Improving Folate Intake in New Zealand

Policy implications

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Foreword

Improving Folate Intake in New Zealand: Policy implications examines the evidence for a very unusual situation in public health. Rarely has there been a case where the science has been so unequivocal, uncontentious and universally accepted, yet the development and implementation of appropriate policy continues to be problematic.

10 September 1992 was a seminal date in the history of public health. On that day the US Public Health Service recommended that women of childbearing age should consume 400 μg of folic acid per day to reduce the risk of neural tube defects (NTDs). NTDs are a major category of birth defects and a leading cause of infant morbidity and mortality.

The recommendation was based on the results of two randomised controlled trials, the so-called 'gold standard' of study designs. The trials emphatically and rigorously confirmed the finding from a number of earlier observational studies that increasing the daily intake of folic acid decreases the risk of NTDs.

Subsequently, a number of other countries, including New Zealand in September 1993, also recommended that women planning a pregnancy increase their daily intake of folic acid.

Folic acid intake can be increased by three methods: increased consumption of a folate-rich diet, taking supplements or tablets containing folic acid, and the population health approach of food fortification.

The current New Zealand policy is to recommend that women planning a pregnancy take 800 μg of folic acid daily for four weeks prior to conception and for 12 weeks after conceiving to reduce the risk of NTDs. Since 1996 voluntary fortification of certain food products with folic acid has been permitted. Evidence shows that New Zealand women do not have a sufficient daily intake of folic acid to reduce the risk of NTDs.

This report links to the New Zealand Disability and Health Strategies by evaluating and discussing the available policy options for increasing folate levels to reduce the occurrence of neural tube defects, a major contributor to infant mortality and morbidity. In addition, the report examines the evidence that folic acid may reduce the risk of other major health conditions while assessing any risks from the increased intake of folic acid.

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Disclaimer

The opinions expressed are those of the authors and do not necessarily reflect the views of the Ministry of Health.

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Executive Summary

In the early 1990s two separate randomised controlled trials found that folic acid supplements reduced both the occurrence and recurrence of neural tube defects (NTDs) by up to approximately 70 percent.

Emerging evidence subsequently suggests that increasing folic acid intake may have other health benefits through the reduction of risk for cardiovascular disease and some cancers. Further research needs to be done in these areas to confirm any definitive cause and effect relationship.

In 1996, in New Zealand, 18 percent of perinatal deaths (stillbirths, and livebirths dying in the first seven days of life) were due to NTDs, compared to 15 percent attributable to congenital heart defects. In 1999 the prevalence of NTDs in New Zealand was 5.0 per 10,000 total births (livebirths and stillbirths).

High doses of folic acid are not known to have any adverse effects on healthy individuals. However, humans have not been exposed to consistently high levels of folic acid for long periods. There is also concern that high levels of folic acid may result in the masking of vitamin B_{12} deficiency in certain sub-populations, particularly the elderly, as well as causing a possible increase in twinning incidence. Taking these considerations into account, the United States Institute of Medicine has set tolerable upper intake levels (TUILs) for folic acid intake. The TUIL for adults has been set at 1000 μg per day of synthetic folic acid.

Current policy

New Zealand has a policy of recommending that women planning a pregnancy take 800 μg folic acid daily for four weeks prior to conception and for 12 weeks after conceiving to reduce the risk of NTDs. Women at high risk of having a baby with an NTD are advised to take 5000 μg folic acid for the same period of time.

Since 1996 legislation in New Zealand has permitted the voluntary fortification of certain food products with folic acid. Apart from breakfast cereal manufacturers there has not been any significant uptake by the food industry of voluntary fortification in New Zealand.

Other countries such as Australia and the United Kingdom also have legislation permitting voluntary fortification. The United States and Canada have legislation for the mandatory fortification of flour products with folic acid.

Evidence suggests that the current policy in New Zealand is not adequate to increase folate status for the reduction of NTDs. The principal aims of this report are to analyse the policy options available to improve folate and folic acid intake in New Zealand for the prevention of disease, and to make recommendations based on this analysis.

Policy options

The evidence connecting folic acid to reduced risk for cardiovascular disease, cancers and Alzheimer's disease is not definitive and will not be considered in the development of policy options. The policy options presented focus on increasing folate intake among women of childbearing age to decrease the incidence of NTDs.

There are four options available for improving folate status among women of childbearing age:

- Option 1: Increasing dietary folate intake
- Option 2: Consumption of folic acid supplements (status quo)
- Option 3: Voluntary fortification of staple food products with folic acid (status quo)
- Option 4: Mandatory fortification of staple food products with folic acid.

Options 1 and 2

Options 1 and 2 have the advantages that they both preserve consumer choice and adverse health effects are unlikely. In addition, current legislation does not need to be changed for these policies to be implemented. A disadvantage of both options is that they depend on knowledge and motivation among women of childbearing age to either change their diet or take daily folic acid supplements. Research indicates that only a small proportion of women take folic acid supplements during the recommended period. Overall, options 1 and 2, on their own, are unlikely to result in a significant number of women consuming adequate amounts of folate/folic acid to reduce the incidence of NTDs in New Zealand.

Options 3 and 4

Fortification has the advantage that the benefits of folic acid are available across the population regardless of socioeconomic status, gender or age, and does not depend on knowledge and motivation. The key issue surrounding fortification is balancing the need to fortify at a level that results in the intended health benefits for the target group against ensuring that excessive amounts of folic acid are not consumed by the general population. Another issue is the need to preserve an element of consumer choice.

Voluntary fortification will result in a significant increase of folic acid intake if bread or flour is fortified. Bread manufacturers and flour millers are reluctant to voluntarily fortify their food products. Therefore, the Ministry of Health should consider mandatory fortification in New Zealand. However, even mandatory fortification on its own is unlikely to result in more than 20 percent of women of childbearing age consuming over 400 μg of folic acid daily. Therefore, regardless of whether fortification is voluntary or mandatory, the recommendation that women consume a folate-rich diet and folic acid supplements should continue.

An additional recommendation is the funding of an ongoing, comprehensive public health campaign to increase folate intake through diet, supplementation and fortification in New Zealand, regardless of what options are selected. This campaign should also aim to increase folate awareness in both health professionals and women of childbearing age.

The key outcome of improving folate intake in New Zealand is the reduction of NTDs. Robust monitoring of the prevalence of NTDs is therefore essential. It is also recommended that termination of pregnancy reporting improve to include the type of NTDs involved.

Taking into consideration the analysis of the policy options available for increasing folate/folic acid consumption among women of childbearing age, the key recommendations made as a result of this report are as follows.

Improving folate intake in New Zealand needs to involve:

- a comprehensive, ongoing national campaign to increase awareness of and consumption of folate through diet, supplements, and fortification in women planning a pregnancy
- considering the mandatory fortification of either bread or flour with folic acid
- continuing the policy of recommending daily folic acid supplements to women planning a pregnancy in New Zealand, either in combination with voluntary fortification (status quo) or with mandatory fortification
- making a lower dose of folic acid (400 μg), as a registered medicine, available to women planning a pregnancy.

Supportive actions to improve folate intake in New Zealand need to involve:

- continuing to monitor neural tube defects in New Zealand
- improving termination of pregnancy reporting to include the type of neural tube defect involved
- monitoring folic acid intakes and folate status of the New Zealand population.

Introduction

In the early 1990s two separate randomised controlled trials found that folic acid supplementation could prevent both the occurrence and recurrence of neural tube defects (NTDs) by approximately 70 percent. As a result of these findings a number of countries worldwide, including New Zealand, have adopted a policy of recommending that women planning a pregnancy take folic acid supplements daily at least four weeks prior to becoming pregnant and for 12 weeks after conception to reduce the risk of an NTD-affected pregnancy.

Because approximately half of all pregnancies are unplanned, a number of countries have gone a step further to ensure adequate consumption of folic acid through the fortification of selected foods. New Zealand, Australia and the United Kingdom are among the countries that allow the voluntary fortification of food products with folic acid, whereas the United States and Canada have a policy of mandatory fortification, as well as voluntary.

New Zealand studies have shown that only a small proportion of women take folic acid supplements prior to pregnancy. In addition, except for breakfast cereal manufacturers, the policy of voluntary fortification has not been significantly taken up by the food industry. As a consequence, an exploration of the policy options surrounding further increasing folic acid intake among women of childbearing age in particular is needed.

Emerging evidence also suggests that increasing the intake of folic acid may have other health benefits through the reduction of risk for cardiovascular disease and some cancers. Further research needs to be done in these areas to confirm any definitive cause and effect relationship.

The principal aims of this report are to investigate and analyse policy options to improve folate and folic acid intake in New Zealand for the prevention of disease, and to make recommendations based on this analysis.

Part I: Background

Folate / folic acid

'Folic acid' refers to pteroylmonoglutamic acid, a synthetic compound used in dietary supplements and fortified foods (Cornel and Erickson 1997). 'Folate' is the generic term for compounds that have a common vitamin activity (COMA 2000) and includes both folic acid and naturally occurring compounds in food.

Folate is necessary in forming coenzymes for purine and pyrimidine synthesis, erythropoiesis, and methionine regulation (Czeizel 1995; Moyers and Bailey 2001; Refsum 2001; Ryan and Weir 2001; Fairfield and Fletcher 2002). Thus folate deficiency inhibits DNA synthesis, leading to limited and/or imbalanced cell growth, followed by cell death. Folate is also involved in the supply of methyl groups to the methylation cycle. A disturbance of the methylation cycle, which also uses a vitamin B_{12}-dependent enzyme, results in hyperhomocysteinaemia, the shortage of methionine, and a deficiency of tetrahydrofolate. Tetrahydrofolate deficiency leads to a lack of methylenetetrahydrofolate, an important cofactor in thymidylate synthase. Lack of thymidylate impairs DNA synthesis and in part causes the megaloblastic haematologic manifestations of both folate and vitamin B_{12} deficiency.

Dietary sources of folate

Because humans cannot synthesise folate they are totally dependent on dietary sources, which are mainly green leafy vegetables, citrus fruits and juices, whole wheat bread and legumes (Czeizel 1995; Steegers-Theunissen 1995; COMA 2000). Animal liver is a rich dietary source of folate, which is also present in yeast, yeast extract and beer. Because inactivation of folate occurs after oxidation and exposure to ultraviolet light and heat (Czeizel 1995; Steegers-Theunissen 1995), some naturally occurring folates are lost in storage and cooking. Principal sources of folate / folic acid in the New Zealand diet are vegetables, bread and breakfast cereals (Russell et al 1999).

Folate bioavailability

Absorption of folate is affected by age, pregnancy and numerous diseases involving the small intestine (eg, coeliac disease and Crohn's disease). Chronic alcohol consumption also negatively affects folate absorption (Donnelly 2001). Non-steroidal anti-inflammatory drugs, oral contraceptive use, methotrexate and other drugs with antifolate activity have been found to impair folate status (Institute of Medicine 1998).

Bioavailability of folate varies depending on the source and ranges from about 100 percent for folic acid supplements taken on an empty stomach, to 85 percent for synthetic folic acid taken with food, to about 50 percent for food folate (Institute of Medicine 1998). Folic acid in a supplement and in fortified bread and breakfast cereal consumed in the context of a normal diet is equally bioavailable (Institute of Medicine 1998).

Recommended dietary intake

New Zealand has adopted the Australian recommended dietary intake (RDI) of folate for adults of 200 μg/day (Truswell et al 1990). This RDI is equivalent to that set by the United Kingdom and the European Union Scientific Committee for Food (COMA 2000).

Tolerable upper intake level

The Institute of Medicine has set a tolerable upper intake level (TUIL) for adults of 1000 μg/day of synthetic folic acid (Institute of Medicine 1998). Table 1 summarises the TUILs set by the Institute of Medicine for all age groups.

Table 1: Tolerable upper intake levels of synthetic folic acid

Age group (years)	Tolerable upper intake (μg/day)
1–3	300
4–8	400
9–13	600
14–18	800
19+	1000

It is important to note that the TUIL relates to *synthetic* folic acid intake, which is *exclusive* of food folate.

The adult TUIL was set by undertaking a review of studies reporting the occurrence of neurological manifestations in people with pernicious anaemia who also consumed folic supplements. The literature indicates that at doses of folic acid of 5000 μg/day and above, there were more than 100 reported cases of neurological progression. At doses of less than 5000 μg/day (330 to 2500 μg/day), there were only eight well-documented cases. As a result of this review, because there was not sufficient data to set a No-Observed-Adverse-Effect Level (NOAEL), the Institute of Medicine set a Lowest-Observed-Adverse-Effect Level (LOAEL) of 5000 μg folic acid/day. An uncertainty factor of 5 (which is relatively large) was selected because of the severity of neurological complications and because a LOAEL was used rather than a NOAEL. The LOAEL of 5000 μg/day of folic acid was divided by the uncertainty factor of 5 to obtain the upper limit for adults of 1000 μg/day of synthetic folic acid.

Other countries have also used the 1000 μg/day as an upper limit when making recommendations on the level of fortification in food products (National Health and Medical Research Council 1995; COMA 2000).

Measuring folate status

Folate status can be assessed by the direct measurement of folate in serum and red blood cells, the deoxyuridine suppression test, and measurement of metabolites such as homocysteine (Donnelly 2001). The measurement of folate in serum and red blood cells is most commonly used to assess folate status. Red-cell folate concentration is an indicator of long-term status (Institute of Medicine 1998), while serum folate indicates folate status at the time the blood sample was drawn. Although plasma homocysteine levels are also used as an indicator of folate status, this test is not highly specific as it can be influenced by vitamin B_{12} status, vitamin B_6 status, age, gender, race, some genetic abnormalities, and renal insufficiency (Institute of Medicine 1998).

Health effects of folic acid

Because of its role in erythropoiesis, folate deficiency is known to result in megaloblastic anaemia. Recent research has uncovered other benefits of adequate folic acid levels such as the prevention of NTDs. There is also emerging evidence of a role in the prevention of heart disease and some cancers.

Neural tube defects

Neural tube defects (NTDs) are a major group of birth defects. In 1996, in New Zealand, 18 percent of perinatal deaths (stillbirths, and livebirths dying in the first seven days of life) were due to NTDs, compared to 15 percent attributable to congenital heart defects (Borman and Brown 1999).

The neural tube usually closes between 15 and 28 days post-conception in humans. Failure of the neural tube to close normally results in an NTD (Czeizel 1995). As a result, NTDs occur so early (ie, before a missed period) that most women are unaware that they are pregnant. Anencephaly and spina bifida are the most common types of NTDs, comprising 90 percent of all cases.

Anencephaly is characterised by the total or partial absence of the cranial vault, the covering skin, and the brain missing or reduced to a small mass (Borman and Brown 1999). Spina bifida describes the lesions due to midline separation of the vertebrae (Elwood et al 1992), and is characterised by herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine (Borman and Brown 1999). The third type of NTD is an encephalocoele, which describes the herniation of meninges and brain tissue outside the cranium, covered by normal or atrophic skin.

All infants with anencephaly die before or shortly after birth, whereas the majority of babies born with spina bifida or encephalocoele grow to adulthood with paralysis of the lower limbs and varying degrees of bowel and bladder incontinence (Czeizel 1995). At least 80 percent of people with spina bifida also have Arnold Chiari malformations and associated hydrocephalus (Kennedy 1998). Spina bifida is the main contributor to the burden of disease due to NTDs in New Zealand as it is associated with high medical and psychosocial morbidity.

Prevalence of neural tube defects

In most countries the occurrence risk of NTDs is between 5 and 30 per 10,000 births (Cornel and Erickson 1997). The prevalence of NTDs at birth (live- and stillbirths) in New Zealand was 5 per 10,000 in 1999.

Women who have had a previous NTD-affected pregnancy are at increased risk (100–500 per 10,000 births) of having an affected foetus in a subsequent pregnancy (Cornel and Erickson 1997). However, of all NTD-affected pregnancies, less than 5 percent occur in families where there has been an earlier NTD-affected pregnancy (Cornel and Erickson 1997).

Causes of neural tube defects

Low serum folate and red-cell levels have been associated with increasing risk of NTDs in a dose–response relationship (Daly et al 1995). Although diet plays a role, genetic factors have also been found to have an influence in the development of NTDs.

A common mutation of the gene coding for methylenetetrahydrofolate reductase (MTHFR), which affects 10 percent of the population, has a higher frequency in women who give birth to infants with NTD. The presence of this MTHFR genotype results in higher doses of folic acid being needed to provide the same amount of enzyme activity as in other genotypes of this gene (Willett 1998). The population-attributable risk due to this genotype in the overall incidence of NTDs has been estimated to be approximately 12–13 percent (Willett 1998; Molloy and Scott 2001).

Approximately 10 percent of NTDs are caused by chromosomal abnormalities such as trisomy 18, triploidy, or by single gene disorders (Kennedy 1998). Women with diabetes or exposure to some anti-convulsants, such as valproic acid and carbamazepine, are also predisposed to having an NTD-affected pregnancy. However, most NTDs are isolated and thought to be caused by an interaction between genetic predisposition and environmental factors (such as diet).

Reduction of neural tube defect incidence

The incidence of NTDs within a population can be reduced through either primary or secondary prevention. Primary prevention involves reducing the occurrence of an NTD, whereas secondary prevention involves the early diagnosis of an NTD within a pregnancy and the subsequent termination of the pregnancy if this is desired.

Observational studies have found that increasing intakes of dietary folate are associated with a lower risk of NTDs (Bower and Stanley 1989; Werler et al 1993). In their case-control study, Bower and Stanley found adjusted odds ratios (with reference to the lowest quartile of intake) of 0.94 (95% CI* 0.38–2.31), 0.61 (95% CI 0.25–1.47) and 0.38 (95% CI 0.14–1.02) when cases were compared to control subjects with no birth defects (p for trend = 0.03). The quartiles of total folate intake (μg) were: 20.0–178.4 (referent), 178.5–239.6, 239.7–350.1 and 350.2–1787.0. Similarly, Werler et al, in their case-control study in the US and Canada, found lower relative risks as dietary folate intake increased: 1.0 (95% CI 0.7–1.5), 0.7 (95% CI 0.4–1.1), 0.6 (95% CI 0.3–0.9), 0.6 (95% CI 0.4–1.1) (p for trend = 0.02). The quintile categories of dietary folate intake (μg) used in this study were: 31–196 (referent), 197–252, 253–310, 311–391 and 392–2195.

Both studies used food frequency questionnaires to determine dietary folate intake. However, because women were asked to record intakes that would have taken place more than six months previously, recall bias may have been an issue with the results. In addition, the higher dietary folate intake categories in both case-control studies would be difficult to achieve in a normal diet.

Folic acid supplementation during the peri-conceptional period is also known to reduce both the occurrence (Czeizel and Dudas 1992) and the recurrence (MRC Vitamin Study Research Group 1991) of NTDs by approximately 70 percent (Wald 1994). A randomised controlled trial conducted by the UK Medical Research Council in 1993 found that a dose of 4000 μg folic acid prevented the recurrence of an NTD-affected infant in women with a previously affected pregnancy (MRC Vitamin Study Research Group 1991). In their randomised controlled trial, Czeizel and Dudas (1992) found an 800 μg folic acid tablet effective in reducing the first occurrence of NTDs.

Since these trials were conducted it has been found that a 400 μg dose of folic acid/day is equally as effective in preventing the first occurrence of an NTD (Berry et al 1999). Berry et al evaluated the outcome of pregnancy in women who took 400 μg folic acid daily peri-conceptionally in two areas of China: a northern region with high rates of NTDs (48 per 10,000 pregnancies of 20 weeks' gestation) and a southern region with lower rates of NTDs (10 per 10,000 pregnancies of 20 weeks' gestation). With peri-conceptional folic acid use, the rates of an NTD pregnancy declined to 10 per 10,000 in the northern region and 6 per 10,000 in the southern region. The greatest decline in NTD risk occurred in the higher prevalence area (80 percent in the north compared to 40 percent in the south). The reduction in risk in both regions was statistically significant. This study suggests that although folic acid supplementation is effective at reducing the incidence of NTD, the effect is smaller in areas of lower NTD prevalence.

Whether doses of folic acid lower than 400 μg daily are also effective in reducing the incidence of NTD recurrence is unknown. Further trials examining this issue would be unethical because women given lower doses may have NTD-affected pregnancies.

Red-cell folate levels have been found to be inversely associated with the risk of an NTD (Daly et al 1995). A randomised controlled trial conducted in Ireland looked at the

* 95% CI = 95% confidence interval.

relationship between increasing doses of folic acid and red-cell folate values in women not planning a pregnancy (Daly et al 1997). The trial found increasing levels of red-cell folate with increasing doses of folic acid. Using red-cell folate levels as an indicator of NTD risk, the authors estimated that delivery of 400 μg, 200 μg or 100 μg via fortification would result in reductions in NTD incidence of 47 percent, 41 percent and 22 percent, respectively.

The mechanism of action whereby folic acid supplementation reduces the incidence of NTDs is not known (Wald 1994; Fleming 2001). There is some suggestion that the occurrence of NTDs may be due to a problem in the uptake and/or metabolism of folate in both maternal and foetal cells rather than a lack of sufficient folate in the diet (Czeizel 1995). Folic acid supplementation may cause an increase in folate concentrations in foetal tissue fluids, and may overcome the failure of folate supply from the mother.

Cardiovascular disease

Studies have suggested a relationship between good folate status and a reduced risk of cardiovascular disease (CVD) – both ischaemic heart disease (IHD) and stroke (Morrison et al 1996; Eikelboom et al 1999; Bazzano et al 2002). Randomised controlled trials are currently under way to determine whether folic acid supplementation will lead to a lower incidence of cardiac events (Eikelboom et al 1999).

There are two potential mechanisms for the beneficial effect of folates in cardiovascular disease: lowering of homocysteine levels and antioxidant actions. Of these, the relationship between folate and homocysteine has created the most research.

Lowering of homocysteine levels

Homocysteine has been shown to promote oxidative modification of low density lipoprotein cholesterol, which can lead to the formation of atherosclerotic lesions. It is also believed that homocysteine has a role in thrombosis by altering normal anti-thrombotic mechanisms (COMA 2000; van der Griend et al 2000). However, there is still controversy over whether the relationship between homocysteine and cardiovascular disease is cause or effect (Brattström and Wilcken 2000). Further work to establish a definitive relationship needs to be done in this area.

In 1995 a meta-analysis found a 5 μmol/L increase in homocysteine levels was associated with increasing odds of 60 percent in men and 80 percent in women for IHD, and a 50 percent increase for stroke in both men and women (Boushey et al 1995). This meta-analysis included three prospective, 19 case-control and five cross-sectional studies.

Two recent meta-analyses also found that elevated homocysteine levels are a predictor for IHD and stroke (Homocysteine Studies Collaboration 2002; Wald et al 2002). The effect of homocysteine and CVD as reported by these two meta-analyses, however, is less than that found by Boushey et al (1995).

Wald et al (2002) conducted a meta-analysis to assess the association of homocysteine concentration with IHD, deep vein thrombosis (DVT) and stroke. The meta-analysis included 20 prospective studies (3144 IHD events and 676 stroke events) of serum

homocysteine and disease risk. In addition, the authors analysed 72 case-control studies of which the prevalence of the MTHFR gene (which increases homocysteine levels) was associated with the three diseases described above (16,849 cases). Both the MTHFR studies and the prospective studies found a significant association between homocysteine and cardiovascular disease (IHD and stroke), with the association being stronger in the MTHFR studies than in the prospective studies. Overall, a 3 μmol/L decrease in serum homocysteine concentrations related to a combined odds ratio (both MTHFR and prospective studies) of 0.84 (95% CI 0.80–0.89) for IHD, 0.76 (95% CI 0.67–0.85) for stroke, and 0.75 (95% CI 0.62–0.92) for DVT. The prospective studies were adjusted for possible confounders and regression dilution.

Compared to Wald et al (2002), the Homocysteine Studies Collaboration (2002) found a smaller but still significant association between homocysteine and CVD. In this meta-analysis, individual participant data from 30 prospective or retrospective studies (5073 IHD events, 1113 stroke events) were analysed. Allowance was made for differences between studies, confounding by known cardiovascular risk factors, and regression dilution in the prospective studies. Stronger associations were observed in retrospective studies than in prospective studies. In the prospective studies, for a 3 μmol/L lower usual homocysteine level, this meta-analysis found odds ratios of 0.89 (95% CI 0.83–0.96) for IHD and 0.81 (95% CI 0.69–0.95) for stroke.

Overall, therefore, the more recent meta-analyses have found that by lowering homocysteine levels by 3 μmol/L, the odds of developing IHD reduced by 11 to 16 percent, the odds of developing stroke reduced by 19 to 24 percent, and the odds of developing DVT reduced by 25 percent.

Two-thirds of all cases of moderate hyperhomocysteinaemia are thought to be due to inadequate blood levels of one or more of folate, vitamin B_{12} and vitamin B_6 (Ward 2001). The association is strongest for folate (Ward 2001). Other causes of hyperhomocysteinaemia are genetic: cystathionine β-synthase (CBS) deficiency, methylenetetrahydrofolate reductase (MTHFR) deficiency, or inborn errors of cobalamin metabolism (Brattström and Wilcken 2000).

Randomised controlled trials have demonstrated that increased intakes of dietary folate or folic acid supplements significantly reduce plasma homocysteine levels (Homocysteine Lowering Trialists' Collaboration 1998; Wald et al 2001). A meta-analysis of such trials found that daily supplementation with doses between 500 and 5000 μg folic acid and about 500 μg vitamin B_{12} would be expected to reduce blood homocysteine concentrations by about a quarter to a third (Homocysteine Lowering Trialists' Collaboration 1998). The effects of folic acid were greater among subjects with higher blood homocysteine concentrations or lower blood folate concentrations before treatment. A more recent randomised controlled trial found that a minimal dosage of 800 μg/day folic acid was necessary to achieve maximum reduction (2.7 μmol/L) in serum homocysteine levels across the range of levels in the population (Wald et al 2001).

Lower levels of folic acid were also found to be sufficient in reducing total homocysteine levels in both men and women in a recent New Zealand study (Venn, Mann et al 2002). This study found that the addition of about 100 μg folic acid, given daily as fortified

breakfast cereal, is as effective in reducing total homocysteine concentrations as fortification at higher levels. Consumption of breakfast cereals fortified with 100 μg, 200 μg and 300 μg folic acid increased serum folate by 28, 60 and 79 percent, respectively, accompanied by reductions in plasma homocysteine of 16, 12 and 17 percent.

Another New Zealand study also looked at the most appropriate means of increasing dietary folate to reduce homocysteine levels (Riddell et al 2000). The study subjects included 25 women and 40 men aged 36–71 years with total homocysteine levels greater than 9 mmol/L. The study compared three approaches for increasing folate and folic acid intake to approximately 600 μg/day: folic acid supplementation, consumption of folic acid-fortified breakfast cereals, and increased consumption of folate-rich foods. Although the dietary folate group consumed more total folate than the other two intervention groups, serum folate did not increase to the same extent. The authors concluded that the daily consumption of folic acid-fortified breakfast cereals and the use of folic acid supplements appeared to be the most effective means of reducing total homocysteine concentrations.

A recent randomised controlled trial found that homocysteine-lowering therapy with folic acid, vitamin B_{12} and vitamin B_6 significantly decreased the incidence of major adverse events after percutaneous coronary intervention (Schnyder et al 2002). Participants (n = 553) were randomly assigned to receive a combination of folic acid, vitamin B_{12} and vitamin B_6 for six months. The incidence of major adverse events was significantly lower in patients receiving the vitamins compared to the controls, both at six months (RR 0.6; 95% CI 0.4–0.91)* and at one year (RR 0.68; 95% CI 0.48–0.96). Adjusting for potential confounders did not significantly change the association. However, the study design was such that the assessment of the separate effects of folic acid, vitamin B_{12} and vitamin B_6 was unable to be determined. In addition, the majority of subjects taking part in the study were male (80 percent) and therefore the results may not be generalisable to women.

Cancer

Folate is essential for the synthesis, methylation and repair of DNA. As a consequence it is biologically plausible that a diminished folate status may contribute to carcinogenesis by alteration of gene expression and increased DNA damage. Reflecting this hypothesis, studies have investigated the association between folate and some cancers, including colon and breast cancer.

Colon cancer

The Nurses' Health study (a prospective study involving 88,756 nurses in the United States) found a 75 percent reduction in colon cancer risk in women using multivitamin supplements containing 400 μg folic acid or above for more than 15 years (Giovannucci et al 1998). The authors acknowledge that a component of multivitamin use other than folate may have accounted for their findings. However, the trend toward protection was over the entire range of folate intake (p for trend = 0.01), whereas supplement users were mostly in the top category.

* RR = relative risk; 95% CI = 95% confidence interval.

The Health Professionals Follow-up study (Giovannucci et al 1995) found that inadequate intakes of folate and methionine when combined with substantial consumption of alcohol among men also increased the risk of colon cancer (RR 3.3; 95% CI 1.58–6.88).

The findings of the Nurses' Health study and the Health Professionals Follow-up study are supported by other research, which also suggests an association between folate intake and colon cancer (Glynn et al 1996; Kato et al 1999).

Breast cancer

Folate consumption has also been linked to lower breast cancer risk, although epidemiological data for this association are limited. The association between breast cancer risk and folate consumption has been investigated in a prospective cohort study. This study used data collected in the Nurses' Health study and found that total folate intake (including natural and synthetic folate) was not associated with risk of breast cancer among the whole cohort or among pre-menopausal women (Zhang et al 1999). However, total folate was found to be weakly inversely associated with risk of post-menopausal breast cancer (p for trend = 0.02). In addition, the study also demonstrated a significant positive association between alcohol intake, folate intake and breast cancer. The risk of breast cancer associated with alcohol intake was strongest among women with a total daily folate intake less than 300 μg (for alcohol intake ≥ 15 g/day vs < 15 g/day, multivariate RR = 1.32; 95% CI, 1.15–1.50).

Other cancers

Folate intake has also been associated with low risk of other cancers, including cervical, pancreatic, oesophageal and primary liver cancers (Czeizel 1995), as well as acute lymphoblastic leukaemia in childhood (Thompson et al 2001).

Dementia and psychiatric disorders

An association between high homocysteine levels and Alzheimer's disease has been found (Seshadri et al 2002). Through its effect in reducing homocysteine levels, increased folic acid consumption could therefore be associated with reduced risk of Alzheimer's disease. Clinical trials need to be done to establish whether reducing homocysteine levels will reduce Alzheimer's disease.

Folic acid deficiency has also been associated with other types of dementia in the elderly (Reynolds 2002). High incidences of folate deficiency occur in elderly populations, especially psychogeriatric patients (Reynolds 2002). Clinical trials suggest that psychogeriatric patients may respond better to psychotropic medication after improvement of folate status (COMA 2000).

A Cochrane review is currently under way looking at the effects that folate supplementation may have in the treatment of depression (Taylor et al 2002).

Other

Reduced folate status has also been linked with risks for cleft lip and palate, limb deficiencies, birth defects of the heart, urinary tract defects, and total rates of major structural defects (Moyers and Bailey 2001).

In addition, folic acid has been found to be of benefit to an improved pregnancy outcome. A recent study conducted in Boston, USA, found that women taking folic acid supplements during pregnancy had a 45 percent lower risk of developing gestational hypertension (Hernández-Díaz et al 2002).

Adverse effects of folic acid

Although there are clear benefits, increased levels of folate through fortification may have an adverse effect on the health of certain sub-populations. Masking of vitamin B_{12} deficiency with increased levels of serum folate is of most concern. Other adverse effects may also include an increased incidence of multiple births, reduced zinc bioavailability, and induction of seizures in susceptible persons (McNulty 1995; Campbell 1996; COMA 2000; Ericson et al 2001; Lumley et al 2002). No adverse effects have been associated with the consumption of excess folate from foods (Institute of Medicine 1998). In addition, for a number of years, over one-third of all adults in the US have taken daily supplements that contain 400 μg folic acid with no reported adverse effects (COMA 2000).

Vitamin B_{12} deficiency

The key features of vitamin B_{12} (cobalamin) deficiency are macrocytic megaloblastic anaemia and neuropathy (Bower and Wald 1995; COMA 2000). The majority of people with vitamin B_{12} deficiency present with symptoms due to their anaemia, with only a third presenting with predominantly neurological symptoms. The neurological abnormalities are due to progressive degeneration of the lateral and posterior columns of the spinal cord, or to peripheral neuropathy, or both (Bower and Wald 1995).

Approximately two-thirds of vitamin B_{12} deficiency is due to pernicious anaemia (Bower and Wald 1995), an autoimmune disorder that results in the malabsorption of vitamin B_{12} (Thurnham et al 2000). Pernicious anaemia is a disease of later life with approximately 1 to 5 percent of people over 65 years affected (Czeizel 1995; COMA 2000).

Because dietary sources of vitamin B_{12} are meat or foods of animal origin (such as milk, cheese and eggs), vitamin B_{12} deficiency can also occur, and should be considered, in strict vegetarians, particularly vegans (who do not consume any animal produce). Elderly people may also have malabsorption of vitamin B_{12} because of gastric atrophy and the absence of hydrochloric acid and pepsin (which are necessary to release vitamin B_{12} from food) in the stomach.

Analysis of the 1997 National Nutrition Survey has found that 10 percent of adults aged over 65 years in New Zealand have vitamin B_{12} deficiency (based on a cut-off of 150 pmol/L vitamin B_{12}) (T Green, personal communication, September 2002). Another New Zealand study found similar levels of vitamin B_{12} deficiency in elderly Dunedin women aged 70 to 80 years. In this group, 13 percent of participants were classified as

having sub-optimal vitamin B_{12} status (using the same cut-off as above) (de Jong et al 2003).

Because vitamin B_{12} is an important factor in the metabolism of folate for DNA synthesis, a deficiency in vitamin B_{12} results in the same type of anaemia as that produced by folate deficiency (COMA 2000). Higher serum and red-cell folate levels are therefore able to resolve vitamin B_{12}-induced anaemia. Extra folic acid in fortified food may prevent or resolve the anaemia of vitamin B_{12} deficiency, thus delaying diagnosis. The delay in diagnosis may then result in irreversible neurological damage.

Taking concerns surrounding the masking of vitamin B_{12} deficiency into consideration, the Institute of Medicine (1998) recommended a tolerable upper intake level of 1000 μg/day of folic acid for adults. How this TUIL was set has been described earlier in this report.

There have been suggestions that including vitamin B_{12} in any folic acid fortification programme might resolve the issue of masking vitamin B_{12} deficiency. However, including vitamin B_{12} may not address the problem, as the usual cause of deficiency is malabsorption of vitamin B_{12}. Fortification of food with vitamin B_{12} may therefore not correct the deficiency in people with pernicious anaemia.

When considering folic acid supplementation or fortification it is important to recognise that vitamin B_{12} deficiency is just that: vitamin B_{12} *deficiency*, not folic acid excess. The concern that folic acid fortification may lead to masking of vitamin B_{12} deficiency could be overcome to some extent by improved awareness among health professionals regarding screening for this deficiency among the elderly population and subsequently improved diagnosis. In addition, it must be kept in mind that not all vitamin B_{12} deficiency will be undiagnosed, and will therefore be treated appropriately. Of those remaining, only a small proportion will be receiving folic acid through fortification above the recommended TUIL.

Recent work by the University of Otago (Venn, Green et al 2002) suggests that the problem associated with masking vitamin B_{12} deficiency through universal folic acid fortification may be overcome by using a different form of synthetic folic acid. A randomised controlled trial looked at the effectiveness of using [6S]-5-methyltetrahydrofolate ([6S]-5-MTHF) compared to folic acid in increasing serum and red-cell folate levels. The trial found that low-dose [6S]-5-MTHF and folic acid supplementation increased blood folate indices to a similar extent. Unlike folic acid, which is able to mask haematological signs of vitamin B_{12} deficiency because it is readily converted to tetrahydrofolate (the form of folate that supports erythropoiesis), [6S]-5-MTHF requires a vitamin B_{12}-dependent enzyme for conversion to tetrahydrofolate. As a result, fortification with [6S]-5-MTHF would have no effect on haematological signs in the presence of vitamin B_{12} deficiency. The stability of [6S]-5-MTHF in food-processing operations needs to be confirmed before it can be considered as a food fortificant.

Multiple births

There has been some suggestion that consumption of folic acid supplements may increase the risk of multiple pregnancies.

A Swedish study found a statistically significant increased rate of twin deliveries associated with the use of 400 μg folic acid after controlling for maternal age and length of involuntary childlessness (Ericson et al 2001). Data for this study were collected retrospectively from the Swedish Medical Birth Registry, which contained detailed information on drug use in early pregnancy as well as prenatal care and delivery data. Overall, 2569 women reported use of folic acid and 1971 women reported use of multivitamins out of a total of 442,906 births between 1995 and 1999. The increased risk seemed to be limited to dizygotic twinning (RR 2.13; 95% CI 1.64–2.74).* The authors suggest that, if causality exists, special consideration needs to be given to a folic acid supplementation policy, particularly in a low NTD-risk area as the benefits in reducing NTD-affected births may not outweigh the risks associated with an increased number of twin births.

A Cochrane review also found a 40 percent increase in multiple gestations associated with folic acid supplementation (Lumley et al 2002). Although the association was not statistically significant, the reviewers were concerned as twins are at increased risk of adverse events perinatally, which could lead to poorer health and development outcomes.

More recently, however, a population-based cohort study did not find a relationship between folic acid consumption and multiple pregnancies (Li et al 2003). This study assessed the occurrence of multiple births in a large cohort of women (n = 242,015) in China. There was no increase in the occurrence of multiple births following consumption of folic acid in women who had a pregnancy unaffected by a birth defect. The rate of multiple births in women who did and did not take folic acid before or during early pregnancy was 0.59% and 0.65%, respectively (rate ratio 0.9; 95% CI 0.82–1.00).*

Reduced zinc bioavailability

There is concern that folic acid supplementation may reduce the absorption of zinc. Zinc is important in the synthesis and stabilisation of proteins, DNA and RNA and plays a structural role in ribosomes and membranes. Zinc is also required for normal spermatogenesis, foetal growth and embryonic development.

A review by Campbell (1996) did not find any convincing data showing an interaction precipitated by folic acid supplements that reduces zinc homeostasis in the long term. This review also found that folic acid supplements have no short-term effect on serum zinc levels. Daily doses of 5000–15,000 μg folic acid over periods of six months to four years have not been found to adversely affect zinc balance in healthy humans (Butterworth and Tamura 1989).

Other

Folic acid administration at high doses to patients with epilepsy has been reported to induce seizure activity (McNulty 1995; Campbell 1996; COMA 2000). A review of the literature on interference with anti-convulsant medication by folic acid supplementation concluded that the evidence does not support a substantial increase in seizure frequency in patients with epilepsy who are treated with oral folic acid (Campbell 1996). Most of the

* RR = relative risk; 95% CI = 95% confidence interval.

studies included in the review looked at levels of folic acid supplementation of up to 15,000 μg/day for one to six months and found no adverse effects.

A Cochrane review found no association between folate supplementation and significant increases in miscarriages, ectopic pregnancies or stillbirths (Lumley et al 2002).

Part II: International Experience

Because of the overwhelming evidence of the benefits of folic acid in the reduction of NTDs, a number of countries have adopted policies to improve folic acid intake among women of childbearing age. This section outlines the experience of selected countries with regard to both supplementation and fortification, and discusses issues and outcomes that have arisen in association with these policies.

Overall, there have been declining rates of NTDs among births in many countries since the early 1980s. This decline was occurring before folic acid supplementation or fortification policies were introduced in some countries. Although some of the decline is attributable to an increased rate of antenatal screening and detection followed by induced abortion of foetuses affected by NTDs, it is not the full explanation.

It is difficult to compare the decline in NTD-affected births between countries as different countries have different definitions of what constitutes an NTD birth. In addition, some countries include abortions and stillbirth data in their NTD incidence data while others only include livebirths.

Many countries, whether they have a fortification programme or not, endorse the supplementation of folic acid at a level of 400 to 500 μg/day peri-conceptionally in women of childbearing age.

A summary of international folic acid supplementation and fortification policies can be found in Appendix 1. No systematic evaluations of the outcomes of national fortification programmes have yet been published (Abraham and Webb 2000).

Australia

In June 1995 the National Food Authority in Australia amended the Food Standards Code to permit the voluntary fortification of a number of foods with folic acid. Fortification was permitted at a level of up to 50 percent of the Australian Recommended Dietary Intake (100 μg per reference quantity of the food). Fortification is permitted for the following foods: flour, bread, some savoury biscuits, breakfast cereals, pasta, yeast and meat extracts, as well as fruit and vegetable juices. In 1998 supplemental foods such as folate-fortified milk products were added to the list (Abraham and Webb 2000). The Commonwealth Department of Health and Ageing recommends that women planning or likely to become pregnant take a daily folic acid supplement of at least 500 μg daily (Cornel and Erickson 1997).

In December 1995 an agreement to establish a joint food-setting system between Australia and New Zealand was signed. The treaty, which came into force on 1 July 1996, serves to harmonise food standards between the two countries, reduce compliance costs for the industry and help remove regulatory barriers to trade in food. As a result of this arrangement, the National Food Authority became the Australia New Zealand Food Authority (ANZFA), which in turn became Food Standards Australia New Zealand (FSANZ) on 1 July 2002.

In November 1998 ANZFA granted approval for a folate and NTD health claim for certain food products as a pilot in a wider review of health claims (Watson and Watson 2001). Foods (both non-fortified and fortified) that contain at least 40 μg of folate per serving (and do not contain more than 14 g of fat, 10 g of added sugar and 500 mg of sodium per serving) are permitted to carry a health claim. This food standard is being extended until February 2004 as agreed by the Australia New Zealand Food Standards Council members in June 2002.

An evaluation of the impact of this pilot health claim in females of childbearing age in Victoria, Australia, has been conducted (Watson and Watson 2001). A survey conducted between November 1998 and November 1999 found that there was an increase in the proportion of women who had heard of folate (82 to 89 percent) and the association between folate and birth defects (33 to 41 percent). Uptake by the food industry was also evaluated by assessing fortification in June 1999 and January 2000. Although there was some uptake of the claim by the food industry, there was no evidence that people were buying foods because they had folate messages.

An interim evaluation of the Australian voluntary folic acid fortification policy was published in 2000 (Abraham and Webb 2000). This evaluation found that the implementation of the folate health claim pilot is having a small but positive effect on increasing the number of fortified products on the market. A price comparison between fortified and non-fortified foods found slightly higher prices in fortified food products. The impact of educational and promotional efforts associated with the fortification policy was difficult to assess due to insufficient national data, but appeared promising.

The authors of the evaluation concluded it was too early to assess the impact of voluntary folic acid fortification on the occurrence of NTDs and that mechanisms were not in place to monitor these or other health outcomes. The authors recommended that the focus shift from health outcomes to the improved implementation of the programme, through collaboration with relevant food industries and government bodies.

Prior to and since the implementation of voluntary fortification there have been national and state-based initiatives aimed at promoting the use of folic supplements by women of childbearing age (Abraham and Webb 2000).

One of the first Australian campaigns to promote folate for the prevention of NTDs took place in Western Australia in 1992 and continued for two and a half years (Bower et al 1997). The aims of this campaign were to inform health professionals about the prevention of NTDs with folate, to inform women about folate and spina bifida, and to encourage women to increase their folate intake. Compared to the beginning of the campaign, there was an increase in the proportion of general practitioners offering folic acid supplements to women planning a pregnancy, as well as an increase in the proportion of general practitioners recommending the correct dose of folic acid. The proportion of women who knew about the association between folate and prevention of spina bifida increased markedly, from 8.2 percent before the project began to 67.5 percent 2.5 years later. Of the women who had planned their pregnancy in 1995, 43.1 percent had taken folic acid supplements before becoming pregnant and a further 5.6 percent had increased their dietary intake of folate. These proportions compare to 19 percent of women with planned

pregnancies who 2.5 years earlier had taken folic acid supplements or increased their dietary intake of folate.

Folate awareness campaigns have also been carried out in the states of Victoria (Watson et al 1999) and South Australia (Chan et al 2001). Increases in awareness and knowledge about folate and its relationship with NTDs followed both campaigns. Neither of these campaigns assessed whether actual consumption of folic acid supplements during the peri-conceptional period increased.

The reported prevalence of NTDs among births has declined in Australia from 15.5 per 10,000 births in 1982 to 6.9 per 10,000 in 1997 (Abraham and Webb 2000). The primary issue of concern in interpreting this trend data is the incomplete national notification of terminations of pregnancy in Australia. Apart from South Australia, where terminations have been legal since 1970 and which has mandatory reporting of terminations, data from other states are variable and uncertain. If termination of pregnancy data is taken into account, it is uncertain whether there has been a decline in NTDs in Australia at a national level (C Bower, personal communication, March 2003).

Although not mandatory, Victoria and Western Australia also have good data on terminations of pregnancy (Owen et al 2000; Bower et al 2002). Recent papers from South Australia (Chan et al 2001) and Western Australia (Bower et al 2002) have demonstrated a fall in total NTDs (including births and terminations of pregnancy) in these two states since 1996. In Victoria the total prevalence of NTDs (including births and terminations of pregnancy) did not decline up to 1997, although there was a sharp decline in 1998 and 1999 in both anencephaly and spina bifida (Owen et al 2000). A 30 percent fall in NTDs (including terminations) was documented in Western Australia from 1996 to 2000. This fall is thought to be due to increased peri-conceptional folate intake in response to the above health promotion campaigns and fortification of selected foods (Bower et al 2002).

United Kingdom

The incidence of neural tube defects in the United Kingdom (UK) has been decreasing since the early 1970s (Kadir et al 1999; Morris and Wald 1999). Since 1992 this rate of decline has stabilised (Kadir et al 1999). The NTD prevalence at birth in 1997 in the UK has been estimated to be 1.4 per 10,000 births compared to 36.6 per 10,000 births in 1970; these figures include stillbirths (Morris and Wald 1999).

Forty percent of the decline in the UK has been attributed to antenatal screening and terminations of pregnancy, with 56 percent of the decline due to a fall in incidence (Morris and Wald 1999). Between the early 1980s and 1997 dietary folate increased by about 20 percent in the UK, and this increase may have contributed to the decline in NTD-affected pregnancies (Morris and Wald 1999).

Voluntary fortification of most breakfast cereals and some bread with folic acid has been in effect in the UK for a number of years. It is estimated that between 80 and 90 percent of breakfast cereals consumed are fortified with folic acid (COMA 2000).

In 2000 COMA recommended universal folic acid fortification of flour at 240 μg/100 g. Since the release of the COMA report there has been considerable public debate in the UK about mandating the fortification of flour with folic acid. In May 2002 the UK Food Standards Agency made a decision not to proceed with mandatory folic acid fortification, concluding that further evidence on the impact on older people needed to be considered, especially regarding masking of vitamin B_{12} deficiency (Food Standards Agency 2002).

In addition to voluntary fortification, the British Department of Health recommends women of childbearing age take 400 μg/day of folic acid during the peri-conceptional period (COMA 2000).

In 1995 the Health Education Authority (HEA) was commissioned by the Department of Health to run a national campaign aimed at increasing the daily intake of folate and folic acid in women who might become pregnant (COMA 2000). The campaign ran until spring 1998 and was targeted at health professionals and women planning pregnancy. Although the campaign ended in 1998, the HEA has continued to promote folic acid advice as part of the work of the Food and Nutrition Programme.

The folic acid campaign has had an influence on women's and health professionals' knowledge of folic acid and its relationship to NTDs (COMA 2000). Spontaneous (unprompted) awareness of folic acid among women of childbearing age increased from 9 percent in 1995 to 49 percent in 1998. The percentage of women claiming to take folic acid when trying to conceive rose from 24 percent of recently pregnant women in 1997 to 38 percent in 1998. Forty-nine percent of health professionals who had seen campaign information claimed to have changed their practice as a result.

United States

In March 1996 the United States (US) Food and Drug Administration (FDA) mandated that, as from 1 January 1998, enriched cereal grain flour be fortified with 140 μg folic acid per 100 g flour. This level of fortification was selected to increase the dietary intake of folic acid in women of childbearing age while at the same time making excessive intakes among those at risk of vitamin B_{12} deficiency less likely to occur. The level of fortification chosen has been estimated to add an additional 100 μg of folic acid to the average woman's diet. Discussion continues regarding the need for a higher level of fortification.

The FDA did not mandate any post-marketing surveillance programme after the initiation of the folic acid fortification programme (Neuhouser and Beresford 2001). However, since the implementation of folic acid fortification, a number of studies have looked at whether fortification has resulted in increased consumption of folic acid, increased serum and red-cell folate levels, as well as a decrease in NTD rates and homocysteine levels.

Shortly after the full introduction of the mandatory fortification programme the food composition databases of two national consumption surveys were updated to reflect folate intakes as a result of fortification (Lewis et al 1999). This study found that more than one-third of foods in the database had higher folate content after the update was complete. This increase in folate content was also evident in foods that were low in folate before fortification, and included foods such as chicken nuggets, cheese pizzas, chocolate cupcakes and TWIX cookie bars. These findings suggest that even people who might not consume diets traditionally high in folate (fruit, vegetables and cereals) are also likely to increase folic acid consumption through fortification.

The updated survey found that 67–95 percent of the population met or surpassed the recommended daily intake of folate/folic acid. However, there were still approximately 68–87 percent of females of childbearing age who had synthetic folic acid intakes below the recommended intake of 400 μg/day after fortification. The study also found that 15–25 percent of children aged one to eight years had intakes above the tolerable upper intake level set by the Institute of Medicine. Although vitamin B_{12} deficiency is rare in the younger age groups, there is relatively little knowledge regarding the adverse effects of high folate intakes among children. The authors recommended continued monitoring.

Red-cell folate and plasma folate concentrations have increased in study populations after the introduction of folic acid fortification (Jacques et al 1999; Lawrence et al 1999; Choumenkovitch et al 2001). Mean total homocysteine concentrations also decreased significantly in subjects examined after the introduction of fortification (Jacques et al 1999).

Since the introduction of mandatory folic acid fortification of the US food supply, a 19 percent reduction in NTD birth prevalence has occurred, from 3.78 per 10,000 live births (October 1995 to December 1996) to 3.05 per 10,000 live births (October 1998 to December 1999) (Honein et al 2001). Whether this decline can be attributed directly to folic acid fortification is difficult to say, as there is one key limitation of the study that may influence the results: the study used birth certificate data as the basis of its analysis. Consequently, pregnancies that were terminated as a result of a prenatal diagnosis of NTD would not be taken into account. If the proportion of NTD terminations remained constant over the study period, the results would not be affected. Although a substantial increase in terminations between 1996 and 1999 is unlikely, we do not know for certain.

In addition to the policy of mandatory fortification, it is recommended in the US that women of childbearing age take 400 μg folic acid daily, especially before and during early pregnancy (March of Dimes 2003).

Canada

Canada has been recommending since the mid-1990s that women of childbearing age take 400 μg of folic acid supplements (Persad et al 2002).

Voluntary folic acid fortification was introduced in Canada in December 1996, phasing into mandatory fortification by November 1998. Folic acid fortification is permitted at a level of 150 μg per 100 g of all flour and enriched cornmeal (O'Connor 2002). Pasta products labelled 'enriched' were mandated to be fortified at a level of 200 μg/100 g. A few other foods, including breakfast cereals, are permitted to contain folic acid but not at levels that would substantially change folate intakes (N Lee, personal communication, September 2002). The level of fortification chosen has been estimated to add an additional 50–150 μg/day of folic acid for women. This level of fortification was aimed at reducing the annual incidence of NTDs by an estimated 22 percent.

A study retrospectively analysing serum and red-cell folate levels since the initiation of the enhanced folic acid fortification programme in Canada found an overall decline of between 59 and 77 percent in the incidence of folate insufficiency (Ray et al 2002). The period from April 1997 to July 1998 was compared to the period from February 1999 to March 2000.

A recently published study looked at the effect of the introduction of folic acid fortification has had on the incidence of NTDs in Nova Scotia (Persad et al 2002). In the period after supplementation began in Canada and before fortification was implemented, the incidence of NTDs had not changed significantly. This study found that after fortification was implemented, the incidence of NTDs decreased by more than 50 percent: the mean annual rate was 25.8 per 10,000 births during 1991–97 compared to 11.7 per 10,000 births during 1998–2000 (RR 0.46; 95% CI 0.32–0.66). The study included all NTD births (livebirths, stillbirths and therapeutic abortions) in their analysis. The decline in NTDs found by this study suggests that fortification at a level of 150 μg/100 g flour may be adequate for the prevention of a significant number of NTDs.

Other

Ireland

There is no mandatory fortification of foodstuffs in Ireland, although breakfast cereals, bread and milk fortified with folic acid are available (Cornel and Erickson 1997). In 1993 the Irish Department of Health issued a recommendation that women likely to become pregnant take an additional 400 μg of folic acid daily prior to conception and during the first 12 weeks of pregnancy (Food Safety Advisory Board 1998). To increase folate intake, women are recommended to: eat more folate-rich foods; eat more foods fortified with folic acid; take folic acid supplements; or a combination of these options. There is a reliance on campaigns promoting increased dietary folate intake and supplements (McDonnell et al 2001).

Because of concerns about the possible low uptake of folic acid supplements, the Irish Food Safety Advisory Board established a Sub-Committee on Folic Acid and Neural Tube Defects (Food Safety Advisory Board 1998). This sub-committee was given the task of looking at issues relating to increasing the intake of folic acid peri-conceptionally to prevent NTDs in Ireland, and commenced its work in October 1996. The Sub-Committee recommended the immediate introduction of a comprehensive and sustained health promotion campaign at both a national and local level to promote the use of peri-conceptional folic acid. In addition, the Sub-Committee recommended the examination of fortification of a staple food or foods with folic acid as an alternative or complementary strategy. The evaluation of peri-conceptional use of folic acid supplements was also recommended.

As a result of the report by the Sub-Committee, a document looking at the benefits and risks associated with fortification of flour with folic acid is currently being prepared and will be made available in mid-2003.

Netherlands

The Netherlands does not have a policy of increasing folic acid intake through fortification. Since November 1993 it has been recommending that all women planning a pregnancy take 500 μg folic acid daily, starting four weeks before conception and continuing until eight weeks after pregnancy is confirmed (de Walle 2001).

In September 1995 the Ministry of Health, Welfare and Sports initiated a mass media campaign about folic acid for health professionals and the general public. A study looking at whether the campaign achieved its aims found an overall increase in folic acid awareness and use among women of childbearing age (van der Pal-de Bruin et al 2000). One year after the conclusion of the campaign 77 percent of all respondents reported knowing about folic acid (compared to 42 percent in 1995). There was also an increase in the percentage of women who used folic acid correctly (21 percent in 1996 compared to 4.8 percent in 1995). No decrease in the difference in use between lower- and higher-educated women was found, however.

It must be noted that the campaign, although intensive, ran only for a short period of time. It is unknown whether these increases in folic acid awareness and use can be maintained.

Chile

Because of the lack of legislation allowing therapeutic abortions, the prevalence of NTDs has remained the same in Chile over the past 30 years (Freire et al 2000).

Chile has been fortifying wheat flour since January 2000 at a level of 220 μg/100 g (Freire et al 2000; Hirsch et al 2002). Baseline information suggests that, at this level of fortification, women would be consuming an average of approximately 490 μg folic acid daily (Freire et al 2000). An evaluation is currently under way in Chile to assess any increase in serum folate and red-cell folate levels in women of childbearing age after the introduction of fortification (Freire et al 2000). The evaluation will also measure any change in the prevalence of NTDs post-fortification.

Part III: Current Situation In New Zealand

Epidemiology

Neural tube defects

The New Zealand Birth Defects Monitoring Programme (NZBDMP), established in 1977, monitors the prevalence at birth of NTDs as well as other birth defects. The programme routinely collects data on all livebirths with a diagnosed birth defect born in, or admitted to, a public hospital. Quarterly and annual tables are available and are also submitted to the International Clearinghouse for Birth Defects Monitoring Systems (ICBDMS) in Rome.

Epidemiological data on the prevalence of NTDs were sourced from the NZBDMP database for birth defects among livebirths between 1996 and 2000. Data on stillbirths for the same period were sourced from the New Zealand Health Information Service (NZHIS). Data from 1998 to 2000 on therapeutic abortions were obtained from Statistics New Zealand, who process data from the Abortion Supervisory Committee. Denominator data were sourced from NZHIS (total live- and stillbirths) and the Abortion Supervisory Committee reports (total abortions).

Historical data from 1980 to 1999 on the prevalence of NTDs in New Zealand were obtained from the ICBDMS 2000 Annual Report.

*Prevalence**

The numbers of NTDs in New Zealand, including livebirths, stillbirths and abortions from 1996 to 2000 are shown in Table 2. Data on stillbirths for 2000 are not yet available from NZHIS (C Lewis, personal communication, September 2002). Data on therapeutic abortions for an NTD-affected pregnancy prior to 1998 are unavailable (B Borman, personal communication, September 2002).

* Prevalence is defined as the number of existing cases of a disease/condition in the total population at a given point in time. Incidence is the number of new cases of a disease/condition during a given period of time in the total population at risk. Because we do not know the number of pregnancies that resulted in a miscarriage, we are unable to quantify the *incidence* of NTDs as we cannot quantify the total population at risk of having a birth defect. As a consequence, when the epidemiology of NTDs (and any other birth defect) is described, prevalence is used rather than incidence (Hennekens et al 1987).

Table 2: Neural tube defects in New Zealand, 1996–2000

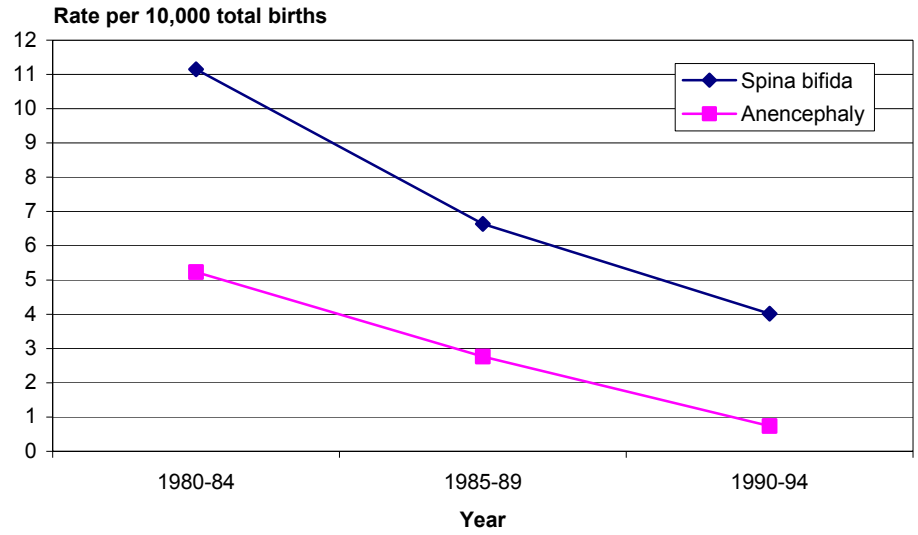
Neural tube defects	1996	1997	1998[1]	1999	2000
Count (numbers)					
Livebirths	33	20	26	18	22
Stillbirths	11	14	13	11	–
Terminations of pregnancy	–	–	41	38	39
Prevalence (rate per 10,000)					
Livebirths and stillbirths only	7.6	5.8	7.0	5.0	–
Livebirths, stillbirths and abortions	–	–	11.3	9.1	–

1 The 1998 statistics were affected by problems relating to the prompt registration of both live- and stillbirths, and the total numbers are estimated to be about 2500 under-reported. The lower denominator has artificially increased the rate for 1998.

In interpreting the numbers and rates of NTDs shown in Table 2, the fact that not all NTDs are diagnosed at birth needs to be acknowledged. As a result, the number of livebirths for each year is not stable as there is a 'rolling' ascertainment period of up to five years, with children added to the NZBDMP for their year of birth as they are diagnosed. As a consequence, earlier years are more likely to truly reflect the prevalence of NTDs than later years as the greater proportion of children born with NTDs in the mid-1990s are likely to have been diagnosed and added to the NZBDMP.

Approximately 80 percent of NTD livebirths in New Zealand are babies with spina bifida. The lower prevalence of anencephaly at birth may be because anencephaly is more likely to be diagnosed prenatally and aborted. Figure 1 shows the trend in both spina bifida and anencephaly live- and stillbirth prevalence in New Zealand over the period from 1980 to 1994. There has been a continuous decline in the prevalence of spina bifida births from 11.15 per 10,000 births in the period 1980–84 to 4.02 per 10,000 births in the period 1990–94 (International Clearinghouse for Birth Defects Monitoring Systems 2001). The prevalence of anencephaly has also been declining, falling from 2.23 per 10,000 in the period 1980–84 to 0.74 per 10,000 in the period 1990–94 (International Clearinghouse for Birth Defects Monitoring Systems 2001). These trends include both livebirths and stillbirths, but not therapeutic abortions. It is important to note that at the end of 1992 an H661 (medical notification of live- and stillbirths) form was no longer required. This meant that after 1992 notification of NTDs was reliant on hospital admission records. This change in ascertainment may have contributed to the decline in NTDs in the early 1990s as fewer NTDs may have been reported.

Figure 1: Prevalence at birth of spina bifida and anencephaly (live and stillbirths) in New Zealand, 1980–94



Source: International Clearinghouse for Birth Defects Monitoring Systems 2001

Since 1980 the annual total of abortions carried out has been increasing steadily – from approximately 6000 in 1980 to 15,000 in 1999 (Abortion Supervisory Committee 2000). This increase in abortions in general may have also resulted in an increase of abortions carried out for NTD-affected pregnancies, contributing to the declining rate. It is important to note that, although reporting of terminations of pregnancy is mandatory, it is not mandatory to specify the type of birth defect if this is the reason for the termination (with no supporting data to confirm the diagnosis). As a consequence, terminations for NTD-affected pregnancies are difficult to quantify.

In September 1995 the definition of foetal deaths changed the gestational boundary and birthweight (New Zealand Health Information Service 1999). Prior to 1995 foetal deaths greater than 20 completed weeks of gestation and less than 28 weeks (intermediate foetal deaths) were legally required to have a death certificate completed by the medical practitioner or midwife present at the confinement. However, there was no requirement for the birth to be registered. Consequently, prior to 1995 there was no count of the actual occurrences of intermediate foetal deaths against which the number of death certificates received by the Ministry of Health could be checked.

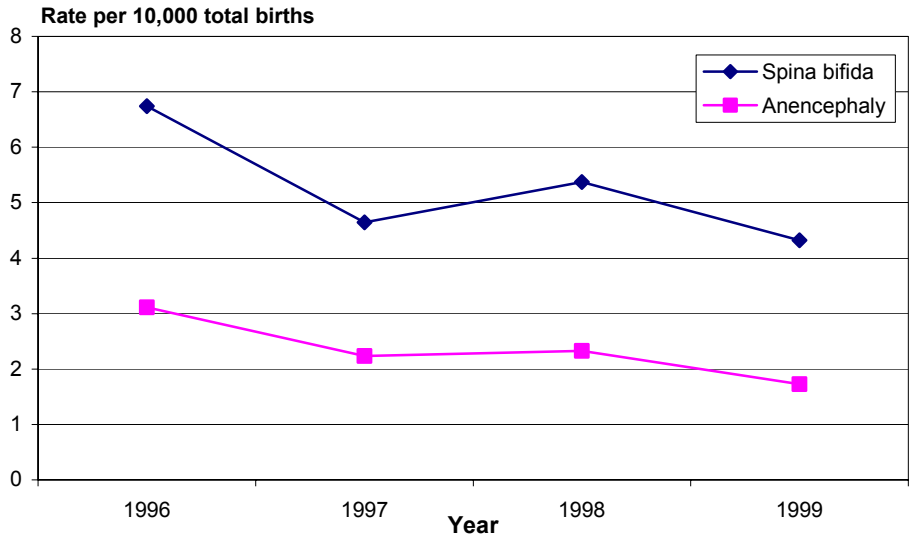
Under the Births, Deaths and Marriages Registration Act 1995, a 'stillborn child' was defined as:

> *'a dead foetus that –*
>
> *a. weighed 400 g or more when it issued from its mother; or*
>
> *b. issued from its mother after the 20th week of pregnancy'* (New Zealand Health Information Service 1999).

This change in definition meant that foetal deaths of 20–27 weeks' gestation were registered and could now be counted in the definition of a 'stillborn child'.

Figure 2 shows the trend in the prevalence of NTDs since 1996. Because of the change in stillbirth definition, the incidence of NTDs born after 1995 is not comparable to the period prior to the change in definition. A declining trend has continued since 1996, although the overall rates are higher than those seen in Figure 1 due to the change in stillbirth definition.

Figure 2: Prevalence at birth of spina bifida and anencephaly (live- and stillbirths) in New Zealand, 1996–99



Source: NZHIS and New Zealand Birth Defects Monitoring Programme

Note: The 1998 statistics were affected by problems relating to the prompt registration of both live- and stillbirths, and the total numbers are estimated to be about 2500 under-reported. The lower denominator has artificially increased the rate for 1998.

Ethnic differences

A previous study of the prevalence of anencephaly and spina bifida in New Zealand found a lower incidence of NTDs among Māori compared to non-Māori (Borman and Cryer 1993).

In the more recent NZBDMP data, the prevalence of NTDs among livebirths appears to be lower among Māori and Pacific peoples compared to non-Māori, non-Pacific people. Between 1996 and 1999 there were 22 live NTD births among Māori, seven among Pacific peoples and 68 among non-Māori, non-Pacific people out of a total of 97 NTD births. These numbers equated to rates of 3.1 per 10,000 (Pacific), 3.5 per 10,000 (Māori) and 4.8 per 10,000 (non-Māori, non-Pacific) among livebirths.

The inclusion of stillbirths in the prevalence estimates raises the Māori prevalence to equal that of non-Māori (6.7 per 10,000 live- and stillbirths). The prevalence of NTDs among Pacific peoples remains lower than that of Māori and non-Māori when both live- and stillbirths are analysed (3.5 per 10,000 live- and stillbirths).

The increase in Māori prevalence to equal that of non-Māori when stillbirths are included in the analysis suggests that a greater proportion of NTDs among Māori result in stillbirth compared to non-Māori. However, this finding should be interpreted with caution for two reasons. Firstly, there are small numbers (even when combining four years), so stable results are difficult to procure. Secondly, ethnic misclassification may have occurred either among livebirths or stillbirths, thus distorting the true prevalence of NTDs among different ethnic groups.

Overall, our results suggest that Pacific peoples have a lower prevalence of NTDs compared to other populations. With Māori the results are more difficult to interpret, with lower rates compared to non-Māori when only livebirths are analysed but similar rates between the two ethnic groups when stillbirths are included.

Cost of neural tube defects in New Zealand

It has been estimated that the 20-year cost of treating, managing and caring for one person with spina bifida in New Zealand is about $355,060 (Singh and Elliott 1997). On average there are approximately 15 children born with spina bifida per year. If we assume that this rate occurs every year for the next 20 years, then the cost of 300 people with spina bifida would come to $106,518,000 over 20 years, which equates to approximately $5 million per year.

These costs do not take into account other potential costs, such as the loss of parental income, special schooling needs, family stress, wheelchairs, crutches and occupational therapy. In addition, the emotional costs associated with stillbirths, miscarriages and therapeutic abortions cannot be quantified.

Cardiovascular disease and cancer

There is some evidence that folic acid supplementation may have benefits in terms of reducing cardiovascular and cancer risk. As a consequence, the epidemiology of these two disease groups will be briefly outlined.

Cardiovascular disease

Cardiovascular disease (CVD), which includes both ischaemic heart disease (IHD) and stroke, is the most common cause of death in New Zealand adults, contributing to 40 percent of all deaths in 1996 (Ministry of Health 1999). Although high rates occur across ethnic groups, overall, Māori and Pacific peoples have higher rates of mortality from cardiovascular disease than non-Māori, non-Pacific people.

Across the population, CVD accounts for the largest share of disability-adjusted life years (DALYs) lost: 24 percent in 1996 (Ministry of Health 2001). DALYs take into account both fatal and non-fatal outcomes due to a particular disease. Māori have higher rates of DALYs lost due to CVD compared to non-Māori.

Cancer

Cancer is the second most common cause of death among New Zealand adults, accounting for 27 percent of all deaths in 1996 (Ministry of Health 1999).

Like cardiovascular disease, cancers are a significant contributor to the burden of disease in New Zealand, ranking second to cardiovascular disease in terms of DALYs (20 percent of total DALYs) (Ministry of Health 2001). Māori have higher rates of DALYs lost due to cancer than non-Māori.

Dietary folate intake of New Zealanders

The 1997 New Zealand National Nutrition Survey (1997 NNS) found that the principal dietary sources of folate in New Zealand were vegetables (18 percent), bread (13 percent) and breakfast cereals (11 percent) (Russell et al 1999).

Approximately half of New Zealanders meet the recommended dietary intake of folate for adults, which is 200 μg/day. The 1997 NNS found that the usual daily median intake of folate from food was 242 μg (males 278 μg, females 212 μg). Women aged 25–44 years had a median intake of 213 μg. Women aged 15–18 years and 19–24 years had lower median intakes of 194 μg and 195 μg, respectively.

In general, males had higher intakes (range 256–286 μg) compared to females (range 194–222 μg). Both Māori males and females (273 μg and 198 μg, respectively) had a slightly lower intake of folate from food compared to non-Māori males and females (282 μg and 215 μg, respectively).

Comparing the 1997 NNS results to the 1991 Life in New Zealand (LINZ) survey (Life in New Zealand Activity and Health Research Unit 1992) shows that median dietary folate intakes increased 40 percent from a usual intake of 170 μg in 1991 to 242 μg in 1997. There has also been a 35 percent increase in median dietary folate intake among women aged 25–44 years from 1991 to 1997 (158 μg and 213 μg, respectively).

A Dunedin-based survey found a similar median dietary folate intake to that of the 1997 NNS among 18–45-year-old women (216 μg) (Ferguson et al 2000). In this study the highest daily intake of folate among women was 926 μg from a combination of diet and supplements. The study also looked at red blood cell concentrations as an indicator of folate status. Ninety-seven percent of the respondents had acceptable red-cell folate levels. However, only 33 percent of women had blood-cell folate concentrations greater than or equal to 906 nmol/L, a level that may be optimal for the prevention of NTDs.

Women were also questioned about their knowledge of the folate content of foods. Although approximately 70 percent of women could name cereals and breads as good sources of folic acid, only 25 percent said they knew some foods that were naturally good sources of folate. Ninety percent of these women could name at least one correct food.

Taking into account the reduced bioavailability of dietary folate, women of childbearing age in New Zealand are not receiving an adequate amount of folate to reduce the risk of an NTD-affected pregnancy. Research has found that 400 μg of synthetic folic acid is required to prevent an NTD occurrence. Because dietary folate has approximately half the bioavailability of synthetic folic acid, to consume the equivalent of 400 μg synthetic folic acid, approximately 800 μg/day of dietary folate needs to be consumed – a four-fold increase from the current median intake of approximately 200 μg. To achieve this level of dietary folate would mean consuming daily the equivalent of 500 g raw spinach or 900 g boiled spinach or raw broccoli (Bower and Wald 1995).

Overall, without supplementation or fortification, it will be difficult to increase folate intake to a level that results in a significant reduction of the prevalence of NTDs.

Folic acid policy in New Zealand

New Zealand currently has a policy of recommending that women of childbearing age take folic acid supplements four weeks prior to conception and for 12 weeks after conceiving to reduce the risk of NTDs. At the same time, legislation allows for the voluntary fortification of selected food products with specified levels of folic acid.

Supplementation

> The current recommendation in New Zealand is that women planning a pregnancy take 800 μg folic acid for four weeks prior to conception and for 12 weeks after conceiving to reduce the risk of NTDs. Women at high risk of having a baby with an NTD are advised to take 5000 μg folic acid a day for the same period of time.

In September 1993 the Public Health Commission (PHC) released an information sheet to health professionals entitled *Reducing the Chances of Spina Bifida by Taking Folic Acid* (Public Health Commission 1993). The information was also released to the public through the media. The information sheet contained the recommendation that women who could become pregnant take folic acid daily, starting four weeks before conception, and continuing daily through to the 12th week of pregnancy. If a woman had not started folic acid before becoming pregnant, it was recommended she start as early as possible after pregnancy was confirmed and continue daily to the 12th week of pregnancy. At the time the only registered medicine available for sale containing folic acid alone was a 5000 μg tablet, and this dose was recommended. Although it was made clear that diet alone cannot be relied on to increase folate levels, women were also advised to increase the amount of folate in their diet by the consumption of plenty of green vegetables and fruit.

In 1995 a lower dose (800 μg) folic acid tablet became available as a registered medicine, and this dose was subsequently recommended to women planning a pregnancy. The higher-dose 5000 μg tablets continued to be recommended for women at high risk of having a baby with an NTD (Public Health Commission 1995a). Information sheets on the importance of folic acid were also made available to women planning a pregnancy (Public Health Commission 1995b). At the same time, the Ministry of Health stated its commitment to investigating whether and to what extent the food supply should be fortified with folic acid.

Folic acid supplements can be bought over the counter at pharmacies or on prescription (Table 3). The price of a year's supply of folic acid supplements is in the range of $12 to $40. An 800 μg folic acid tablet is recommended in New Zealand simply because 400 μg tablets of folic acid are not currently available as a registered medicine in this country.

Table 3: Price of folic acid supplements registered as medicines

Folic acid supplements	Price	Amount
Over-the-counter (800 μg)	$9.95	120 tablets (four months' supply)
Prescription without community services card (800 μg and 5000 μg)	$9.95	90 tablets (three months' supply)
Prescription with community services card (800 μg and 5000 μg)	$3.00	90 tablets (three months' supply)

Folic acid supplement use

Three New Zealand studies looking specifically at folic acid supplementation have found that although women are aware of the relationship between folate and NTDs, the reality is that this knowledge does not result in action.

A survey carried out by Bourn and Newton in 1998 in New Zealand found that only 56 percent of women aged 25–44 years were aware of the relationship between folate / folic acid and NTDs (Bourn and Newton 2000).

A Dunedin-based study found that 38 percent of women interviewed knew that folate / folic acid helped prevent birth defects such as spina bifida, but only 11 percent of those who had been pregnant in the previous five years had taken a folic acid supplement prior to pregnancy (Ferguson et al 2000).

A study carried out in Christchurch in 1999 (Schader and Corwin 1999) also looking at the proportion of women using folic acid supplements in early pregnancy had similar findings to the Dunedin study (Ferguson et al 2000). Ninety-one percent of the women studied had heard of folic acid, and 63 percent knew that folic acid reduces the risk of spina bifida. However, only 17 percent had taken peri-conceptional folic acid supplements – the majority of women having taken these supplements had planned their pregnancy. Fifty-five percent of pregnancies were unplanned and only three women in this group had taken peri-conceptional folic acid. A limitation of this study is that it is not generalisable to the rest of the New Zealand population as it was under-representative of Māori, Pacific

peoples and other minority ethnic groups (81 percent of the participants were of New Zealand European background).

A study of 504 pregnant female volunteers in the northern half of the North Island of New Zealand looked at ethnic differences in supplement use. Overall, 37 percent of respondents had taken folic acid supplements in the year before their pregnancy (Watson and McDonald 1999). Almost half of 'European' women had taken a folic acid supplement in the year prior to pregnancy compared to 10 percent of Māori and 8.7 percent of Pacific peoples. It is not clear, however, from the study report what effect recall bias may have on the results. In addition, there is no indication about the frequency of supplement use in the year before pregnancy, and whether the amount of folic acid taken was greater than 400 μg (if it was part of a dietary supplement, it might have been a lower dose). However, this study gives an indication that Māori and Pacific women are less likely to take folic acid supplements.

There is evidence that, in New Zealand, approximately 50 percent of pregnancies are unplanned (Schader and Corwin 1999). This proportion is comparable to that cited overseas (Czeizel 1995; COMA 2000; Sillender 2000; McDonnell et al 2001).

There has been no publicly funded awareness campaign in New Zealand surrounding the consumption of folic acid supplements by women of childbearing age. However, since 1999 New Zealand CCS has been undertaking an annual folate awareness campaign, which focuses around a 'folate awareness day'. If an ongoing campaign were to occur, it would be expected that there would be some increase in the number of women of childbearing age who would consume folic acid supplements. Overseas evidence suggests that where campaigns do occur they have resulted in up to 40 percent of women planning a pregnancy taking folic acid during the recommended period. However, the considerable proportion of unplanned pregnancies in the New Zealand population suggests that the supplementation policy, on its own, will not be effective for a significant number of women.

Dietary supplement use

The supplements described above are registered medicines and can only be obtained through a pharmacy, either over the counter or by prescription. Folic acid is also present in dietary supplements (such as multivitamins), which can be bought from supermarkets, pharmacies and health shops. Dietary supplements are not regulated medicines and can currently only contain up to 300 μg of folic acid per daily dose (Dietary Supplements Regulations 1985).

The 1997 NNS found that 51 percent of the New Zealand population (59 percent of females, 42 percent of males) were regular or occasional users of vitamin and/or mineral supplements (Russell et al 1999) (see Table 4).

Table 4: Vitamin and mineral supplement use in the last year, by sex and age group, 1997

	Age group (years)	Consumption frequency (%)		Percentage of population consuming supplement	
		Regular[1]	Occasional[2]	Multivitamin and/or mineral	Folic acid
New Zealand population	15+	28	23	19	1
Male	15–18	19	36	17	0
	19–24	18	33	15	0
	25–44	21	26	16	0
	45–64	22	13	10	0
	65–74	21	4	8	0
	75+	19	5	13	0
	15+	21	21	14	0
Female	15–18	29	37	16	0
	19–24	33	36	32	0
	25–44	37	27	27	2
	45–64	36	20	24	0
	65–74	35	15	16	1
	75+	26	8	11	0
	15+	34	25	24	1

Source: Russell et al 1999

1 'Regular' includes all those who used any supplement at least once per week.

2 'Occasional' includes all those who used any supplement, no more than three times per month, during the year preceding the survey.

Only 2 percent of females aged 25–44 had consumed folic acid dietary supplements in the year preceding the survey. None of the 15–24-year-old females sampled had consumed folic acid supplements.

Among the 25–44-year-olds, 3 percent of New Zealand Europeans and other females consumed folic acid dietary supplements compared to 1 percent of Māori and no Pacific women (see Table 5).

Table 5: Vitamin and supplement use among females in the last year, by ethnic group, 1997

	Age group (years)	Consumption frequency (%)		Percentage of population consuming supplement	
		Regular[1]	Occasional[2]	Multivitamin and/or mineral	Folic acid
NZ Māori	15–24	22	20	9	0
	25–44	29	25	20	1
	45+	22	14	18	0
	15+	25	21	16	0
Pacific peoples	15–24[3]	10	12	6	0
	25–44	11	14	9	0
	45+[3]	12	8	11	0
	15+	11	12	9	0
Other	15–24	35	43	31	0
	25–44	39	29	29	3
	45+	35	17	20	0
	15+	37	26	26	1

Source: Russell et al 1999

1 'Regular' includes all those who used any supplement at least once per week.

2 'Occasional' includes all those who used any supplement, no more than three times per month, during the year preceding the survey.

3 Limited sample size, 25 < n < 50, so caution should be exercised in interpretation of data.

Folic acid levels found in multivitamin tablets range from 30 to 350 μg (Borman and Brown 1999). One dietary supplement containing iron and folic acid has been found to contain 350 μg of folic acid even though the Dietary Supplements Regulations 1985 currently only permit levels up to 300 μg. Dietary supplements containing solely folic acid have been found to contain levels up to 300 μg (Borman and Brown 1999). As a consequence, even if greater proportions of women were to take folic acid-containing dietary supplements, the level of folic acid (multivitamin and folic acid only) in these supplements may not provide sufficient daily folic acid to prevent NTDs.

Voluntary fortification in New Zealand

In December 1995 an agreement to establish a joint food-setting system between Australia and New Zealand was signed. In 1995 legislation to allow the voluntary fortification of specified food products with folic acid was passed in Australia. The establishment of ANZFA and the desire for consistency in food standards between New Zealand and Australia resulted in the adoption of similar regulations in New Zealand. The Food Regulations 1984 were amended to allow for the voluntary fortification of specified food products with folic acid in New Zealand, effective from January 1996.

A list of the foods that can be fortified with folic acid in New Zealand under the Food Regulations 1984 can be found in Appendix 2.

Based on New Zealand Manufactured Food Database information, for the year ending December 2002 there were 81 foods reported by manufacturers to be fortified with folic acid (New Zealand Manufactured Foods Database 2002). Over half of these foods were breakfast cereals. The New Zealand Manufactured Food Database is not comprehensive as it relies on food manufacturers to participate voluntarily and does not usually include non-packaged food. As a result, the list provided may not be a complete list of all manufactured food currently fortified. Appendix 3 contains a list of foods fortified with folic acid in New Zealand for the year ending December 2002.

In November 1998 ANZFA granted approval for a folate and NTD health claim (P170) for certain food products as a pilot in a wider review of health claims (Watson and Watson 2001). The pilot was adopted in New Zealand and the Medicines Regulations 1984 were amended to allow a folate health claim. Foods (both non-fortified and fortified) containing at least 40 μg of folate per serving and the same criteria as Australia for sugar, fat and salt were permitted to carry a health claim. The uptake of the health claim by the New Zealand food industry has been low (E Aitken, personal communication, September 2002).

In order to estimate the change in folic acid intake following voluntary fortification, the University of Otago has conducted a modelling exercise for the Ministry of Health using the 1997 NNS database (Newton et al 2001). The 1997 NNS data and the DIAMOND computer programme were used to estimate folic acid intakes from various simulated universal fortification scenarios. The DIAMOND computer programme has been developed by ANZFA for the purpose of modelling different scenarios including fortification and assessing levels of contaminants.

The authors estimated a median increase in folic acid intake for women of childbearing age of 17 μg/day folic acid intake by August 2000 following the introduction of voluntary fortification in 1996. In addition, less than 4 percent of women were achieving folic acid intakes greater than 400 μg/day. Over 60 percent of women were receiving no additional folic acid under voluntary fortification. Only 27 percent of the target population consumed ready-to-eat breakfast cereals, which account for the majority of folic acid-fortified foods in New Zealand. The results presented need to take into consideration that they are based on a 1997 survey and that food consumption patterns may have changed since then, although major changes are unlikely.

Key stakeholders from the Millers' and Bakers' Associations were contacted regarding their views on fortification of foods with folic acid. The two associations do not have a collective view on fortification. The NZ Association of Bakers is wary of moving collectively towards fortification, unless it has an assurance of minimal commercial risk. Its requirement is that consumers and political parties support the addition of folic acid to a staple food. In addition, because 50 percent of flour produced is used outside the NZ Association of Bakers' companies (eg, by supermarkets, confectioneries and the biscuit industry) the association stresses that the support of these industries is also important. The NZ Association of Bakers is concerned that Australian competitors might be able to capitalise on a negative consumer reaction and gain market share with non-fortified flour.

New Zealand CCS supports folic acid fortification of flour or bread and has been advocating to the Millers' and Bakers' Associations that voluntary fortification be fully implemented (H Potter, personal communication, September 2002).

Mandatory fortification

Because implementation by the food industry (apart from breakfast cereal manufacturers) of existing voluntary fortification provisions has been poor, mandatory fortification is another option in New Zealand. Because this would clarify what foods are fortified and at what level, monitoring of health benefits would be more feasible under mandatory fortification.

The University of Otago modelling exercise already described looked at the different levels of fortification that would ensure women of childbearing age receive at least 400 μg folic acid/day while minimising exposure to high levels of folic acid (Newton et al 2001). In the study, three food vehicles were selected for fortification: bread, flour* or milk. These food vehicles were selected as they are commonly consumed by the target population: bread and milk by approximately 80 percent of the target population, and white flour by approximately 90 percent of the target population. Using these food vehicles, 12 fortification scenarios were modelled using the DIAMOND programme, with four fortification levels for each food vehicle.

Table 6 summarises the proportions of New Zealanders that would be exposed to folic acid intakes exceeding the TUIL under the different fortification scenarios.

Table 6: Percentage of the adult New Zealand population, by sex and age group, receiving folic acid intakes above the tolerable upper intake levels, from fortified foods and folic acid supplements, under simulated fortification scenarios[1, 2]

Fortification scenario		General population (%)	15–19 years		20–46 years		50–69 years		70+ years	
Fortification vehicle	Fortification level		Females (%)	Males (%)	Females (%)	Males (%)	Females (%)	Males (%)	Females (%)	Males (%)
Breads	100 μg/100 g	0.2	0	0.4	0.4	0.1	0.1	0.1	0	0
	200 μg/100 g[3]	0.9	1.1	2.8	0.9	1.3	0.1	0.2	0	0
	300 μg/100 g	3.9	3.4	12.9	2.4	6.9	0.6	2.2	0.9	1.3
	400 μg/100 g	10.8	12.4	23.3	7	19.5	2.2	9	1.5	2.8
White flour	140 μg/100 g	0.5	0	2.6	1	0.1	0.1	0.2	0	0
	285 μg/100 g[3]	2.1	2.7	8.6	2.3	2.8	0.3	0.6	0	0
	430 μg/100 g	6.8	10.2	17.3	4.8	11.8	1.1	3.4	1.9	1.7
	570 μ/100 g	14.3	22.3	32.2	9.9	25	3.7	9.5	2.1	2.7
Liquid milk	50 μg/200 mL	0.3	0	0	0.7	0.1	0.1	0	0	0
	100 μg/200 mL	0.9	0.3	1.2	1.2	1.5	0.2	0.3	0	0
	150 μg/200 mL	2.1	6.1	4.6	2.7	2.2	0.2	0.6	0.2	0.8
	200 μg/200 mL	2.2	6.1	6.6	2.8	2.4	0.2	0.6	0.2	0.8

Source: Newton et al 2001

1 Values are population-weighted estimates.

2 Tolerable upper intake level (TUIL) for 14–18 years is 800 μg folic acid/day and 1000 μg folic acid/day for 19 years and over.

3 Current permitted levels of fortification.

* The term 'flour' in this document refers to wheat flour.

Table 7 shows the estimated percentages of women of childbearing age consuming specified amounts of folic acid from fortified foods and dietary supplements under the simulated fortification scenarios.

Table 7: Estimated percentages of women of childbearing age consuming specified amounts of folic acid from fortified foods and dietary supplements, under simulated fortification scenarios

Fortification scenario		Percentage of women (15–49)		
Fortification vehicle	**Fortification level**	**0–199 μg/day**	**200–399 μg/day**	**≥ 400 μg/day**
Breads	100 μg/100 g	85.6	10.1	4.4
	200 μg/100 g*	54.6	31.4	14.0
	300 μg/100 g	39.7	29.6	30.7
	400 μg/100 g	26.3	26.8	46.9
White flour	140 μg/100 g	80.1	13.9	6.0
	285 μg/100 g*	44.9	34.6	20.5
	430 μg/100 g	27.8	30.8	41.5
	570 μg/100 g	20.0	24.5	55.5
Liquid milk	50 μg/200 mL	79.5	14.0	6.5
	100 μg/200 mL	65.7	22.0	12.3
	150 μg/200 mL	57.3	25.1	17.6
	200 μg/200 mL	55.9	25.6	18.4

Source: Newton et al 2001

* Current permitted levels of fortification

Tables 6 and 7 show that it is difficult to fortify food at a level that ensures that the majority of women of childbearing age will consume greater than 400 μg folic acid/day without many in the general population being exposed to folic acid in amounts in excess of the TUIL.

The two options most attractive for New Zealand are fortification of white flour at a level of 140 μg/100 g or bread at 200 μg/100 g. There has been a decline in the prevalence of NTDs in both the United States and Canada since the introduction of mandatory fortification of flour at a level of 140–150 μg/100 g. As a consequence, these levels of fortification (bread 200 μg/100 g or white flour 140 μg/100 g) may be enough to see benefits in the target population. In addition, these fortification levels are unlikely to expose sub-populations to excessive amounts of folic acid.

It must be noted that the scenarios modelled above do not apply to children aged under 15 years, as they were not included in the 1997 NNS. Because children are high consumers of non-bread products containing flour, as well as bread and milk, the above scenarios may expose them to high levels of folic acid, particularly as they have a lower TUIL than adults. The Children's Nutrition Survey, currently under way in New Zealand, could be used for further modelling and assisting with planning for appropriate fortification scenarios.

Fortification of flour at 140 μg/100 g

Fortifying white flour at a level of 140 μg/100 g would result in fortification levels similar to those mandated in the United States and Canada. At these levels, very small proportions of the population would be consuming levels above the TUIL (0.5 percent of the general population and less than 0.2 percent of those aged over 50 years). Approximately 6 percent of women of childbearing age would be consuming levels above 400 μg folic acid/day, with 20 percent exposed to levels between 200 μg and 400 μg.

Fortification of bread at 200 μg/100 g

Another option for fortification would be the fortification of breads at 200 μg/100 g. This level of fortification would result in approximately 31 percent of women of childbearing age consuming 200–399 μg/day folic acid and 14 percent consuming more than 400 μg/day. Although this fortification level would result in fewer women receiving the recommended dose of folic acid per day compared to higher levels, modelling suggests that only a very small proportion of the total population would exceed their TUIL (0.9 percent of the general population and less than 0.2 percent of those aged over 50 years).

Following mandatory fortification, Nova Scotia has experienced an approximately 50 percent decline in the prevalence of NTDs. However, Nova Scotia has a higher prevalence of NTDs (25.8 per 10,000 births including therapeutic abortions) compared to New Zealand (9.0 per 10,000 births including therapeutic abortions). As a consequence, if fortification is the cause of the decline in Nova Scotia, with similar fortification levels it is unlikely that New Zealand will experience the same decrease in the prevalence of NTDs. On the other hand, the United States has a similar prevalence of NTDs as New Zealand. A 19 percent decrease in NTDs occurred in the period following folic acid fortification in the US. If the decline in NTDs in the US was due to fortification, then using the same fortification levels in New Zealand could result in approximately 13–16 NTD pregnancies being avoided per year.

Costs of mandatory fortification

It is estimated that the cost to the baking and milling industry of fortifying all flour milled at a level of 140 μg/100 g is approximately $2.5 million for the first year ($1 million for the installation of dosing equipment at each mill, $1.2–1.6 million labelling costs and $80,000–$120,000 folic acid) (L Powell, personal communication, April 2003)). After the first year, the costs associated with fortification will only include the cost of folic acid ($80,000–$120,000).

These costs are for *all* flour. Further work needs to be done to estimate the costs associated with fortifying only bread-making flour. The only difference in costs would be at the fortification level, as equipment and packaging costs are likely to be similar. It is unlikely that the costs involved in fortifying bread-making flour would be much greater than those estimated above.

It is estimated that the financial burden of treating spina bifida cases in New Zealand equates to approximately $5 million per year. With a fortification level of 140 μg/100 g white flour, as is currently in place in the United States, it is estimated that there would be 20 percent fewer spina bifida cases per year. If New Zealand selects a similar level of fortification, a saving of approximately $1 million per year would be made.

Compared to white flour being fortified at a level of 140 μg/100 g, approximately twice as many women would be exposed to folic acid levels greater than 400 μg if bread were fortified at 200 μg/100 g. This would result in 40 percent fewer spina bifida cases per year, resulting in a saving of $2 million annually.

Once fortification equipment has been installed and labelling changed, the annual cost of fortifying is small compared to that of treating spina bifida cases.

The evaluation of the Australian voluntary fortification programme found evidence of small differences in price between fortified and unfortified products, with fortified foods being slightly more expensive. If mandatory fortification is implemented, care has to be taken to ensure price increases do not further disadvantage sub-populations already living in poverty.

According to the fortification modelling, approximately 0.2 percent of adults over 50 years old would be exposed to folic acid levels greater than 1000 μg per day. Applying this figure to the 2001 census population over 50 years (n = 1,023,426), approximately 2000 adults may be exposed to high levels of folic acid. Of these adults, approximately 5–10 percent may have vitamin B_{12} deficiency. Levels of fortification of 140 μg/100 g (flour) or 200 μg/100 g (bread) may thus put 100–200 people at risk of developing neurological complications due to masking of the vitamin deficiency. This estimation assumes undiagnosed vitamin B_{12} deficiency, a situation that is unlikely to occur in all 100–200 people.

Technical considerations

Technically, folic acid can be added to flour after it has been milled and prior to its being packaged and blended – either to all flour or just to bread-making flour. Adding components of wheat back into white flour produces wholemeal and wholegrain flour. Folic acid, if it is to be added, will be added to white flour prior to the production of wholemeal and wholegrain flour.

Folic acid can also be added to bread at the improver stage. However, as with adding folic acid at the flourmill, it is difficult to exclude wholemeal and wholegrain bread from white bread as they often use the same improver. The advantage of adding folic acid to bread at the improver stage is that this process is better controlled.

To ensure that the amount of fortificant in the product as purchased is not less than the amount claimed on the label, manufacturers usually add more nutrients than necessary (overage) to take account of losses during processing and storage (COMA 2000). If overage were used in fortifying foods with folic acid, people would be exposed to higher than expected levels. A study after the introduction of mandatory fortification in the US found that for many enriched cereal-grain products, there were higher amounts of folate on analysis than indicated on the food label (Rader et al 2000). We do not know to what extent overage occurs in New Zealand. If fortification of bread or white flour is implemented, regular monitoring of fortification levels of folic acid within food products should be carried out.

Other examples of fortification in New Zealand include the fortification of salt with iodine (to prevent diseases caused by iodine deficiency such as goitre, stunted growth and mental retardation in children). Water supplies around the country are also fluoridated to prevent the occurrence of dental caries. In these instances of fortification, the initiative has been successful in providing health benefits to a large number of the population at minimal cost while maintaining safe intakes.

Part IV: Policy Options

The evidence connecting folic acid to reduced risk for cardiovascular disease, cancer and Alzheimer's disease is not definitive, and will not be considered in the development of policy options. The policy options presented focus on increasing folate intake among women of childbearing age to decrease the incidence of NTDs.

There are four approaches for improving folate status among women of childbearing age:

- increasing dietary folate intake by promoting consumption of vegetables, fruit and legumes
- increasing consumption of folic acid supplements
- voluntary fortification of staple foods with folic acid
- mandatory fortification of staple foods with folic acid.

This section outlines the policy implications of each of these four options. The advantages and disadvantages of each option will be discussed by considering the following issues:

- ensuring women of childbearing age receive adequate amounts of folic acid to prevent an NTD-affected pregnancy
- not exposing sub-populations to high levels of folic acid
- respecting consumer choice
- ensuring equitable outcomes.

Policy options were identified by considering the literature review, international experience and consultation with stakeholders. Each policy option was then analysed taking into account both international and New Zealand evidence for its effectiveness, acceptability, advantages and disadvantages. The analysis was used to formulate recommendations.

What needs to be considered in each policy option is the extent to which each approach provides the greatest benefits for preventing NTD-affected pregnancies, while avoiding harm in other population groups and preserving consumer choice. Any issues with regard to implementation of the different policy options will also be considered.

Option 1: Increased dietary folate intake

This option preserves consumer choice. It is also unlikely, under this policy scenario, that anyone in the population will be exposed to folate levels high enough to potentially cause adverse health effects.

As discussed in the previous chapter, on its own this option is unlikely to result in women of childbearing age consuming adequate amounts of folate to prevent NTDs. The consumption of a diet with plenty of vegetables and fruit should, however, continue to be recommended to the general population for its wider health benefits.

Option 1: Increased dietary folate intake

Recommendation:

- Continue the recommendation that women of childbearing age eat folate-rich foods as part of a healthy diet.

This option is not recommended on its own as a policy to increase folate intake.

Option 2: Folic acid supplementation

The key advantage of this option is that it targets the group that current research suggests would derive the most benefit from folic acid supplementation – women planning a pregnancy. The dose consumed by the women is controlled – only 800 μg tablets are available for the majority of women. As a consequence, the risk of 'overdosing' on folic acid is reduced. Consumer choice is retained as women are able to choose whether to take folic acid supplements.

However, this policy is not recommended on its own because of the problems discussed in the previous chapter. These problems include:

- inadequate knowledge of the benefits of folic acid, resulting in poor compliance with supplementation, even among women planning a pregnancy
- Māori, Pacific women, women of low income, and women with unplanned pregnancies are less likely to consume supplements
- the financial cost of supplements may be a barrier to some women
- lack of knowledge of the benefits of folic acid among health professionals.

It is therefore recommended that this policy of advising women planning a pregnancy to take folic acid daily and improving nutrition continues in New Zealand, either in combination with voluntary fortification (status quo) or mandatory fortification.

Some of the problems associated with supplementation might be overcome with awareness and educational campaigns and strategies to reach the 'hard to reach'. Because neither voluntary nor mandatory fortification is likely to occur at a level that will be able to provide the recommended folic acid dose to the majority of women of childbearing age, an effort to increase supplementation in New Zealand needs to occur. As a consequence, a comprehensive campaign to increase consumption of folic acid supplements and fortified foods during the peri-conceptional period is recommended.

Campaigns need to be ongoing and comprehensive to achieve any results. Campaigns conducted overseas have only resulted in 20 to 40 percent of women planning a pregnancy taking folic acid during the recommended period (Bower et al 1997; COMA 2000; de Walle 2001). Although this proportion may seem low, supplementation, in combination with a voluntary fortification policy and a health promotion campaign, has the potential to reduce the prevalence of NTDs, as has been shown in Western Australia (Bower et al 2002). If fortification is mandatory, the incidence of NTDs can potentially be reduced even further.

Most recent evidence shows that 400 μg folic acid daily is adequate to reduce the occurrence of NTDs (Berry et al 1999). Currently, the lowest dose of folic acid available as a registered medicine in New Zealand is 800 μg. It is recommended that the Ministry of Health review the availability of a lower-dose folic acid tablet for women planning a pregnancy in light of recent evidence. The lower dose is recommended as a registered medicine as this will ensure that access to folic acid supplements by women with a Community Services Card will remain affordable.

Option 2: Folic acid supplementation

Recommendations:

- Continue the policy of recommending daily folic acid supplements to women planning a pregnancy in New Zealand, either in combination with voluntary fortification (status quo) or with mandatory fortification.
- Make a lower dose of folic acid (400 μg), as a registered medicine, available to women planning a pregnancy.
- Conduct a comprehensive, ongoing national campaign to increase awareness of and consumption of folic acid supplements in women planning a pregnancy.

Compared to options 1 and 2 (which are targeted approaches), the fortification options 3 and 4 have the potential to increase folate levels in the whole population. Fortification has the advantage that the benefits of folic acid, if it is added to a staple food, are available across the population regardless of socioeconomic status, gender or age and do not depend on knowledge and motivation. As a result, there is the potential for all women of childbearing age (including Māori, Pacific women and low-income women) to be exposed to increased amounts of folate / folic acid. Fortification therefore has the potential to greatly reduce the incidence of NTDs even among those with unplanned pregnancies.

On the other hand, disadvantages of fortification include the exposure of the whole population to folic acid, whether they want it or not. In particular, if all flour is fortified there is concern that individuals will lose control over what they eat as flour is present in a large number of foods. Because exposure levels are variable, fortification has the potential to expose certain populations to folic acid levels exceeding the TUIL.

The consideration of fortification as a policy option needs to take into account the level of fortification that will convey the most benefit and result in the least harm. There are two options with regards to folic acid fortification of food products: voluntary fortification or mandatory fortification.

Option 3: Voluntary fortification (status quo)

Currently, legislation in New Zealand allows the voluntary fortification with folic acid of food products. Apart from breakfast cereal manufacturers, uptake of voluntary fortification in New Zealand has been very limited. An update of the food composition database used for the 1997 NNS has found that, taking into account the number of foods fortified by August 2000, fewer than 4 percent of women were achieving folic acid intakes (from fortified foods and dietary supplements) greater than 400 μg/day (Newton et al 2001). Over 60 percent of women were receiving no additional folic acid under voluntary fortification. These figures reflect the fact that only 27 percent of women of childbearing age consume ready-to-eat breakfast cereals. Eighty to ninety percent of the target population consume bread and white flour. If voluntary fortification is to be successful in reducing NTD-affected births, either bread or flour needs to be fortified.

In 2001 the Ministry of Health held a meeting with the NZ Association of Bakers regarding the voluntary uptake of folic acid fortification. The NZ Association of Bakers requested full cross-party (political) support for fortification. Representatives of almost all political parties signed a letter in July 2001 confirming strong cross-party support for the voluntary fortification of bread. The letter included a statement regarding having a range of clearly labelled products available – both fortified and unfortified – for consumers to choose from. The NZ Association of Bakers requested that this element of choice be removed, as it is technically difficult to implement. Although there is general support across political parties for voluntary fortification, some members also wish to ensure an element of choice.

The current Minister of Health has indicated that she is ready to request FSANZ to explore mandatory folic acid fortification.

Barriers to full fortification under a voluntary policy include:

- the fear among food manufacturers that if they fortify their food they will lose a 'competitive edge' – particularly if consumers prefer non-fortified foods
- the wariness of food manufacturers to carry the risk of vitamin B_{12} deficiency being masked in elderly people consuming their products.

A key disadvantage of voluntary fortification over mandatory fortification is not only the poor uptake, but also that it is more difficult to monitor. With mandatory fortification it is better known what foods are fortified, and as a result any health benefits or adverse effects associated with fortification can be monitored more easily. On the other hand, voluntary fortification, because it is unlikely to be universal will preserve an element of consumer choice.

Voluntary fortification in combination with supplementation has been associated with a 30 percent decline in NTDs in Western Australia since 1996 (Bower et al 2002). This decline has been attributed to ongoing health promotion campaigns and fortification of selected foods. A recent case control study in Western Australia looking at sources of folate in women's diets found that 93 percent of women received some of their daily folate from fortified foods, and about a third had over 200 μg folate from fortified foods daily (C Bower, personal communication, March 2003).

Increased uptake of voluntary fortification by the food industry will only occur if there is an increased demand for folic acid-fortified foods. Demand will only increase if awareness of the benefits of folic acid increases among the New Zealand population. Again, a sustained health promotion campaign will be of benefit for improving folate intakes through a policy of voluntary fortification.

Option 4: Mandatory fortification

As sectors of the food industry appear to be reluctant to fortify food products voluntarily, mandatory fortification needs to be considered as an option.

The University of Otago modelling study recommends bread or flour as the preferred vehicles for mandatory fortification (Newton et al 2001). Further investigation of the technical issues surrounding the most appropriate vehicle (bread or flour) needs to occur. It must be kept in mind that the fortification scenarios were modelled using adult data. Further work needs to be done to ensure that children under 15 years will not be exceeding their TUIL. Alternative options for fortification levels may need to be considered if results suggest current recommendations will expose too many children to levels above the TUIL. Because of this, although possible levels of fortification were discussed in the previous chapter, this report will not be recommending specific levels of fortification. Appropriate levels will need to be investigated if a decision to proceed with mandatory fortification is made.

In addition, the University of Otago modelling did not consider the combined effects of voluntary fortification, as it now exists, on mandatory fortification. Some populations (eg, young males) would be consuming more than the TUIL if both bread or flour and breakfast cereals are fortified. If mandatory fortification proceeds, consideration needs to be made to limiting or removing some of the voluntary provisions.

As discussed in the previous chapter, because mandatory fortification is likely to only result in 6–14 percent of women of childbearing age consuming folic acid levels of greater than 400 μg, a supplementation policy needs to continue in combination with this policy.

Although voluntary fortification is currently permitted under the Australia New Zealand Food Standards Code, a change in the regulations would be required to make the provisions mandatory. For mandatory fortification to occur, an application would have to be made to go through the joint food standards setting process. This process is likely to take at least a year and is more likely to be accepted if there is support from Australia. Full public consultation will occur as part of this process.

Taking into account that it might be difficult to exclude wholemeal flour or bread from being fortified from a technical perspective, it will be difficult to provide consumer choice under the proposed scenarios. Allowing organic flour and bread to remain unfortified could preserve consumer choice. Doing this would mean that there will be parts of the population who may not be able to afford to make the choice, as organic goods tend to be more expensive. The provision of consumer choice needs to be weighed against the greater benefits the fortification of flour or bread with folic acid provides. Further discussion on whether an element of choice can be preserved needs to occur.

Other issues surrounding fortification

Masking of vitamin B_{12} deficiency

One of the major concerns surrounding a universal fortification policy is that certain sub-populations would be exposed to high levels of folic acid. This is of particular concern in the elderly who have an increased vulnerability to vitamin B_{12} deficiency. Indeed, this was the reason why the UK Food Standards Agency recently decided against mandatory fortification. Based on the University of Otago modelling work, levels of fortification of 140 μg/100 g flour or 200 μg/100 g bread will only expose a very small proportion of elderly people to high enough folic acid levels that would put them at risk of masking vitamin B_{12} deficiency.

The direct and indirect costs of neurologic sequelae among individuals with undiagnosed vitamin B_{12} deficiency need to be estimated. The costs of diagnosing vitamin B_{12} deficiency also need to be considered.

Monitoring

Whether voluntary fortification continues or mandatory fortification is implemented, monitoring of folate, vitamin B_{12} and homocysteine levels in the New Zealand population is required. The studies by the University of Otago provide some information on baseline serum and red-cell folate levels. The University of Otago has also analysed serum from the 1997 NNS for vitamin B_{12} levels.

The Ministry of Health should consider the inclusion of folate (serum and red blood cell), vitamin B_{12} and homocysteine levels in the next National Nutrition Survey (not due until 2006/07).

The New Zealand Birth Defects Monitoring Programme will continue to monitor the prevalence at birth of NTDs as well as other birth defects. Currently, reporting of terminations of pregnancy is mandatory. However, if a birth defect is the reason for termination, it is not mandatory to specify the type of birth defect (eg, NTD). Mandatory reporting of terminations of pregnancy due to NTD (as well as specifying the type of NTD) would result in more accurate monitoring of any trends in NTDs that may be associated with policies implemented.

Humans have not been exposed to high doses of folic acid for long periods of time prior to the introduction of fortification programmes, and it is unknown whether prolonged high doses of folic acid are associated with any long-term health effects. As a consequence, if fortification is mandated, a surveillance system should be considered to monitor the occurrence of any adverse outcomes, particularly the masking of vitamin B_{12} deficiency and the incidence of twinning.

Evaluation

Whether the uptake of voluntary fortification is increased or mandatory fortification is implemented, the Ministry of Health and FSANZ need to be committed to carrying out an evaluation of the policy selected. Any evaluation should look at implementation issues (including the accuracy of claims on labels and folic acid levels in food), the monitoring of adverse effects, and the monitoring of any decrease in NTDs (and possibly cardiovascular disease and colon cancer).

Taking into account the issues discussed above, any consideration of mandatory fortification needs to include assessing the feasibility of:

- undertaking further modelling to identify the intake of folic acid among children under different fortification scenarios and to use this information to determine appropriate fortification levels
- investigating the technical issues surrounding the most appropriate vehicle (bread or flour) for fortification
- establishing systems to facilitate the monitoring of possible adverse effects associated with folic acid fortification, such as masking of vitamin B_{12} deficiency and an increased incidence of twinning
- establishing systems to facilitate the evaluation of a fortification policy, including implementation issues, the accuracy of claims on labels and folic acid levels in foods.

Options 3 and 4: Fortification

Recommendations:

- Conduct a comprehensive, ongoing national campaign to increase awareness of and consumption of folic acid-fortified foods in women planning a pregnancy.
- Consider mandatory fortification of either bread or flour with folic acid.
- Continue to monitor the incidence of neural tube defects in New Zealand.
- Improve termination of pregnancy reporting to include the type of neural tube defect involved.
- Include monitoring folic acid intakes and folate status of the New Zealand population in a national nutrition survey.

Part V: Conclusion

This report has explored the policy options available to increase folate intake among New Zealand women to reduce the incidence of NTDs. Four options were identified: increasing dietary folate intake, increasing consumption of folic acid supplements, or the voluntary or mandatory fortification of staple foods with folic acid.

Table 8 provides a summary of the advantages and disadvantages of each policy option.

Table 8: Advantages and disadvantages of each policy option

Advantages	Disadvantages
Option 1: Increased dietary folate intake	
• Consumer choice preserved • Adverse health effects unlikely • No legislative change • Improved maternal nutrition	• Levels of folate intake to reduce risk of NTDs unlikely to be achieved • May disadvantage low-income populations due to price of vegetables and fruit • Depends on knowledge of what are folate-rich foods
Option 2: Folic acid supplementation	
• Targeted to women of childbearing age • Consumer choice preserved • Adverse health effects unlikely • No legislative change	• Low awareness of need for increased folic acid intake among women of childbearing age • Compliance with supplementation low • Impact low because approximately half of all pregnancies are unplanned • Potential to disadvantage low-income populations as supplements must be paid for • Possible increased risk of twin pregnancies • Requires ongoing, comprehensive public health campaign to increase uptake
Option 3: Voluntary folic acid fortification	
• No legislative change • Potential to reach all women of childbearing age regardless of socioeconomic status • Does not rely on compliance • Reaches those with unplanned pregnancies	• Uptake by food industry is low – current levels of fortification are unlikely to decrease risk of NTD-affected pregnancy • Difficult to monitor • Consumer choice limited • Risk of high folic acid intake of sub-populations • Possible masking of vitamin-B_{12} deficiency • Possible increased risk of twin pregnancies • Potential problems with overage • Possible increase in cost of foods • Requires ongoing, comprehensive public health campaign to implement and gain acceptance
Option 4: Mandatory folic acid fortification	
• Potential to reach all women of childbearing age regardless of socioeconomic status • Does not rely on compliance • Reaches those with unplanned pregnancies • Monitoring more feasible	• Requires legislative change • Consumer choice limited • Risk of high folic acid intake of sub-populations • Possible masking of vitamin-B_{12} deficiency • Possible increased risk of twin pregnancies • Potential problems with overage • Possible increase in cost of foods • Requires ongoing, comprehensive public health campaign to implement and gain acceptance

A combination of options (dietary, supplementation and either voluntary or mandatory fortification) is needed to reduce NTDs in New Zealand. Regardless of what option, or combination of options, is selected, an ongoing, comprehensive public health campaign should be funded to support any policy implemented. In addition, systems in place to monitor the implementation of policy are also important to ensure success.

Part VI: Recommendations

Taking into consideration the analysis of the policy options available for increasing folate / folic acid consumption among women of childbearing age, the key recommendations made as a result of this report are as follows.

Improving folate intake in New Zealand needs to involve:

- a comprehensive, ongoing national campaign to increase awareness of and consumption of folate through diet, supplements, and fortification in women planning a pregnancy
- considering the mandatory fortification of either bread or flour with folic acid
- continuing the policy of recommending daily folic acid supplements to women planning a pregnancy in New Zealand, either in combination with voluntary fortification (status quo) or with mandatory fortification
- making a lower dose of folic acid (400 μg), as a registered medicine, available to women planning a pregnancy.

Supportive actions to improve folate intake in New Zealand need to involve:

- continuing to monitor neural tube defects in New Zealand
- improving termination of pregnancy reporting to include the type of neural tube defect involved
- monitoring folic acid intakes and folate status of the New Zealand population.

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Appendix 1: Summary of International Folic Acid Supplementation and Fortification Policies

Country	Supplementation policy	Fortification policy				
		Voluntary/ mandatory	Year of initiation	Foods that may be fortified	Level of fortification	Expected effect on folate intakes
Australia	Women planning or likely to become pregnant take a daily folic acid supplement of at least 500 μg daily, in addition to consuming a diet rich in folate	Voluntary	1995	Flour; savoury biscuits; breads; breakfast cereals; pasta; yeast extracts; fruit and vegetable juices; beverages derived from legumes; textured vegetable protein; food supplements and meal replacements since 1998	100 μg/ reference quantity	Increase of 250 μg/day among women
United Kingdom	All women who are planning a pregnancy are advised to take 400 μg folic acid/day from when they begin planning to conceive until the 12th week of pregnancy	Voluntary	Mid-late 1980s	Bread Breakfast cereals	Claim to contain: ~ 120 μg/100 g of flour 125–200 μg/ 100 g	
United States	Women capable of becoming pregnant take 400 μg of synthetic folic acid daily, from fortified foods or supplements or both, in addition to consuming food folate from a varied diet	Mandatory	Phased in between February 1996 and January 1998	Enriched cereal grain products including: bread, rolls and buns; flour, self-raising flour; corn grits; corn meals; farina; rice; macaroni products; noodle products; breakfast cereals (voluntary only)	140 μg/100 g of enriched cereals	Mean increase of 100 μg/day for women; more for men
Canada	Women planning a pregnancy take 400 μg of folic acid supplements daily	Voluntary Mandatory	December 1996 November 1998	White flour; enriched cornmeal Enriched pasta Pasta and cornmeal not labelled 'enriched' may contain added folate but it is not mandatory. Other foods may contain folic acid but not at levels that would substantially change folate intakes	150 μg/100 g 200 μg/100 g (higher because of anticipated cooking losses)	Increase of 50–150 μg/day

Adapted from: Abraham and Webb 2000

Appendix 2: Foods Permitted to Fortify with Folic Acid

Food	Reference quantity	Maximum claim per reference quantity (proportion RDI)
Biscuits (containing not more than 20% fat and not more than 5% sugar)	35 g	100 μg (50%)
Breakfast cereals	Normal serving	100 μg (50%)
Breads	50 g	100 μg (50%)
Flour, wholemeal or wholemeal flour, rye flour, rye meal or kibbled rye, oat flour or oatmeal or rolled oats, maize flour or maize meal, rice flour (or any mixture of any two or more of the foregoing)	35 g	100 μg (50%)
Pasta	35 g uncooked dried pasta	100 μg (50%)
Fruit juice, concentrated fruit juice – all varieties	200 ml	100 μg (50%)
Vegetable juice (including tomato juice and concentrated tomato juice)	200 ml	100 μg (50%)
Fruit nectar, fruit drinks containing at least 25% juice or other portions of fruit, and fruit drink concentrates/bases (that when made up according to directions produce a fruit drink containing at least 25% juice or other portions of fruit)	200 ml	Proportional to juice content
Protein products:		
• Beverages derived from legumes	200 ml	No claim permitted
• Textured vegetable protein	100 g	No claim permitted
• Extracts of meat, vegetable or yeast (including modified yeast) and foods containing not less than 80% of the extracts of the above	5 g	100 μg (50%)

Source: Food Regulations 1984 (Amendment 12)

Appendix 3: Fortified Foods in New Zealand

The following table lists foods reported by manufacturers as fortified with folic acid for the year ending December 2002.

Foods fortified	Amount
Bread	
Holsoms – Sunflower & Poppyseed; 9 grain; Original Swiss; Soy, Linseed & Canola	200 μg/100 g
Burgen – Oatbran & Honey; Soy Lin	200 μg/100 g
Healtheries – Gluten-free bread mix	285 μg/100 g
Breakfast cereals	
Sanitarium – Cornflakes; Light 'N' Tasty; Maximize; Weet-Bix	333 μg/100 g
Tasti – Blueberry Morning	333 μg/100 g
Tasti – Cranberry Bran; Tropicana Sunrise	334 μg/100 g
Pam's – Nutra Bites; Cornflakes	333 μg/100 g
Budget – Cornflakes	108 μg/100 g
Basics – Cocoa Rice Poppas; Powergrain; Rice Poppas	167 μg/100 g
Basics – Wheat Biscuits	100 μg/100 g
Signature range – Wheat biscuits	100 μg/100 g
Signature range – Bran & Sultana	222 μg/100 g
Signature range – Cornflakes; Power Stars; Rice Poppas	333 μg/100 g
Signature range – Honey Nut Flakes	193 μg/100 g
Freedom Foods – Rice Flakes with Psyllium	200 μg/100 g
Hubbards – Cornflakes; Bugs 'N' Mud; Rice Pops	333 μg/100 g
Hubbards – Home Sweet Home	167 μg/100 g
Kellogg's – Bran Flakes; Cornflakes; Mini-Wheats; Special K; Special K Red Fruits	333 μg/100 g
Kellogg's – All-Bran; Just Right; Just Right Grains; Sultana Bran; Sustain	222 μg/100 g
Kellogg's – Coco Pops; Crispix; Crunchy Nut Corn Flakes; Fruit Loops; Frosties; Nutri-Grain; Rice Bubbles; Cocoa Crispix	167 μg/100 g
Lowan Whole Foods – Flake Medley with Wild Berries	115 μg/100 g
Extracts of meat, yeast or vegetables	
Marmite	2000 μg/100 g
Food drinks	
Healtheries – Naturally Slim	360 μg/100 g
Healtheries – Vitaplan	55 μg/100 g
Complan	90.9 μg/100 g
Sanitarium – Up & Go	40 μg/100 g
Sanitarium – So Good Essential	35 μg/100 g
Sanitarium – Fast Break	33 μg/100 g
Naturalea – Smoothies	16.7 μg/100 g

Fruit drinks and fruit nectar	
Baker Halls Original Nectar Sensations	25 μg/100 g
Citrus Tree – Orange with Calcium and Folate	40 μg/100 g
Miscellaneous	
Freedom Foods – Enriched Pasta	285 μg/100 g
Chisel – Protein Bars	83 μg/100 g
Vitasoy – Vitality +	32 μg/100 mL
Wattie's – Cheesy Breadsticks; Cheesymite Breadsticks	140 μg/100 g

Source: New Zealand Manufactured Foods Database 2002

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