)	16.6	36%	$28,729	$21,166	Increase in supplement use from the SA stud al, 2001)
Bioavailability	100	85%	$63,710	$44,058	Figure if taken with food
Dose of supplement	500 (800)	400	$67,298	$70,344	Recommended intake
High estimate costs- upfront	5m (1.1m)	7m (1.6m)	$64,184	$44,742	Estimate
Low estimate costs- upfront	5m (1.1m)	2.5m (560,550)	$43,711	$30,470	Estimate
High estimate costs- ongoing	1m (224,200)	2m (448,440)	$87,422	$60,941	Estimate
Low estimate costs- ongoing	1m (224,200)	500000 (112,110)	$38,916	$27,128	Estimate
NTDS- lower 95% confidence interval	27.11 (8.72)	14 (5)	$106,668	$66,968	Roughly based on CIs from Bower and DeKle
NTDS- higher 95% confidence interval	27.11 (8.72)	49 (13)	$30,477	$25,757	Roughly based on CIs from Bower and DeKle
Intervention B- indigenous targeted					
BASE CASE			*$60,523*		
Effectiveness (% increase supplements) upper estimate	18%	58%	$30,261		Number reporting daily use
Effectiveness alternative	18%	19%	$58,760		Alternative from Georgia study
Reduced scope of intervention- 50% of live births potentially affected	9,049	4,524.5	$121,045		Intervention only potentially affects half of live
Bioavailability	100%	85%	$75,653		Figure if taken with food
Dose of supplement	500 (800)	400µg	$75,653		Recommended intake
Cost of intervention- +50% (upfront/ongoing)	562,148/266,099	843,222/399,149	$90,784		plus 50%
Cost of intervention- -50% (upfront/ongoing)	562,148/266,100	281,074/133,050	$30,261		minus 50%
NTDS- lower 95% confidence interval	5	3	$100,871		Roughly based on CIs from Bower and DeKle
NTDS- higher 95% confidence interval	5	8	$37,827		Roughly based on CIs from Bower and DeKle

			AUS	NZ	
	Base case AU (NZ)	**Sensitivity AU (NZ)**	**dis $/NTD avoided**	**dis $/NTD avoided**	**Source of estimate**
Intervention C- physician targeted					
BASE CASE			*$23,097*	*$16,079*	
Effectiveness (% increase in supplements)	15.90%	12.80%	$14,048*	$9,661*	Control group effect
Increased scope of intervention- 100% of live births potentially affected	255,095 (54,733)	127,548 (27,367)	$11,544	$8,030	Intervention potentially affects all live births
Reduced scope of intervention- 25% of live births potentially affected	255,095 (54,733)	63,774	$46,176	$32,120	Intervention only potentially affects 1/4 of live
Bioavailability	100%	85%	$13,368*	$9,213*	Figure if taken with food
Dose of supplement	500 (800)	400	$14,113*	$14,745*	Recommended intake
NTDS- lower 95% confidence interval	26.09 (8.41)	16 (5)	$18,824*	$13,506*	Roughly based on CIs from Bower and DeKle
NTDS- higher 95% confidence interval	26.09 (8.41)	37 (12)	$8,140*	$5,628*	Roughly based on CIs from Bower and DeKle
Cost of intervention also includes GP obstetricians	560,715/264,666	905,976/609,927	$24,777*	$17,235 *	Also includes number of GP obstetricians in A
Cost of intervention- +50% (upfront/ongoing)	560,715/264,666	841,073/396,999	$17,316*	$12,045 *	plus 50%
Cost of intervention- -50% (upfront/ongoing)	560,715/264,666	280,358/132,333	$5,772*	$4,015 *	minus 50%
*analyses based on 100% of live births affected					
Voluntary					
BASE CASE			*$14,922*	*$7,859*	
Level of folic acid- upper estimate[a]	136 (119)	153 (136)	$9,420	$6,128	Provided by FSANZ
Level of folic acid- lower (industry) estimate[b]	136 (119)	115 (97)	$58,612	$12,516	Provided by FSANZ
NTDS- higher 95% confidence interval	7.07 (3.01)	12 (6)	$8,792	$3,943	Roughly based on CIs from Bower and DeKle
NTDS- lower 95% confidence interval	7.07 (3.01)	4 (1)	$26,375	$23,656	Roughly based on CIs from Bower and DeKle
Cost- zero cost	0	0	Dominates	Dominates	Assumes industry will not uptake without expe profits
Costs- lower[c]	500k/50k	100k/10k	$2,984	$1,572	Estimate
Costs- higher[d]	500k/50k	1m/100k	$29,845	$15,718	Estimate
Upper estimate folic acid & high estimate costs	a & d	a & d	$18,840	$12,257	FSANZ folic acid, our estimate costs
Lower (industry) estimate folic acid & low estimate costs	b & c	b & c	$11,722	$2,503	FSANZ folic acid, our estimate costs
Mandatory					
200ug flour- high cost					
BASE CASE			*$617,405*	*NA*	
Cost of loss of consumer choice	0	16,433,424	$1,307,595		$ per person not in target group

			AUS	NZ	
	Base case AU (NZ)	**Sensitivity AU (NZ)**	**dis $/NTD avoided**	**dis $/NTD avoided**	**Source of estimate**
Including cost of monitoring/evaluation	0	435,000/205,000	$627,206		Provided by FSANZ
NTDS- higher 95% confidence interval	23.81	33	$445,467		Roughly based on CIs from Bower and DeKle
NTDS- lower 95% confidence interval	23.81	14	$1,050,029		Roughly based on CIs from Bower and DeKle
200ug flour- low cost					
BASE CASE			*$84,437*	*NA*	
Cost of loss of consumer choice	0	16,433,424	$774,627		$ per person not in target group
Including cost of monitoring/evaluation	0	435,000/205,000	$94,238		Provided by FSANZ
NTDS- higher 95% confidence interval	23.81	33	$60,922		Roughly based on CIs from Bower and DeKle
NTDS- lower 95% confidence interval	23.81	14	$143,603		Roughly based on CIs from Bower and DeKle
135ug bread					
BASE CASE			*NA*	*$553,555*	
Cost of loss of consumer choice	0	16,433,424		$1,029,964	$ per person not in target group
Including cost of monitoring/evaluation	0	67,200/50,400		$561,116	Provided by FSANZ
NTDS- higher 95% confidence interval	6.94	12		$320,139	Roughly based on CIs from Bower and DeKle
NTDS- lower 95% confidence interval	6.94	4		$960,418	Roughly based on CIs from Bower and DeKle
Natural folate					
Scenario 1- health promotion natural only					
BASE CASE			*$338,628*	*$352,462*	
Bio availability	60%	80%	$250,562	$261,593	Results from Winkels et al, 2007
High estimate costs- upfront	5m (1.1m)	7m (1.6m)	$394,564	$410,683	Estimate
Low estimate costs- upfront	5m (1.1m)	2.5m (560,550)	$268,709	$279,686	Estimate
High estimate costs- ongoing	1m (224,200)	2m (448,440)	$537,418	$559,373	Estimate
Low estimate costs- ongoing	1m (224,200)	500000 (112,110)	$239,233	$249,007	Estimate
DFE- mid estimate (a)	14.7	32.4	$156,536	$163,336	
DFE higher estimate (b)	14.7	44.1	$116,305	$121,319	
NTDS- lower 95% confidence interval	4.41 (0.95)	2 (0.2)	$746,675	$1,674,196	Roughly based on CIs from Bower and DeKle
NTDS- higher 95% confidence interval	4.41 (0.95)	7 (3)	$213,336	$111,613	Roughly based on CIs from Bower and DeKle
Scenario 1- targeted natural only					
BASE CASE			*$619,749*	*$641,582*	

			AUS	NZ	
	Base case AU (NZ)	**Sensitivity AU (NZ)**	**dis $/NTD avoided**	**dis $/NTD avoided**	**Source of estimate**
Bio availability	60%	80%	$458,995	$478,640	Results from Winkels et al, 2007
Cost of intervention- +50%	1.6m/1.3m	2.4m/2.0m	$929,623	$962,373	Estimate
Cost of intervention- -50%	1.6m/1.3m	800,514/654,407	$309,874	$320,791	Estimate
Increase in plasma folate rather than natural folate	29.4ug natural	0.7 plasma	$255,191	$266,853	Alternative from same study- different outcom measure
NTDS- lower 95% confidence interval	2.17 (0.47)	1 (0.1)	$1,344,855	$3,015,434	Roughly based on CIs from Bower and DeKle
NTDS- higher 95% confidence interval	2.17 (0.47)	5 (1.0)	$268,971	$301,543	Roughly based on CIs from Bower and DeKle
<u>Scenario 2- health promotion all dietary</u>					
BASE CASE			*$153,321*	*$100,552*	
Bio availability	60%	80%	$136,629	$93,530	Results from Winkels et al, 2007
High estimate costs- upfront	5m (1.1m)	7m (1.6m)	$178,647	$117,162	Estimate
Low estimate costs- upfront	5m (1.1m)	2.5m (560,550)	$121,664	$79,790	Estimate
High estimate costs- ongoing	1m (224,200)	2m (448,440)	$243,328	$159,581	Estimate
Low estimate costs- ongoing	1m (224,200)	500000 (112,110)	$108,318	$71,038	Estimate
DFE- mid estimate (a)	33.1 (53.8)	50.7 (71.5)	$101,796	$76,975	
DFE higher estimate (b)	33.1 (53.8)	62.5 (83.2)	$83,521	$66,834	
NTDS- lower 95% confidence interval	9.74 (3.33)	5 (1)	$298,670	$334,839	Roughly based on CIs from Bower and DeKle
NTDS- higher 95% confidence interval	9.74 (3.33)	17 (6)	$87,844	$55,807	Roughly based on CIs from Bower and DeKle
<u>Scenario 2- targeted all dietary</u>					
BASE CASE			*$255,676*	*$266,853*	
Bio availability	60%	80%	$192,122	$201,029	Results from Winkels et al, 2007
Cost of intervention- +50%	1.6m/1.3m	2.4m/2.0m	$383,514	$400,279	Estimate
Cost of intervention- -50%	1.6m/1.3m	800,514/654,407	$127,838	$133,426	Estimate
Increase in plasma folate rather than natural (a)	74.4ug natural	0.93 plasma	$196,616	$205,132	Alternative from same study- different outcom measure
Increase in plasma folate rather than natural (b)	74.4ug natural	1.7 plasma	$115,537	$120,617	Alternative from same study- different outcom measure
NTDS- lower 95% confidence interval	5.26 (1.13)	3 (0.5)	$448,285	$603,087	Roughly based on CIs from Bower and DeKle
NTDS- higher 95% confidence interval	5.26 (1.13)	8 (2.0)	$168,107	$150,772	Roughly based on CIs from Bower and DeKle

* adjusted by taking out effect for those with planned pregnancies (proxy for more motivated)

CHAPTER 7 OTHER DECISION MAKING CRITERIA

7.1 Equity

Each proposal will impact on segments of the population differentially. But it has not been possible to undertake a full impact assessment by population sub-group. Only one of the proposals, the promotion of supplement use in minority young women that specifically targets disadvantaged groups and those at higher risks of NTDs. The impact of mandatory and voluntary fortification depends on the dietary behaviour of the population, about which there is little current evidence. Despite bread being a staple, consumption varies widely between individuals, with some women consuming little bread or similar products, with consumption particularly low in certain ethnic groups. It is not clear whether mandatory fortification is pro disadvantage. In relation to voluntary fortification, industry has indicated that if information were provided concerning food stuffs consumed by those at high risk of NTDs/with low folate levels, these foods could be fortified and selectively promoted.

In short we are not able to differentiate between proposals on equity grounds, except for the promotion of supplement use amongst minority young women. We note that the physician-based intervention could also be targeted by a focus on disadvantaged regions. If equity is a major issue, then a targeted approach is preferable.

7.2 Feasibility/sustainability

All the proposals reviewed are feasible, except arguably the optimistic voluntary scenario, which is not considered by industry to be realistic. The primary issue is funding and organisation. In relation to public health interventions it is always necessary to identify a funding source. Most proposals assume an up-front cost as well as an on-going financial commitment. A long term financial commitment by relevant agencies is clearly desirable.

7.3 Certainty

The proposals vary in terms of quality of evidence, although all suffer from major evidence gaps and evidence of poor to mediocre quality. None of the interventions could be modelled using the highest quality evidence.

In terms of effectiveness the mandatory and voluntary scenarios are probably most certain at least in terms of impact on folate consumption, although how this translates into reduced NTDs is subject to wide confidence intervals. The cost of these interventions is also highly uncertain.

In relation to both promotion of supplement use and a campaign to promote a folate rich diet, the quality of evidence is poor and based on a small number of poorly designed trials, which are not necessarily readily transferable to the current Australian setting.

A subjective view of performance in relation to these attributes is provided below in Table 7.1.

Table 7.1 Performance of Options –Other criteria

	Equity	Feasibility/ sustainability	Certainty/ confidence in estimates
Supplement use			
o health promotion campaign	#	#	#
o target minority young women	# # #	#	#
o physician advice	# #	#	#
Extended voluntary	#	# #	# #
Mandatory	#	# #	# #
Dietary folate			
o targeted campaign- natural folate	#	#	#
o targeted campaign natural + fortified	##	#	#
o National health promotion campaign- natural	#	#	#
o National health promotion campaign- natural + fortified	#	#	#

Note, # the more stars the better.

CHAPTER 8 DISCUSSION

8.1 Key Issues

This economic evaluation of interventions for the reduction of NTDs should be viewed as preliminary. There are many reasons for this. Notably there are important gaps in the evidence base. This reflects a combination of poor quality data – typified by poor trial design and simple gaps in the evidence base where relevant studies have just has not been conducted. One outcome of this type of study is to highlight data gaps and propose data collections most urgently needed to inform policy.

Another issue is the nature of the relationship between intervention elements. These need to be understood in order for the 'ideal' suite of policy instruments to be devised.

As raised in Chapter 4, mandatory fortification with folic acid is partly designed to combat the nutrition depletion of our food supply. This is a matter of broad concern with wide-ranging impacts. It is not clear who has the mandate to address this broader issue. But before moving to a single nutrient solution, alternative means to reintroduce nutritional quality into staple foods should be explored. As discussed in Chapter 4, aleuron flour looks to be a far more effective means of reintroducing nutritional quality back into wheat flour back – incorporating not just very high levels of natural folate but other important nutrients which are deficient in much of the population, such as calcium.

8.2 Data Quality/Data Gaps/Monitoring

The quality of the Clinical trial evidence available to support this economic analysis is overall exceedingly poor. This applies to all intervention options. There is a dearth of randomised control trials of supplement use or of well designed health promotion trials to promote healthy eating. In relation to mandatory fortification, drawing any lessons from overseas experience is confounded by the differences in base-line characteristics, particularly in terms of already fortified foods, eating habits of the population, their current folate status and pattern of taking folate supplements.

While monitoring of the introduction of mandatory fortification, if it proceeds, is identified by FSANZ as a priority, it is not clear whether a robust design can be devised, and even less certainty about implementation. It will be critical to collect high quality baseline data on consumer dietary habits, folate levels and rate of NTDs and be able to monitor for possible confounders. The relatively small impact expected at ~8% NTDs together with wide confidence limits around this means the capacity to observe whether the policy is or is not working is highly dubious.

8.3 Combined impact of interventions

It is widely accepted that promotion of supplement use by women planning (or capable of) a pregnancy must remain a core component of a strategy to minimise NTDs. The literature also suggests some success in targeting vulnerable and high risk groups with clinical campaigns – which translates into what seems to be potentially effective and cost-effective options. Certainly, if equity is a concern support for targeted promotion of supplement use seems appropriate.

There is les agreement about the promotion of folate rich foods – in natural folate and fortified folate, but our analysis suggests this is likely to be an efficient component of an NTD reduction strategy.

In relation to mandatory fortification, the likely impact on other strategy components, both existing and potential is quite unpredictable. Both positive and negative synergies are possible,

and exactly where the net effect will lie is hard to gauge. For instance if all bread is fortified consumers may loose interest in obtaining folate from other foods or even chose to avoid them, or on the other hand may develop a greater interest in fortified foods. Similarly, in relation to folate supplements, women may think they are getting enough folate from bread and not take supplements or may become more aware of the value of folate ad increase use. While, a public health promotion campaign could be simultaneously funded to reduce the risk of an adverse outcome, this is by no means certain and has not been included in the base-case costing for mandatory.

Continuing supplement use is clearly critical. Even after mandatory fortification of cereals and grains with folic acid in the United States, taking vitamin supplements regularly has a large effect on serum folate status. Women who did not consume folic acid supplements were 8 times more likely to have serum folate values in the lowest quartile than women who were consistent vitamin users. (Table 8.1)

Table 8.1 Serum folate status compared with vitamin use

Vitamin Category	Lowest 25th percentile ≤ 16.2 ng/ml N	%	Crude odds ratio
Consistent users	295	9	1.00
Nonusers	1558	45	8.4
Starters	405	17	2.1
Former users	99	31	4.51

8.4 Scope of study/intervention options

The study is limited in scope in two ways. First we are not confident that all plausible intervention options have been included in the analysis. As raised in chapter 4, at the very least, a full analysis of aleuron flour as a possible alternative approach to fortification would seem a potentially effective alternative. Whether it is cost-effective or even feasible at the population health level is yet to be established.

Second outcomes have been limited to NTDs and the associated DALY consequences, and the number of persons exceeding the NHMRC specified upper limit. While there is a small literature on the consequences of high folic acid levels, especially in the face of vitamin B deficiency, this is not of a quality that would allow the translation of upper limit excedences into adverse events or associated costs.

Other possible benefits from the interventions have also been ignored. The most notable will be wider health benefits from the promotion of folate rich foods especially foods rich in natural folate, largely green vegetables, nuts and grains and fruits. Mortality and morbidity benefits are associated with foods consistent with a diet high in natural folate. The dietary interventions will thus confer additional benefits which have not been measured. Similarly increased population folate levels may well generate benefits beyond those associated with the reduction in NTDs. This benefit should however be similar across all interventions, and unlikely to affect the comparative performance.

8.5 Conclusion

There are a number of strategies which taken in combination can increase folate consumption and reduce slightly the incidence of NTDs.

It is not clear however, that we yet have the evidence to determine the optimal components of a national strategy. We are not yet able to conclude that mandatory fortification of bread making flour with folic acid is part of that optimal strategy. While it appears slightly more effective than some strategies, it is still estimated to reduce NTDs by only 8% and at relatively high cost and lower cost-effectiveness than other options.

There is also the issue of whether folate and NTDS should be considered in isolation or as part of a broader approach to improving nutrition quality. The broader approach might identify other cost-effective option. Scientific data on aleuron flour suggests this as a potentially effective option to reduce NTDs and address other nutrient deficits in the population. A feasibility study of options for promoting enriched flours, as a means to reintroducing nutrient quality into staple foods would also be valuable.

However, what is clear is that, in terms of public heath policy, investing in the more cost-effective strategies to reduce NTDs is highly appropriate given the low cost per benefit derived (as captured in the DALY. It also appears clear that investing in the promotion of folate supplement use in women who may become pregnant will be part of any optimal strategy to reduce NTDs and to promote an equitable outcome, this should include a sub- component targeting high risk women.

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Appendix 1

Potential Alternative Intervention to increase population-wide folate - Wheat aleurone flour[7]

Wheat aleurone flour (ALF) is a food product/ingredient made from the aleurone layer of cells in the wheat grain (Figure A1). ALF contains significant amounts of naturally occurring nutrients including; i) minerals such as magnesium, calcium, iron and zinc, ii) dietary fibre, iii) protein, iv) antioxidant phenolic compounds and v) B vitamins including folate. (Tables A1-3) [1-3]. The aleurone cells, together with the germ, contain the wheat grain's essential nutrients required for the growth and development of the embryo [4, 5]. Because the bran fraction of wheat contains the aleurone layer of cells, the phytochemicals, vitamins, minerals, fibre and protein in aleurone cells are lost when wheat grain is refined to make white flour. Consequently, in recent years there has been interest in devising milling technologies to purify the aleurone fraction of the wheat grain and make it available for human consumption. A unique and commercially viable milling process was developed by Goodman Fielder Pty. Ltd., (Australia) that enabled the isolation of the aleurone cell layer and at the same time split the cell walls to release the contents of these cells [6,7]. Another method of extraction of aleurone cells from wheat bran has been developed by Buhler AG and patented (patent WO 02/15711). A schematic representation of the isolation of aleurone is shown in figure 2. The sheared aleurone cells, together with a small amount of wheat germ has been formulated into the novel aleurone flour. ALF has been available commercially internationally since the mid 1990s and is sold widely as a major ingredient of bread and other cereal products such as pasta.

A feature of the composition of ALF is the high level of folate, which is present at a concentration between 340-515µg/100g wet weight [1, 2]. This natural level of folate is higher than that observed in wheat bran, fruits and vegetables (usually between 20 ug/100g and 200 ug/100g wet) [13, 14] and is comparable to folate/folic acid levels in fortified flour and cereal that provide 50% RDI per serve (assuming an RDI of 400µg and a serving size of 40g wet weight) [15]. Two studies by CSIRO Human Nutrition show that folate from aleurone flour has a bioavailablity and bioefficacy similar to that of a 500ug folic acid tablet [1,2]. For a description of these studies see Annex to this Chapter.

The scope of our research program did not allow for the conduct of a cost-effectiveness analysis of aleuron flour as an alternative approach to mandatory fortification to increase folate levels in the population. The scientific evidence concerning the concentration and bio-availability of folate from aleuron flour strongly suggests that fortification with aleuron flour would represent a most effective means for increasing folate levels of the population. It also is not associated with constraints associated with Upper Limit exceedences as it uses natural folate, not folic acid. Also given its nutrient qualities, it would address a number of common nutrient deficits, generating additional health benefits. But, while technical feasibility is established at the product level, it has not been explored at the population level. Commissioning a study to explore the technical feasibility, cost and cost-effectiveness of the mandatory incorporation of alueron flour at the population level would seem highly desirable.

Bioavailability and Bioefficacy of Folate from Aleurone flour – Human Studies

CSIRO Human Nutrition has completed two studies on the bioavailablity and bioefficacy of folate from aleurone flour. These are summarised here, [1, 2].

[7] The material on aleuron flour has been prepared by Dr Michael Fenech, Senior Scientist, CSIRO Division of Human Nutrition.

The aim of the first CSIRO study was to determine the relative bioavailability of natural folate from aleurone flour when ingested as a cereal. Using a series of randomized short-term intervention trials with a cross-over involving 8 men and 8 women aged between 29 and 50 years, the increment of plasma folate following ingestion of (a)100 g wheat bran cereal (low folate control), (b)100 g aleurone cereal and (c)a tablet containing 500 ug folic acid taken together with 100g wheat bran cereal (high folate control). Folate absorption was measured by estimating the area under the plasma folate concentration versus time curve. The extent of increase in plasma folate over the 7 hour period following ingestion of aleurone cereal was more than four-fold greater than that observed following the wheat bran cereal ($P<0.0001$) and not different from that observed following the 500 ug folic acid tablet taken with wheat bran cereal (Figure A3). These results were also significant when data for males and females were analysed separately ($P<0.001$). This study shows that cereal made from wheat aleurone flour is an excellent source of bioavailable natural folate.

The objective of the second CSIRO study was to establish whether intake of ALF can significantly improve red cell folate status and reduce plasma homocyst(e)ine. A randomized, controlled intervention was performed of 16 weeks duration in healthy individuals (mean age 46-52y). Participants were assigned to one of three group; a)ALF, 175g aleurone flour bread and placebo tablet each day; b) PCS, 175g pericarp seed coat flour bread and placebo tablet each day (low folate control); c) FA, 175g pericarp seed coat flour bread and 640µg folic acid tablet each day (high folate control). The daily folate intake contributed by the bread and tablet was 233µg in the PCS group, 615µg in the ALF group and 819µg in the FA group. The number of participants completing all phases of the PCS, ALF and FA interventions were 25, 25 and 18 respectively. Plasma and RBC folate increased significantly ($P<0.0001$) and plasma homocyst(e)ine decreased significantly ($P<0.0001$) in the ALF and FA groups only (Fig A4). Plasma folate and RBC folate in the ALF group (mean, 95% CI) increased from base-line values of 12.9 (9.9, 15.7) nmol/L and 509 (434,584) nmol/L to 27.1 (22.5, 31.7) nmol/L and 768 (676, 860) nmol/L, respectively. Plasma homocyst(e)ine in the ALF group decreased from 9.1 (8.2, 10.0) µmol/L at base-line to 6.8 (6.2, 7.5) µmol/L after 16 weeks. This study demonstrates that dietary intake of ALF can increase red cell folate and decrease plasma homocyst(e)ine to an extent similar to that produced by a folic acid tablet.

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Table A1 Elemental analysis (mg per 100 g wet weight)[1,2]

	Ca	Cr	Cu	Fe	K	Mg	Mn	Na	P	Se	Zn
Aleurone Flour	77.1	0.024	1.13	20.6	832	341	7.47	3.36	901	0.028	6.35
White Flour	20.5	0.020	0.16	1.15	141	33.8	1.11	1.29	124	0.009	0.54
Australian RDI (mg/d) children-adults	*700 - 1200*	*0.033*	*0.5 - 0.6*	*6 - 18*	*980 - 5460*	*80 - 320*	*<2*	*320 - 2300*	*500 - 1200*	*0.025 - 0.085*	*4.5 - 18*

1. Values are means ± SD of 3 determinations except for Cr and Se.
2. Unpublished CSIRO data

Table A2 B vitamins analysis (mg per 100g wet weight)[1]

Sample ID	Thiamin (B1) mg/100g	Niacin mg/100g	Total Folates µg/100g
Aleurone flour	2.10	25.0	570
White flour	0.83	1.1	17
Australian RDI children-adults	*0.9-1.2*	*8-16*	*300-400*

1. Unpublished CSIRO data

Table A3 Proximate analysis of aleurone flour[1]. Data from Fenech et al [1].

Constituent	aleurone flour (g/100g)
Total Starch	36.5
Total Dietary Fibre	15.4
Total Fat	6.5
Total Protein	23.6
Total Free sugars	7.2
Total Ash	4.1
Total Moisture	5.1
Sum total	98.4

[1]Values are means of duplicate analyses.

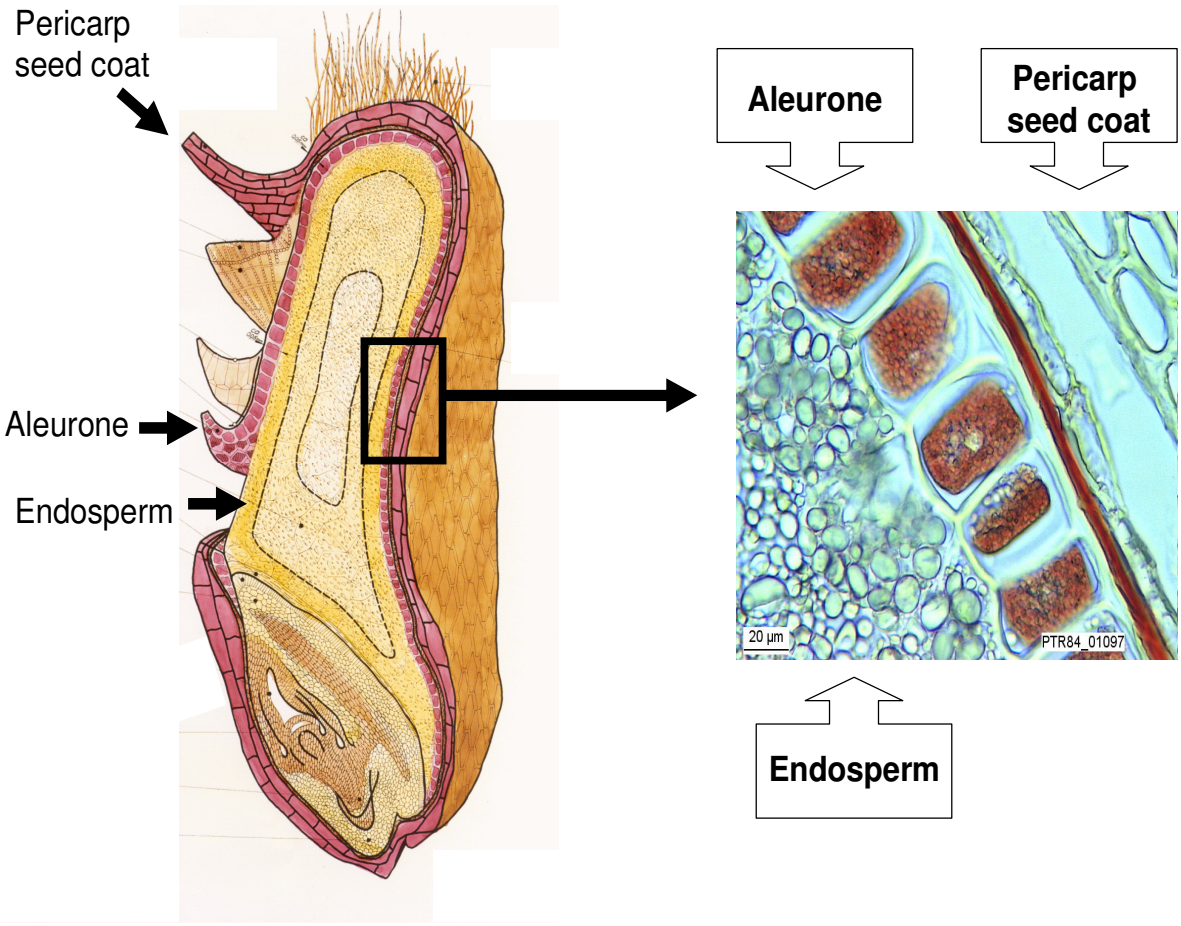


Figure A1 Diagram showing structure of the wheat grain and the spatial relationship of the aleurone layer relative to pericarp seed coat and the endosperm.

Figure A2 A schematic diagram showing the key steps in the isolation of wheat bran and aleurone flour.

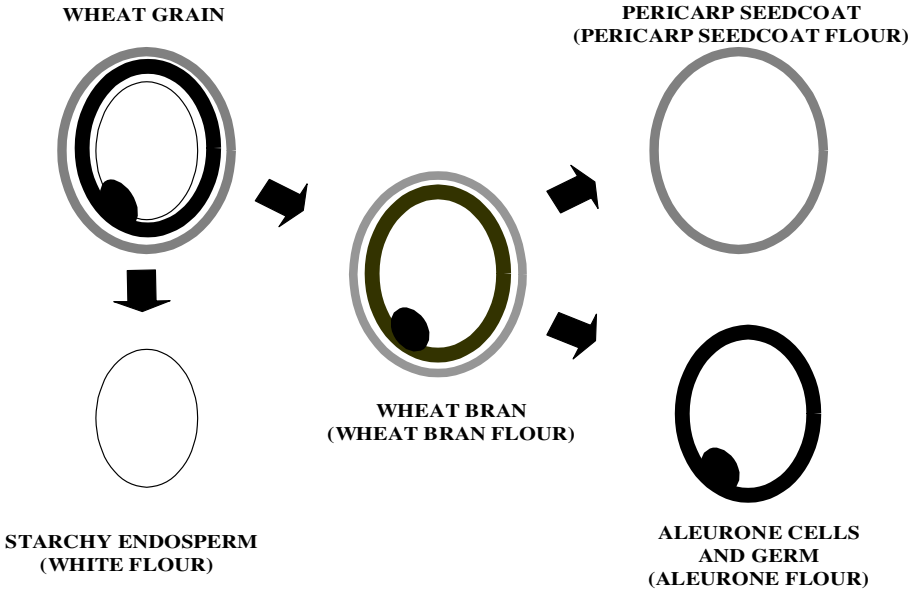
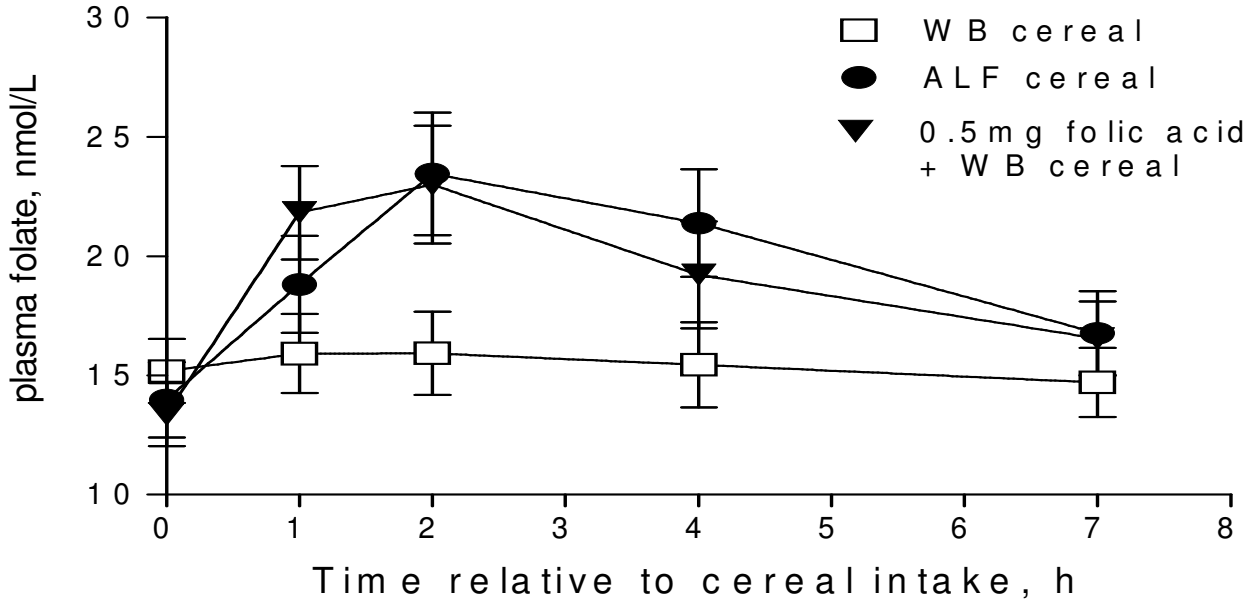


Figure A3. Change in plasma folate following ingestion of WB cereal, ALF cereal and 0.5 mg folic acid with WB cereal.



Note: Results represent the mean ± SEM, n = 16. The ANOVA P values for the change in plasma folate with time for the WB cereal, ALF cereal and 0.5 mg folic acid with WB cereal were 0.1139, < 0.0001, < 0.0001 respectively. WB = wheat bran cereal; ALF = aleurone flour cereal. Data from Fenech et al (1)

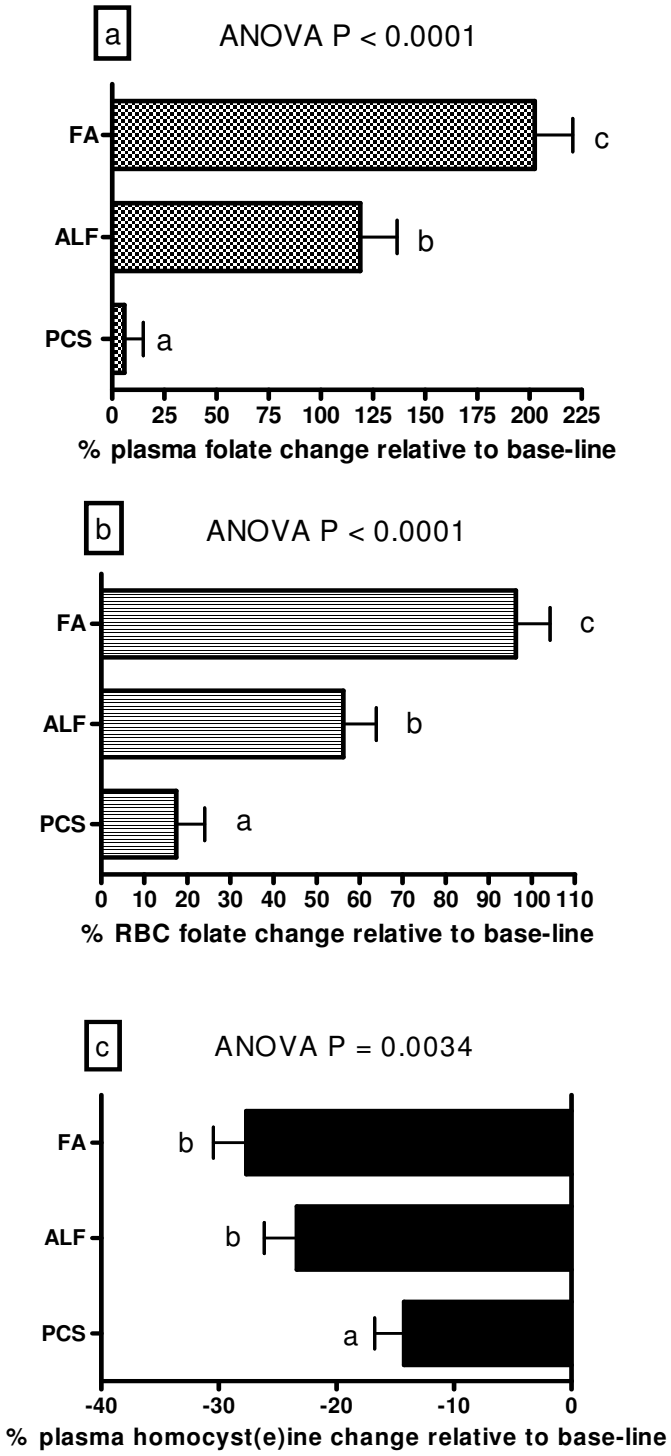


Figure A4 Percentage change in (a) plasma folate, (b) RBC folate and (c) plasma homocyst(e)ine at 16 weeks relative to base-line.

Percentage change was adjusted for base-line value. Mean values that do not share a common letter are significantly different from each other. FA, ALF & PCS refer to the treatment groups. FA group: PCS bread + folic acid tablet (high folate control, N = 18). ALF group: ALF bread + placebo tablet (N = 25); PCS group:PCS bread + placebo tablet (low folate control, N =25). FA = 640μg folic acid group; ALF = aleurone flour group; PCS = pericarp seed coat group. Data from Fenech et al (2).