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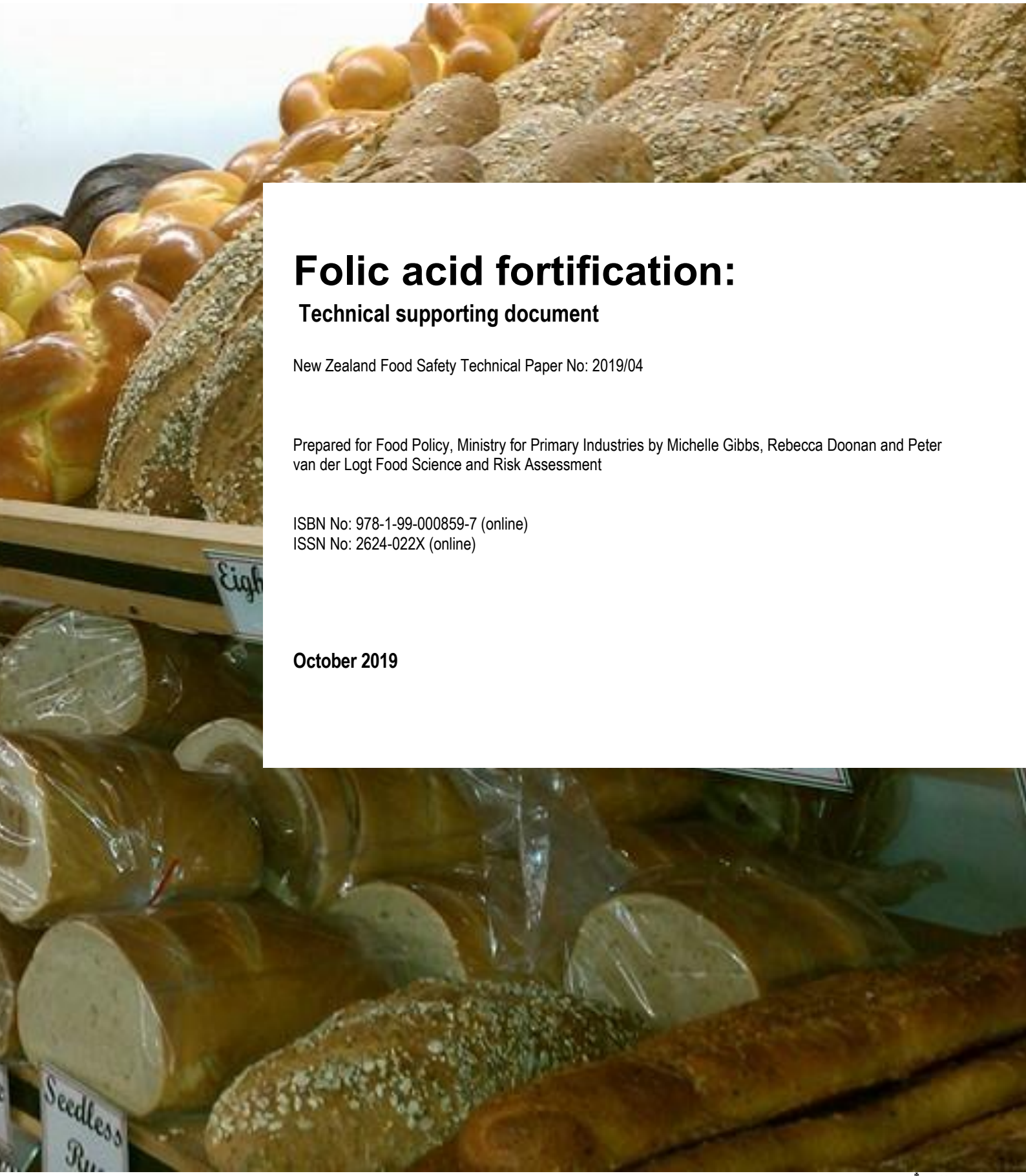

Folic acid fortification:

Technical supporting document

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Errata July 2021

In the Executive Summary a typographical error has been corrected in the reported number of NTD-affected pregnancies that could have been prevented since 2009 (page 8). The reported numbers now align with the Plain English summary (page 2) and Chapter 6: Modelling the impact of fortification (page 47) and Chapter 7: Conclusion (page 51).

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Plain English Summary

Folic acid is a B vitamin that helps prevent major birth defects of the baby's brain and spine. These birth defects are collectively known as neural tube defects (NTDs). It is very important that women get enough folic acid before and during early pregnancy to help prevent NTDs. Because it is difficult to get enough of this vitamin from our diet alone many countries allow folic acid to be added to food, known as folic acid fortification. In New Zealand bakers are encouraged to add folic acid to packaged sliced bread, but it is not required by law. The rate of NTDs in New Zealand is higher than countries where folic acid fortification is required by law (such as the United States, Canada and Australia).

The Ministry for Primary Industries (MPI) is seeking views on whether New Zealand would benefit from another approach to folic acid fortification to help reduce NTDs by raising the blood folate levels of women who could become pregnant.

The aim of this paper was to see whether other approaches to fortification would change the risk of NTDs in New Zealand. Three different fortification options were investigated:

1. Current fortification (38% packaged sliced bread fortified);
2. Increased uptake, but still voluntary (80% of packaged sliced bread to be fortified); and
3. Mandatory fortification, where manufacturers are required by law to add folic acid to all products within a food category.

For Option 3 we looked at three sub-options for folic acid fortification based on what and how much people eat. They were, to require that folic acid was:

a. Added to all bread-making wheat flour at the mill;
b. Added to all bread at the bakery during bread production; or
c. Added to all wheat flour.

For each fortification option we estimated how much extra folic acid people would eat and how this would change the number of NTDs in New Zealand.

The best approach is one where women of childbearing age get enough folic acid to reduce the risk of NTDs, but ensuring that the rest of the population do not get too much folic acid. We showed that other adults would not get too much folic acid from any of the options, but over one third of children aged 5-8 years would get too much folic acid if all wheat flour was fortified (Option 3c).

Compared with current fortification, we estimated that enhanced voluntary fortification would reduce NTDs by ~3-10%. Mandatory fortification of bread (Options 3a and 3b) would reduce NTDs by ~10-20%. Mandatory fortification of all wheat flour (Option 3c) would reduce NTDs by ~15-30%.

If mandatory fortification of bread-making flour had occurred in 2009 when it came into effect in Australia, it is estimated that 134 to 180 pregnancies affected by an NTD could have been prevented over the last ten years in New Zealand.

Mandatory folic acid fortification was found to be the most effective approach to further reduce NTDs in New Zealand. Mandatory fortification of all wheat flour (Option 3c) may result in children getting too much folic acid. Of the mandatory fortification options, bread (Options 3a and 3b) is considered the most suitable as it limits the risk of children getting too much folic acid in their diet.

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Abbreviations

08/09ANS	2008/2009 Adult Nutrition Survey
2002NCNS	2002 National Children's Nutrition Survey
CI	Confidence Interval
DFE	Dietary Folate Equivalents
EAT	Eating Assessment in Toddlers
FDA	United States Food and Drug Administration
FFQ	Food Frequency Questionnaire
FSA	Food Standards Agency
FSANZ	Food Standards Australia New Zealand
MPI	Ministry for Primary Industries
97NNS	1997 National Nutrition Survey
NRV	Nutrient Reference Values
NTD	Neural Tube Defects
NZAB	New Zealand Association of Bakers
NZBDR	New Zealand Birth Defects Registry
NZTDS	New Zealand Total Diet Study
PMCSA	Prime Minister's Chief Science Advisor
RBC	Red Blood Cell
UK	United Kingdom
UL	Upper Level of Intake
WCBA	Women of Childbearing Age

Symbols

%	percent
$	dollars
µg	microgram
g	gram
kg	kilogram
L	litre
mg	milligram
nmol	nanomole

Executive Summary

INTRODUCTION

Folic acid is the synthetic form of the essential B vitamin folate, which is added to manufactured foods and drinks, or taken as a vitamin supplement. Women who don't get enough folic acid before and during the early stages of pregnancy have a higher risk of their baby developing birth abnormalities known as neural tube defects (NTDs). NTDs are serious birth defects that affect babies' brains and spines and can result in lifelong and usually severe disabilities or death. The most common forms of NTDs are spina bifida and anencephaly.

There is unequivocal evidence that maternal folic acid supplementation early in pregnancy protects against serious birth defects of the brain and spine called NTDs. NTDs occur during the early weeks of pregnancy, often before women are aware they are pregnant.

NEW ZEALAND CONTEXT AND INTERNATIONAL APPROACHES

Policies to increase the intake of folic acid in New Zealand women of childbearing age (WCBA) have been in place since 1993. This began with the Ministry of Health recommending that women who are pregnant or planning pregnancy take a registered folic acid tablet; and in 1996 with the permission for industry to voluntarily add folic acid to certain foods. In 2012 a New Zealand Food Standard permitting the voluntary fortification of bread with folic acid was issued, supported by an industry code of practice. This code of practice commits signatories to fortify 25% to 50% of the packaged sliced bread they produce at a target level of 200 µg of folic acid per 100 g. The latest industry audit from 2017 reported that 38% of packaged sliced bread were fortified with folic acid by signatories at a median folic acid content of 164 µg per 100g.

MPI, a business unit of the Ministry for Primary Industries (MPI), is currently consulting on options for increasing the availability of folic acid through fortification of food. The Food Science and Risk Assessment directorate of MPI New Zealand Food Safety have prepared this technical report to inform the current consultation. This paper provides: background on the New Zealand context of folic acid fortification and rates of NTDs; a summary of international approaches; and evaluates potential food vehicles for mandatory fortification. Based on these findings feasible fortification scenarios were identified and for each of these scenarios a dietary intake assessment was undertaken and their subsequent impact on NTDs modelled.

In New Zealand fortification of foods with folic acid is part of a package of initiatives, that includes health promotion and education strategies (including recommendations to take folic acid tablets), aimed at improving the folate status of WCBA. There has been an increase in the number of women dispensed a subsidised folic acid tablet, however only 8.7% of all women who had a live or stillbirth in 2015 were dispensed these tablets before pregnancy, partly attributable to over 50% of pregnancies in New Zealand being unplanned. Self-reported folic acid supplement usage prior to pregnancy was lower in younger age groups and in Māori and Pacific women.
Over 80 countries have introduced mandatory folic acid fortification of food staples, including the United States (in enriched cereal grains), Canada (in enriched flour and bread), and Australia (in bread-making flour). New Zealand and most European countries have adopted voluntary fortification programs. The prevalence of NTD-affected pregnancies in New Zealand is estimated to be 10.6 cases per 10,000 births (data from 2011-2015). This is higher than countries with established mandatory fortification programmes including the United States (~7.0 cases per 10,000 births), Canada (~8.6 cases per 10,000 births) and Australia (~8.7 cases per 10,000 births).

DETERMINING FEASIBLE FORTIFICATION OPTIONS AND THEIR IMPACT

Mandatory fortification is required where it has been assessed as the most effective public health strategy. Appropriate food vehicles for fortification need to be efficacious and effective for the target group, and safe for target and non-target groups. Analysis using updated consumption data supported Food Standards Australia New Zealand's (FSANZ) previous 2006 conclusion that bread is the most feasible food vehicle for fortification of the food vehicles assessed. Fortification of wheat flour, which has been a successful vehicle for mandatory fortification in other countries, was also considered as a possible feasible alternative.

It was determined that bread (either as bread or bread making flour) and wheat flour should be further considered as potential food vehicles for mandatory folic acid fortification. Therefore, further detailed analysis was undertaken on the following scenarios:

1) status quo (current fortification levels);
2) enhanced voluntary fortification (80% of packaged sliced bread fortified);
3) mandatory fortification of:
    a) all bread (excluding organic);
    b) all bread-making wheat flour (excluding organic);
    c) and all wheat flour (excluding organic).

The aim of any fortification program is to ensure that folic acid intakes are maximised for the target groups whilst minimising intakes for all population groups that exceed the upper level of intake (UL). The UL is the highest average daily nutrient intake level likely to pose no adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.
Detailed dietary analysis found that the likelihood of dietary intakes of folic acid exceeding the UL for adults is very low (<1%) in all scenarios assessed. A higher proportion of children aged 5-8 years exceeded the UL in one scenario: all wheat flour (36%). The mandatory fortification of all bread, all bread-making wheat flour or all wheat flour would deliver a sufficient amount of folic acid to the target group, even those with the lowest intakes.

Based on the overall analysis five folic acid fortification options were provided by the Food Science and Risk Assessment directorate of MPI New Zealand Food Safety for the present consultation. These fortification options, along with their impacts, are summarised in the following table.

Summary of the predicted impact of proposed fortification scenarios on the prevalence of NTDs in comparison to current fortification levels

Scenario	Fortification Concentration	Predicted NTD rate per 10,000 births (range)	Number of NTDs prevented per year from current fortification levels	% reduction from current fortification levels	% children aged 5 - 8years above the UL
Status quo	Target 200 µg/100g bread	7.7 – 11.4	-	-	<1%
Enhanced voluntary[1]	Target 150 µg/100g bread	7.3 – 11.0	2 - 5	3-11%	<1-2%
All bread[2]	100 to 200µg/100g bread	6.5 - 10.5	5 - 9	8-19%	1 - 6%
All bread-making wheat flour[2]	200 to 300 µg/100g flour	6.7 - 10.3	5 - 8	9-17%	<1 - 6%
All wheat flour[2]	200 to 300 µg/100g flour	6.0 - 9.8	8 - 14	14-29%	5 - 36%

Notes

1. Fortification of 80% packaged sliced bread
2. Excludes organic

Modelling the impact of the fortification scenarios on the prevalence of NTDs demonstrated that the enhanced voluntary and mandatory fortification scenarios are all effective in further reducing NTD-affected pregnancies in New Zealand. The mandatory fortification options were the most successful at reducing NTD-affected pregnancies, with the all bread and all bread making-flour scenarios reducing NTDs by approximately 10-20% and the all wheat flour by approximately 15-30%. It was estimated that approximately 5-9 NTD-affected pregnancies could be prevented each year if all bread was fortified (Options 3a and 3b). Furthermore, if mandatory fortification of bread had occurred in 2009, it is estimated that 134 to 180 pregnancies affected by an NTD could have been prevented over the last ten years.

Of the mandatory fortification options, the mandatory fortification of bread or bread-making flour are the most suitable. These two scenarios can effectively reduce NTD-affected pregnancies without exposing the sub-groups of the population to excessive intakes of folic acid.

1 Introduction

1.1 FOLATE AND FOLIC ACID

Folate is an essential B vitamin important for new cell formation (Whitney, 2011). Rich natural sources of folate include dark leafy green vegetables (such as spinach and broccoli), liver, citrus fruit and beans (Whitney, 2011). Folic acid, the synthetic form of folate, is more stable and bioavailable than natural folate and is used extensively in dietary supplements and food fortification (Whitney, 2011). The term dietary folate equivalents (DFE) is used to accommodate the varying bioavailability of folate and folic acid, where 1 µg DFE is equivalent to 1 µg food folate or approximately 0.6 µg of folic acid (NHMRC, 2006).

In Australia and New Zealand the recommended dietary intake of folate for adults is 400 µg per day (in DFE), with increased requirements during pregnancy (600 µg per day) and lactation (500 µg per day) (NHMRC, 2006). The requirements for younger age groups are based on those for adults and adjusted for their lower body weight (NHMRC, 2006).

Inadequate folate intake can lead to megaloblastic anaemia, which is characterised by large, immature red blood cells (Whitney, 2011). High intakes of naturally occurring folate from food is not linked with adverse health effects, however high intakes of folic acid can potentially conceal vitamin B12 deficiency and delay diagnosis of neurological damage in the elderly (NHMRC, 2006). Therefore a UL has been established for folic acid of 1000 µg per day for all adults (this is lower for younger age groups relative to their lower body weight) (NHMRC, 2006).

1.2 PREVENTION OF NEURAL TUBE DEFECTS

NTDs are major birth defects of the brain and spinal cord that occur during the early weeks of pregnancy, often before women are aware they are pregnant. The most common form of NTDs are spina bifida (opening in the spine) and anencephaly (improper closure at the upper end of the neural tube), less common is encephalocele (opening in the centre of the skull) (PMCSA, 2018). NTDs can lead to miscarriage, stillbirth or to lifelong and usually severe disabilities.

Unequivocal evidence from clinical trials in the 1990s demonstrated maternal folic acid supplementation early in pregnancy protects against NTDs (MRC, 1991; Czeizel, 1992). Approximately 70% of NTDs are sensitive to folic acid and with comprehensive folic acid fortification and supplementation it is predicted that the birth prevalence of NTD-affected pregnancies could be reduced to approximately 5-6 per 10,000 births (Crider, 2011 & 2014; Kancherla, 2017).

Since 1993 the New Zealand Ministry of Health have recommended women who are pregnant or planning a pregnancy take a registered folic acid tablet for at least four weeks prior to and for 12 weeks following conception (Ministry of Health, 2018). Folic acid supplementation is highly effective at optimising folate status in women who take their supplements as recommended. However, research globally, and in New Zealand, indicate that the majority of women do not adhere to these recommendations. This is partly attributable to over 50% of New Zealand pregnancies being unplanned (Hohmann-Marriot, 2018; Mallard, 2011). There is particular concern that Māori and Pacific women, younger women and women with lower education and income are less likely to follow these recommendations (Mallard, 2011).

To support WCBA to consume more folic acid, many countries have introduced fortification of staple foods with folic acid on a mandatory or voluntary basis (Food Fortification Initiative, 2018). Fortified foods have been permitted in New Zealand since 1996. In 2012 a New Zealand Food Standard permitting the voluntary fortification of bread with folic acid was issued (MPI, 2012a). This is supported by an industry code of practice that commits the New Zealand Association of Bakers (NZAB) to fortify a minimum of 25% and up to 50% of bread they produce (NZAB, 2014). In 2017, 38% of packaged sliced bread was fortified by signatures to the code of practice, lower than the aspirational 50% goal (NZAB, 2014).

1.3 RECENT REPORTS ON FOLIC ACID FORTIFICATION IN NZ

There have been two recent publications in New Zealand on folic acid fortification: a monitoring report on folic acid fortification and review of health benefits and risks of folic acid fortification. The two publications are briefly outlined below.

Ministry for Primary Industries 2018 Voluntary Folic Acid Fortification: Monitoring and Evaluation Report

In February 2018, the MPI Science and Risk Assessment directorate published a monitoring report on the implementation of the fortification policy in New Zealand (MPI, 2018a). This report provided updates on the uptake of voluntary fortification by industry, the folate status of WCBA, consumer attitudes to folic acid fortification, and the prevalence of NTD-affected pregnancies.

The report highlighted that there has been an increase in the number of fortified foods available for sale in New Zealand and a decrease in the NTD birth prevalence, although more NTDs could still be prevented as blood folate levels in New Zealand WCBA remain low.

Prime Minister's Chief Science Advisor and the Royal Society Apārangi 2018 report on the health benefits and risks of folic acid fortification of food

In April 2017, the Ministry of Health commissioned the Office of the Prime Minister's Chief Science Advisor (PMCSA) and the Royal Society Te Apārangi to review the health benefits and risks of folic acid fortification of food (PMCSA, 2018). This involved a literature review and analysis of the available scientific evidence from New Zealand and internationally. An expert panel was appointed to oversee the review which included one lay member as an observer.

Published in June 2018, this report highlights there is compelling evidence that mandatory folic acid fortification is associated with lower rates of NTDs, and that taking folic acid supplements at the recommended dose in pregnancy has no adverse effects on pregnancy outcome or the child's health. No evidence was found to link the use of folic acid supplements or fortification to increased risks of neurological/cognitive decline, diabetes, or cardiovascular disease; nor was there evidence that unmetabolised folic acid is harmful.

The report concluded that the benefits of mandatory fortification of packaged bread with folic acid outweigh any potential adverse health effects.

1.4 PURPOSE OF THIS REPORT

In response to the two recent publications on folic acid fortification in New Zealand MPI is consulting on whether New Zealand would benefit from a different approach to folic acid fortification. This technical report was prepared by the Food Science and Risk Assessment directorate of MPI New Zealand Food Safety to inform the present consultation. This report aims to build on these recent reports and covers the following areas:

- An update on the current New Zealand context;
- A summary of international approaches to folic acid fortification;
- Potential food vehicles for mandatory folic acid fortification in the New Zealand population;
- Dietary intake assessment for children and adults under several folic acid fortification policy scenarios; and
- Assessment of potential NTD reductions that could be achieved under several folic acid fortification policy options in New Zealand.

This report does not cover issues related to the health benefits and risks of folic acid fortification as these were comprehensively assessed in the PMCSA (2018) report.

2 Current New Zealand context

2.1 FOLIC ACID POLICIES

Since 1993, the New Zealand Ministry of Health has recommended women who are pregnant or planning a pregnancy take a registered folic acid tablet (Ministry of Health, 2018a). Women at a low risk of an NTD-affected pregnancy who plan to become pregnant, are recommended to take 800 µg of folic acid daily for at least four weeks prior to and 12 weeks following conception. A daily folic acid tablet of 5 mg is also recommended for women: at higher risk of a NTD; those taking insulin treatment for diabetes; or those taking medications known to affect folate metabolism such as anti-convulsants, infertility treatments, vitamin A and some anti-tumor agents (Ministry of Health, 2018a).

Voluntary fortification of certain food products with folic acid has been permitted in New Zealand since 1996, including in breakfast cereals, yeast-based spreads, fruit and vegetable juices, and milk alternatives (FSANZ, 2002). In 2012, the New Zealand Government issued a Food Standard permitting the voluntary fortification of bread with folic acid at a level of no more than 2.5 mg per kg in total (MPI, 2012a). This Standard is supported by an industry code of practice signed by members of the NZAB in 2014 (NZAB, 2014). This code of practice commits signatories to fortify a minimum of 25% (by production volume) of the packaged sliced bread they produce and over time to work towards an aspirational goal of fortifying up to 50%. The target level of folic acid in bread was set at 200 µg per 100 g (or 2 mg per kg) of finished product.

The standard was aimed at improving the folate status of WCBA alongside existing health promotion and education strategies, including the ongoing recommendation to take folic acid tablets.

2.2 FOLIC ACID SUPPLEMENT USE

There is limited published data on supplementation usage during the peri-conceptional period in New Zealand. Folic acid supplement use amongst New Zealand women was not included in the 2018 MPI folic acid monitoring report, but was included in the previous 2012 MPI folic acid monitoring report (MPI, 2012b). At this time two studies investigating self-reported maternal dietary supplement use in New Zealand WCBA were available (results summarised in Table 2.1).

Table 2.1: Self-reported maternal dietary supplement use in two cohorts of New Zealand women

	Growing up in New Zealand (Morton, 2010)[1] ***N=6161***	**Vitamins and Minerals in Pregnancy survey (Mallard, 2011)[2]** ***N=707***
Unplanned pregnancy	8.9%	3.6%
Planned pregnancy	58.3%	56.4%
All pregnancies	**38.7%**	**33.2%**

Notes:

1. Supplement use classified as ever taking a supplement containing folic acid in the three months before pregnancy
2. Supplement use recorded as taking a supplement containing ≥400ug of folic acid either daily or on most day one month before conception until the end of the third month post-conception

These studies demonstrated that the advice to take a folic acid tablet consistently during the peri-conceptional period was not followed by the majority of women in the target group, with between 33% and 39% of women taking a folic acid supplement (Mallard, 2011; Morton, 2010). As expected self-reported supplement usage in the peri-conceptional period is affected by whether the pregnancy is planned or unplanned, with unplanned pregnancies having a much lower self-reported supplement use. Of an estimated 95,335 pregnancies in New Zealand in 2008, over half (53%) were unplanned (Hohmann-Marriott, 2018).

Since the publication of the 2018 MPI folic acid monitoring report, the Ministry of Health have provided data from two nationally representative, but previously unpublished, data sets with updated information on folic acid supplement usage by WCBA in New Zealand:

1. The 2014/15 Sexual and Reproductive Health module of the New Zealand Health Survey; and
2. Ministry of Health Pharmaceutical and Maternity collections (extracted October 2016).

2.2.1 The 2014/15 Sexual and Reproductive Health module of the New Zealand Health Survey

From 1 July 2014 to 30 June 2015, 10,198 adult participants from the 2014/15 New Zealand Health Survey completed a sexual and reproductive health module. This module asked respondents a range of questions related to their sexual and reproductive health (Ministry of Health, 2016). Female participants aged 16-44 years who had been pregnant in the last 5 years were asked whether they had done anything to improve their health in preparation for their most recent pregnancy. A range of response options were possible including 'took folic acid tablets/supplements'[1].

Almost half (47.6%) of the women who had been pregnant in the past five years reported taking a folic acid supplement/tablet (dose unspecified) prior to their most recent pregnancy (Table 2.2). This is likely an overestimate of peri-conceptional folic acid supplement use given an estimated 53% of pregnancies are unplanned in New Zealand (Hohmann-Marriott, 2018). This survey relied on recall of behaviour (up to five years previous) and respondents may not have distinguished between folic acid supplement usage prior and during pregnancy.

Self-reported folic acid supplement/tablet usage was:

- significantly higher in older age groups (62.8% in the 35-44 age group vs. 20.8% in the 16-24 age group);
- significantly higher in non-Māori compared with Māori and non-Pacific compared to Pacific (approximately 20% and 33% higher respectively), after adjusting for age; and
- no different by deprivation group after adjusting for age and ethnicity.

This is similar to previous research where self-reported supplement use was lower in Māori, Pacific and younger women. However this research also found lower usage amongst Asian women and women with lower education and income (Mallard, 2011).

Table 2.2: Folic acid supplementation prior to most recent pregnancy in past five years among women aged 16-44

	% (95% CI)
Total	47.6 (43.9-51.4)
Age group (years)	
16-24	20.8 (16.0- 26.6)
25-34	46.9 (41.1- 52.7)
35-44	62.8 (56.1- 68.9)
Ethnic group (total response)	
Māori	34.3 (28.7- 40.4)
Pacific	31.4 (21.6- 43.1)
Asian	54.1 (40.8- 66.8)
European/Other	49.6 (45.4- 53.9)
Neighbourhood deprivation (NZDep2013)	
Quintile1 (least deprived)	50.2 (37.8- 62.5)
Quintile 2	56.8 (47.9- 65.2)
Quintile 3	50.1 (41.8- 58.5)
Quintile 4	45.5 (36.7- 54.7)
Quintile 5 (most deprived)	39.5 (33.9- 45.3)

Source: 2014/15 Sexual and Reproductive Health module of the New Zealand Health Survey (unpublished, supplied by Ministry of Health)

2.2.2 **Ministry of Health Pharmaceutical and Maternity collections** (extracted October 2016)

The Ministry of Health provided data on the number and percentage of babies delivered where the mother was dispensed a folic acid tablet (5 mg or 0.8 mg) by stage of pregnancy[2] and year (2008-2015) (Table 2.3). This information was obtained through the linkage of two datasets: the maternity

[1] The remaining response options included: stopped or cut down smoking; stopped or cut down drinking alcohol, ate more healthily; sought medical/ health advice; took some other action; I did not do any of the above before my pregnancy; Don't know; and Choose not to answer.

[2] Dispensings are linked to pregnancy events based on date estimates using delivery date and gestational age (if available). Some relevant dispensings may be missed if they occur earlier or later than the defined time periods.

collections and pharmaceutical collections database. This only includes information on government subsidised folic acid tablets (0.8 mg or 5mg) dispensed; medicines purchased privately or dispensed within a hospital are not included.

Table 2.3: Percentage of pregnancies where folic acid tablets (0.8 mg or 5 mg) were dispensed by pregnancy stage and year of delivery

	Year of delivery (%)							
Pregnancy stage[1,2,3]	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
At any time between the 90 days before the pregnancy and the 30 days after	23.4	29.3	33.7	40.4	46.7	51.2	53.9	57.0
90 days before pregnancy	2.6	3.9	4.8	5.8	6.7	7.3	8.4	8.7
1st Trimester	20.3	25.0	28.6	34.4	40.0	44.1	46.3	49.4
2nd Trimester	1.9	2.4	2.9	4.0	5.2	5.5	5.6	5.7
3rd Trimester	0.5	0.8	0.9	1..4	1.8	2.0	2.0	1.9
30 days after delivery	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.1

Source:
Ministry of Health Pharmaceutical and Maternity collections (extracted October 2016) (unpublished, Ministry of Health)
Notes:

1. Pregnancies are only included where births result in live-born babies (born at any gestation) and stillborn babies (born at 20+ weeks' gestation or with a birthweight of 400g or more).
2. A valid National Health Index (NHI) number is required to be recorded on the supplement dispensed in order to be able to identify the number of dispensing's during pregnancy. The NHI reporting for folic acid supplements is relatively constant from year to year, sitting at approximately 98%.
3. Only includes information on government-subsidised dispensed pharmaceuticals; medicines purchased privately or dispensed within a hospital are not included

The percentage of women who were dispensed a government subsidised folic acid tablet (0.8 mg or 5 mg) at any time between the 90 days prior to and 30 days following delivery increased from 25.9% in 2008 to 60% in 2015. The proportion was relatively similar by deprivation (range 36.5%-44.7%) and ethnicity of the mother (range 39.8%-49.4%) (combined data from 2008-2015, not presented).

In 2015 only 8.7% of pregnancies that resulted in a live or stillbirth were dispensed folic acid in the critical period before pregnancy. This is lower than previous estimates where 33% and 39% of women reported taking a folic acid supplement consistently in the peri-conceptional period (Morton, 2010; Mallard, 2011). There could be a number of factors contributing to this lower estimate. The data is limited to those that were dispensed a government subsidised folic acid tablets and did not include: privately purchased folic acid supplements, privately purchased folic acid tablets, or those tablets that were dispensed in the hospital. This dataset also includes a broader range of pregnancy outcomes i.e. live and stillbirths, whereas previous estimates only included mothers with live births. Furthermore this dataset is based on dispensing data rather than self-reported behaviour.

2.3 VOLUNTARY FOLIC ACID FORTIFICATION

Since the introduction of the voluntary folic acid fortification standard in 2012 the number of folic acid fortified products available for sale in New Zealand has increased (432 products in 2017 vs. 321 products in 2013) (MPI, 2018a). In 2017 breakfast cereals were the most commonly fortified food in New Zealand (34%) followed by bread (10%) and breakfast beverages (8%). The number of breads containing folic acid increased from 31 in 2013 to 45 in 2017.

The Baking Industry Research Trust annually audit compliance with the industry code of practice. From 2012 to 2016 the proportion of packaged sliced bread fortified by signatures to the code of practice increased from 14% to 38% (by production volume) (Watson, 2018). This proportion remained stable at 38% in their most recent 2017 audit. This is below the aspirational 50% goal. Also reported in this audit, the median folic acid content for all bread was 164 µg per 100 g in 2017; also below the 200 µg per 100 g target.

For more information on the availability of folic acid fortified food in New Zealand please refer to the 2018 MPI folic acid monitoring report and the annual Baking Industry Research Trust audits (MPI, 2018a; Watson, 2018).

2.4 RATES OF NEURAL TUBE DEFECTS IN NEW ZEALAND

Data on NTDs are collated by the New Zealand Birth Defects Registry (NZBDR) which is funded by the Ministry of Health. The NZBDR has been monitoring the occurrence of all birth defects (including NTDs) since 1977. Since the 1990s birth defect data have been collected from multiple sources and include live births, patients requiring treatment in a public hospital, foetal deaths (stillbirths) and all death records. Data on NTD-affected pregnancies which have resulted in a termination have been included in the database since 2008.

The NZBDR receives quarterly updates from the Ministry of Health records of live births with a diagnosed birth defect and admissions to a public hospital for birth defects. From 2011 onwards, the NZBDR has collaborated with the Ministry of Justice and the Abortion Supervisory Committee to implement a voluntary system for the notification of birth defects in terminations of pregnancy.

The NZBDR has a rolling period of ascertainment. Therefore if a person born in 2000 with no defect diagnosed at birth is admitted to hospital in 2007 and a defect is reported, then the case would be retrospectively added to the 2000 birth cohort. Data on live births and stillbirths are available up to 2015; data on terminations are currently available from 2008 to 2015 only.

2.4.1 Classification of neural tube defects

The classification of birth defects among live births and stillbirths in the NZBDR is in accordance with the definitions used by the International Clearinghouse for Birth Defects Surveillance and Research and follows that of the International Classification of Diseases (ICD-9) (WHO, 2014). The classification of birth defects among terminations of pregnancy uses the Perinatal Society of Australia and New Zealand's perinatal death classification and neonatal classification.

The classification of NTDs includes the following types of birth defects:

- Anencephaly – total or partial absence of the upper part of the brain, the bones of the top of the skull, and the covering skin. There may be disorganisation or damage to the remaining brain tissue.
- Spina bifida – exposure of the spinal cord, nerves of the tissues that covers them through an opening in the skin and one or more of the backbones (the spinal column). The exposed nerves and spinal cord may be disorganised or damaged.
- Encephalocele – exposure of part of the brain or the tissues through an opening in the skin and skull bones.

The NTD prevalence rate is the number of NTD-affected pregnancies that resulted in a birth (live birth or stillbirth) or termination, divided by the population of total births (live births and stillbirths) in a specified time period.

2.4.2 NTD Prevalence

Overall, the NTD prevalence rate for 2011 to 2015 was 10.6 per 10,000 births. This equates to an average of 64 NTD affected pregnancies per year, of which 29 are estimated to be terminations and 26 live births and 9 stillbirths. Terminations of pregnancy accounted for almost half of all NTDs during this period. As NTD rates fluctuate from year to year more precise estimates of overall prevalence of NTDs can be obtained by aggregating data over a period of years. In line with the FSANZ (2006a) draft assessment report for the consideration of mandatory fortification with folic acid (proposal P295), five years of NTD rates were aggregated to determine the overall prevalence.

Table 2.4: Total number of live birth, stillbirth, and termination cases associated with NTD-affected pregnancies in New Zealand and the prevalence rate for total NTD-affected pregnancies

	Number			Total NTD-affected pregnancies[1]		
	Live births	**Stillbirths**	**Terminations**	**Number**	**Rate**	**95% CI**
2011	33	17	31	81	13.1	10.4, 16.3
2012	24	8	28	60	9.7	7.4, 11.4
2013	18	6	27	51	8.6	6.4, 11.4
2014	30	9	39	78	13.5	10.7, 16.9
2015	25	5	19	49	8.0	5.9, 10.6
Total	**449**	**188**	**237**	**520**	**-**	**-**
Average 2011-2015	**26**	**9**	**29**	**64**	**10.6**	**9.5, 11.8**

Source
New Zealand Birth Defects Registry, August 2018
Notes
1. Prevalence per 10,000 total births; 95% confidence interval (CI)

In 2018 MPI published data on the prevalence of NTD-affected pregnancies in New Zealand (MPI, 2018a). The data had been extracted from the NZBDR in August 2017 and provided information on live births up to 2015, and up to 2013 for stillbirths and terminations of pregnancies. Statistical analysis was undertaken at the Ministry of Health to determine if there had been a decline in the number of pregnancies affected by an NTD and to determine if there were ethnic differences in the birth prevalence (MPI, 2018a).

Spina bifida accounts for the majority of all NTD-affected live births across all years. From 2000 to 2015 there has been a statistically significant decline in the live birth prevalence of spina bifida and all NTDs. There was no statistically significant trend for anencephaly or encephalocele over this time (MPI, 2018a).

To determine if there were differences in the live birth prevalence of NTDs by ethnic group, data were pooled across all years. From 2000 to 2015 the live birth prevalence of NTDs were significantly higher in Māori women (4.6 per 10,000 live births) compared to women of NZEO ethnicity (excluding women of Pacific Island ethnicity) (2.8 per 10,000 live births). Pacific women also had higher live birth prevalence of NTDs over this time (4.1 per 10,000 live births) compared to NZEO women, however this was not statistically significant (MPI, 2018a).

In August 2018 the NZBDR provided MPI New Zealand Food Safety with additional data on stillbirths and terminations for the years 2014 and 2015. Table 2.4 shows the total number and rate of NTD-affected pregnancies in New Zealand from 2011 to 2015, by pregnancy outcome for all years of available data. A more detailed table with NTD rates from 2000-2015 by pregnancy outcome can be found in Appendix 1.

2.4.3 Costs associated with NTDs

NTDs cost New Zealand more than $24 million every year[3]. The additional average lifetime societal cost of an NTD-affected live birth, compared to the general population, was estimated in 2019 to be $938,000 (discounted rate) (Sapere, 2019). This includes lost productivity of the affected person and their caregivers, health care costs, educational support, and the deadweight cost of taxation. More than 60% of this cost is for productivity loses, with the majority of this due to decreased employment from higher mortality and morbidity. Healthcare costs are also significant, contributing more than 20% to the lifetime cost of an NTD.

[3]based on the cost of one live NTD being $938,000 and that there is on average 26 NTD-affected live births each year.

2.5 SUMMARY

The rate of NTD-affected pregnancies was 10.6 per 10,000 births from the year 2011 to 2015, an average of 64 pregnancies each year. In 2019 the financial cost alone of a single NTD live birth was estimated at $938,000. However, the burden is not spread equitably, Māori women have a higher rate of live births affected by an NTD than NZEO women. Spina bifida accounts for the majority of all NTD-affected live births and stillbirths across all years.

Policies to increase the intake of folic acid in WCBA have been in place since 1993. This began with the Ministry of Health recommending that women who are pregnant or planning pregnancy take a registered folic acid tablet. In 1996 industry were permitted to voluntarily add folic acid to foods (Ministry of Health, 2018a; MPI, 2012a).

There has been an increase in the number of women dispensed a government-subsidised folic acid tablet, however only 8.7% of all women who had a live or stillbirth were dispensed these tablets up to three months before pregnancy in 2015. In 2015 self-reported folic acid supplement/tablet usage prior to pregnancy was lower in younger age groups and in Māori and Pacific women.

Since the introduction of the voluntary folic acid fortification standard the number of folic acid fortified products in New Zealand have increased (MPI, 2018a). In 2017, 38% of packaged sliced bread was fortified by signatures to the code of practice, lower than the aspirational 50% goal (Watson, 2018).

3 International approaches to folic acid fortification

Over 80 countries have introduced mandatory folic acid fortification of food staples, such as flour or cereals (Food Fortification Initiative, 2018). New Zealand and most European countries have adopted voluntary fortification programs.

3.1 VOLUNTARY FORTIFICATION IN EUROPE

European Union legislation permits the voluntary addition of folic acid at any level to most foods[4] (Office Journal of the European Union, 2006). Very few European countries have regulations for mandatory folic acid fortification and uptake of voluntary folic acid fortification across Europe is generally low (Food Fortification Initiative, date not specified). A large study using pooled data from a number of population based registries in Europe[5] found that the overall total prevalence of NTDs had not decreased from 1990 to 2011 (Khoshnood, 2015). Fortification approaches of the United Kingdom (UK) and Ireland are briefly summarised in more detail below.

3.1.1 United Kingdom

The UK currently permits the voluntary fortification of foods with folic acid. From 1991 to 2012, the prevalence of NTD-affected pregnancies in the UK remained stable at around 12.8 per 10,000 total births (Morris, 2016).

The Scientific Advisory Committee on Nutrition, who advise Public Health England and other UK government organisations, has consistently recommended mandatory fortification of flour with folic acid in reports from 2006, 2009 and 2017 (SACN, 2017). This recommendation was based on extensive review, which included consideration of the links between folic acid and NTDs and any potential adverse effects of folic acid fortification. The UK has required the fortification of wheat flour with iron and other key nutrients since the 1940s (Food Fortification Initiative, date not specified).

Food Standards Scotland (2017) commissioned modelling work to estimate the potential impact of fortification of flour with folic acid in the UK. Three different fortification strategies were considered: fortification of wheat flour in bread (using two different bread definitions) and fortification of all wheat flour. This concluded that fortifying all wheat flour (excluding wholemeal) rather than bread only would lead to a considerably larger effect on both folic acid intake and NTD risk (at higher fortification levels NTD risk was reduced by 20-25% or more).

In June 2019 the UK government and devolved administrations published a proposal seeking views on introducing mandatory fortification of non-wholemeal flour with folic acid (GOV.UK, 2019). This consultation closed on the 9th September 2019 and considered the health benefits and risks as well as the practically of the proposal.

3.1.2 Ireland

Folic acid fortified foods were first introduced in Ireland on a voluntary basis in the early 1980's. At one time Ireland had extensive voluntary fortification of foods with folic acid but the percentage of folic acid fortified foods, as well as the levels of folic acid being added to foods, have decreased in recent years (FSAI, 2016).

Similarly the NTD prevalence in Ireland has fluctuated. A large decrease in NTD prevalence was observed from the early 1980's stabilising from mid-1990, and more recent studies suggest the prevalence increased between 2005/6 and 2009/11 to 10.4 NTD-affected pregnancies per 10,000 births[6] (FSAI, 2016). Although it is difficult to obtain reliable estimates of current NTD prevalence in Ireland due to the absence of a comprehensive register of pregnancies affected by NTDs.

[4] There are restrictions for alcohol and unprocessed foods (e.g. fruit, vegetables, meat, poultry and fish). Folic acid can be added to food at any level provided it is safe and in significant amounts to ensure fortification is beneficial to health. Current regulations allow for the setting of maximum amounts of added micronutrients to food (Article 6 (1) of Regulation 1925/2006) however, maximum amounts have yet to be established by the EU. In the absence of European maximum amounts, national rules apply if present.

[5] 28 population based registries in 18 European countries covering approximately 12.5 million births in Europe over the period of 1991 to 2011

[6] There is insufficient data to determine if there is a definite upward trend

A report prepared by the Scientific Committee of the Food Safety Authority of Ireland in 2016 presented two options to reduce the risk of NTD-affected pregnancies in Ireland: the mandatory fortification of bread with folic acid; or voluntary fortification with guidance for food industry (FSAI, 2016). The authors concluded that there was stronger evidence that mandatory fortification was effective in further reducing NTD rates than voluntary fortification. Both options would require ongoing monitoring and be accompanied with advice on supplementation.

3.2 COUNTRIES WITH MANDATORY FORTIFICATION

Table 3.1 lists the countries with legislation to mandate folic acid fortification of at least one industrially milled cereal grain (Food Fortification Initiative, 2018). All countries had legislation to fortify wheat flour alone or in combination with maize flour and/or rice.

Table 3.1: Countries mandating folic acid fortification of wheat flour, maize flour or rice

Antigua and Barbuda	Ghana	Nicaragua‡
Argentina	Grenada	Niger
Australia	Guatemala‡	Nigeria‡
Bahamas	Guinea	Oman
Bahrain	Guyana	Palestine Occupied Territory
Barbados	Haiti	Panama‡
Belize	Honduras	Paraguay
Benin	Indonesia	Peru
Bolivia	Iran	Saint Kitts and Nevis
Brazil‡	Iraq	Saint Lucia
Burkina Faso	Jamaica	Saint Vincent and the Grenadines
Burundi‡	Jordan	Saudi Arabia
Cameroon	Kazakhstan	Senegal
Canada	Kenya‡	Sierra Leone
Cape Verde	Kiribati	Solomon Islands
Chile	Kosovo	South Africa‡
Colombia	Kuwait	Suriname
Costa Rica‡	Kyrgyzstan	Tanzania‡
Cote d'Ivoire	Liberia	Togo
Cuba	Malawi‡	Trinidad and Tobago
Djibouti	Mali	Turkmenistan
Dominica	Mauritania	Uganda‡
Dominican Republic	Mexico‡	United States of America‡
Ecuador	Moldova	Uruguay
Egypt	Morocco	Uzbekistan
El Salvador‡	Mozambique‡	Yemen
Fiji	Nepal	Zimbabwe‡

Source:
Food Fortification Initiative, 2018
Notes:
‡ Mandates folic acid fortification of multiple food vehicles

Most of the countries mandating fortification are of low or middle income and have done so to address nutritional deficiencies in addition to reducing NTD rates (PMCSA, 2018). Countries that have adopted mandatory folic acid fortification for the primary purpose of NTD reduction include the United States, Canada, and Australia. The fortification approaches of these countries are summarised in Table 3.2. These countries all observed a significant decrease in their NTD rate following the introduction of mandatory fortification. The magnitude in the reduction is dependent on multiple factors including: the proportion of WCBA consuming the fortified food vehicle and amount consumed, fortification of other food, prevalence of folate deficiency or insufficiency, rates of periconceptional folic acid supplement use and NTD rates (WHO, 2009).

Table 3.2: Countries with mandatory folic acid fortification for the primary purpose of NTD reduction

Country	Year introduced	Food vehicle	Level of fortification (mg/kg)	Notes	Sources
Mandatory folic acid fortification					
United States	1998	Enriched[1] cereal grain products including: wheat flour, bread rolls, cornmeal, farina, rice and macaroni products.	1.4 (or 140 µg/100 g)	• Approach chosen as enriched cereal grain products were staples for most of the population (including 90% of WCBA) and had a long history of being successful vehicles for fortification (the FDA previously required the addition of niacin, thiamin, and riboflavin to enriched cereal grains to improve the daily intake of these nutrients). Predicted that with fortification lower level consumers of cereal grains would consume about 320 µg/day folic acid. • Post fortification the combined prevalence[2] of spina bifida and anencephaly reduced by 35% from 10.7 to 7.0 cases per 10,000 live births.	• FDA, 1996 • Yang, 2007 • Williams, 2015
Canada	1998	Enriched flour (all white flour must be enriched); enriched cornmeal, enriched pasta, enriched pre-cooked rice Bread (white enriched)	1.5 (or 150 µg/100 g) 1.0 (or 100 µg/100 g)	• Approach chosen as simulated dietary intake analyses indicated that average folic acid intakes in WCBA would be increased by ~30-70%, without posing a risk to the general public. Further rationale was to harmonise levels of nutrient addition to flour with USA. • NTD rates (live & stillbirths, terminations) fell by 46% post mandatory fortification from 15.8 per 10,000 births to 8.6 per 10,000 births.	• Government of Canada, 1998 • De Wals, 2007
Australia	2009	Wheat flour for bread making purposes (organic bread exempt)	2 -3 (or 200- 300 µg/100 g) Predicted post-fortification estimate was 120 µg/100 g in bread.	• Expected to increase folic acid intake in WCBA by 100 µg/ day. • Post mandatory fortification the level of folic acid in bread increased from 20-29 µg/100g to 124-200 µg/100g and the mean folic acid intakes in WCBA increased by 142% to 247 µg/day. • NTD rates (live & stillbirths, terminations) fell by 14% post mandatory fortification from 10.2 per 10,000 births (October 2006- December 2007) to 8.7 per 10,000 births (October 2009-2011). Modelling showed ~14 NTDs (of the 32 fewer total NTDs) were estimated to be directly attributable to the introduction of the standard.	• Australian Health Ministers' Advisory Council, 2017 • Australian Institute of Health and Welfare, 2016 • FSANZ, 2002

Notes:

1. In the United States, 'enriched' refers to the addition of a nutrient to a food that has been lost during the course of food processing or during normal storage and handling, up to the nutrient's level in the food before the processing, storage and handling

2. Only includes prevalence rates from states with prenatal ascertainment. Prenatal ascertainment monitored birth defects among live births, stillbirths, and elective terminations, and included collection of information from prenatal sources, such as prenatal diagnostic facilities.

3.2.1 Australia

Australia introduced mandatory fortification of wheat flour for bread-making flour purposes with folic acid in 2009. Initially mandatory folic acid fortification was intended to apply across Australia and New Zealand (FSANZ, 2006a). However, in 2007 New Zealand opted out of the joint food standard in favour of a New Zealand only standard to mandate the addition of folic acid to bread (rather than bread-making flour). This standard was subsequently replaced with the current voluntary standard before it came into force.

A comprehensive review examining the effectiveness and cost-effectiveness of mandatory folic acid fortification in Australia concluded that mandatory folic acid fortification was more effective than the pre-mandatory fortification suite of policies (Ministerial Council, 2017). As summarised in Table 3.2, within 18 months of implementing mandatory fortification the NTD rate significantly reduced by 14.4% (Australian Institute Health and Welfare, 2016). Mandatory folic acid fortification demonstrated improved equity in outcomes. In particular, it reduced the NTD rate for babies of indigenous mothers by 74% and babies of teenage mothers by 55%. The policy was also estimated as value for money and is estimated to save AUD $2 million per year each year it is in place (Australian Health Ministers' Advisory Council, 2017).

3.3 NEURAL TUBE DEFECT RATES

Direct comparisons of the NTD rates of different countries can be challenging due to differences in their surveillance systems (i.e. passive vs. active); and whether the data includes all NTD types (spina bifida/anencephaly/encephalocele) and pregnancy outcome (live births/stillbirths/terminated pregnancies).

New Zealand's estimated NTD rate (10.6 per 10,000 births) is similar to that of other countries with voluntary fortification, including Ireland (10.4 per 10,000 births) and the UK (12.9 per 10,000 births) and the NTD rate in countries prior to the introduction of mandatory fortification (Australia had a NTD rate of 10.2 per 10,000 births and United States 10.7 per 10,000 births prior to introducing mandatory folic acid fortification).

New Zealand's NTD rate is higher than countries that have implemented mandatory folic acid fortification, including the United States (7.0 per 10,000 births), Canada (8.6 per 10,000 births) and Australia (8.7 per 10,000 births) (Williams, 2015; De Wals, 2007; AIHW, 2016).

With comprehensive folic acid fortification and supplementation it is predicted that the birth prevalence of NTD-affected pregnancies could be reduced to approximately 5-6 per 10,000 births. (Crider, 2011 & 2014; Kancherla, 2017).

4 Potential food vehicles for mandatory folic acid fortification in the New Zealand population

In considering options to increase folic acid fortification in New Zealand, we first undertook analysis to determine whether bread remained an effective food vehicle to achieve the stated policy objective or whether other food vehicles should be considered further.

4.1 PRINCIPLES FOR SELECTING A FOOD VEHICLE

Governments tend to institute mandatory fortification where a proportion of the general population has a significant public health need which can be ameliorated or minimised through providing additional nutrients in the food supply. Mandatory fortification is only required in those instances where it has been assessed as the most effective public health strategy (Ministerial Council, 2004).

In determining appropriate food vehicles for the purpose of fortification it is important to ensure that it is efficacious and effective for the target group, and safe for target and non-target groups alike. In general, basic commodities are more suited to mandatory fortification due to their widespread and regular consumption. FSANZ previously considered which food vehicle would be best suited for folic acid fortification in Australia and New Zealand (2006a; 2007). In determining which food(s) would be most suitable for mandatory fortification, FSANZ considered whether the food:

- is regularly consumed by the population at risk in stable, predictable amounts;
- is available to the target population regardless of socio-economic status;
- supplies optimal amounts of the micronutrient without risk of excessive consumption or toxic effects;
- retains high level stability and bioavailability of the added micronutrient under standard local conditions of storage and use;
- is economically feasible;
- is centrally processed so that quality control can be effectively implemented; and
- does not interact with the fortificant or undergo changes to taste, colour or appearance as a result of fortification.

Foods initially considered by FSANZ as potential food vehicles included: milks (full fat and reduced fat), fruit juices, breakfast cereals, yoghurts and soy beverages as well as bread and bread products (FSANZ, 2006a; 2007). Based on the criteria, milk and milk products and bread and bread products were identified as the most suitable food vehicles for mandatory fortification. However, due to high consumption of milk by young children relative to adults, milk products were considered less suitable than bread. Further it was considered that fortification of flour and foods made from flour is consistent with overseas implementation of mandatory fortification.

Since the original FSANZ proposal in 2006 more up-to-date food consumption data is available in New Zealand (University of Otago, 2011; Mills, 2015). MPI New Zealand Food Safety has replicated some of the original work conducted by FSANZ to ensure that bread would still be considered a suitable fortification vehicle. This work focused on looking at the food consumption patterns of the target group (WCBA) and young children, who were previously identified as being most at risk of over consumption of folic acid.

4.2 FOOD CONSUMPTION PATTERNS OF WOMEN OF CHILDBEARING AGE

The 2008/09 Adult Nutrition Survey (08/09ANS) provides the latest comprehensive data on food consumption patterns of a representative sample of New Zealand adults (University of Otago, 2011). The methodology of the 08/09ANS is described in more detail in section 5.2.1.

4.2.1 Regular consumption of food vehicle

Analysis of changes in the food choices of New Zealand adults between the 1997 National Nutrition Survey (97NNS) and 08/09ANS in adults aged 19 years and over provide high-level detail on the food choices of WCBA over time (Smith, 2015). Results were published for women aged 19 to 30 and 31 to 50 years, therefore for this work we considered consumption patterns in women aged 19 to 30 and 31 to 50 years to represent WCBA.

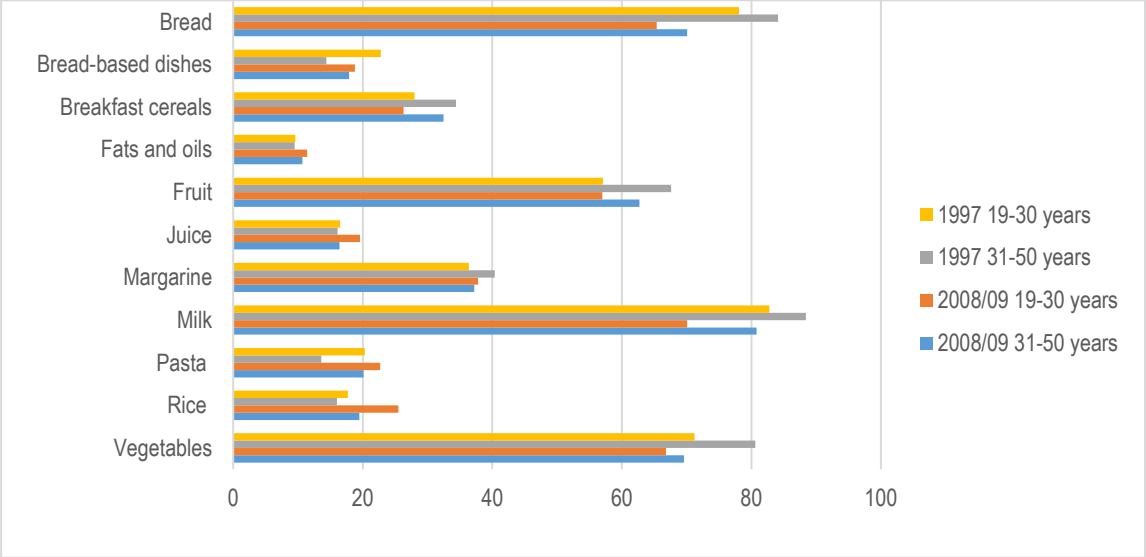
Figure 4-1 shows the percentage of women reporting consumption of various foods on the day of the 24 hour recall in the 08/09ANS and the 97NNS. Milk, bread, fruit and vegetables were the foods that were reported to be consumed by the largest proportion of women in the 08/09ANS (i.e. greater than 50%) (Smith, 2015).

In the 08/09ANS, 65.4% of women aged 19 to 30 years and 70.1% of women aged 31 to 50 years, reported consumption of bread on the day of the 24 hour recall. The proportion of women aged 19 to 30 years who reported consuming milk was 70.1% and 80.8% in women aged 31-50 years. The percentage of women reporting consumption of other foods which can be voluntarily fortified was approximately 30% for breakfast cereals, 20% for pasta and between 15-20% for juice (Smith, 2015).

As fruits and vegetables are not technically feasible to fortify, milk and bread remain the only food vehicles considered technically feasible to fortify and consumed by a sufficient proportion by WCBA (i.e. greater than 50%). Dairy products, including milk, are not currently permitted to be fortified in Australia and New Zealand and would require a specific New Zealand only standard or changes to the Food Standards Code to enable them to be fortified.

Between the two surveys, there was a significant decrease in the percentage of participants reporting the consumption of bread and milk. Overall, there was no evidence of change in the percentage reporting consumption of the following foods: bread-based dishes, breakfast cereals, fruit, juice, fats and oils, and margarine.

Figure 4-1: Percentage of women reporting consumption of potentially fortifiable foods in the 2008/09 Adult Nutrition Survey in comparison the 1997 National Nutrition Survey



4.2.2 Changes in bread consumption over time

Although bread consumption was found to decrease between the two nutrition surveys, bread remains the largest source of energy for females for all ages (approximately 10% of total energy) (Table 4.1) (University of Otago and MoH, 2011). To verify that bread is still widely consumed by WCBA, MPI commissioned a survey of 1000 WCBA in 2017. The survey found that 87% of WCBA reported eating bread, consuming an average of approximately two slices of bread a day (MPI, 2017).

Table 4.1: Proportion of energy from various food groups in the 08/09ANS

	Females			All males
	15-18 years	19-30 years	31-50 years	(15years +)
Bread	9.8%	8.6%	10.5%	11.4%
Bread-based dishes	8.9%	4.9%	4.4%	6.0%
Grains and pasta	7.9%	8.7%	7.1%	7.1%
Fruit	4.3%	4.8%	5.8%	4.3%
Vegetables	2.4%	3.5%	4.1%	3.1%
Milk	4.0%	4.2%	5.8%	4.7%

4.2.3 Consistent consumption of bread across the target population

The criteria for selecting a suitable food vehicle also require that it is regularly consumed by the population at risk in stable, predictable amounts; and is available to the target population regardless of socio-economic status (FSANZ, 2006a).

Data from the 08/09ANS was analysed further to determine the amount of bread consumed by WCBA, by age group, ethnicity and neighbourhood deprivation index (Parnell, 2012) (Table 4.2). This analysis included bread from all sources, including: bread rolls, specialty breads, English muffins, pita bread, tortillas, bagels, sweet buns, bread crumbs and bread-based dishes.

The median bread intake amongst WCBA was 68 g. This was comparable to the median intake amongst priority groups within WCBA including younger women (72 g in women aged 15-18), Māori (73 g), Pacifica (71 g) and those living in the most deprived areas (68 g). This demonstrates that bread is eaten by the target population regardless of socio-economic status, ethnicity and is consumed in relatively stable and predictable amounts.

Table 4.2: Intake of total bread consumed by women of child bearing age in the 2008/09 Adult Nutrition Survey

		Amount of bread consumed (g)	
	N	**Mean (95% CI)**	**Median (IQR)**
Total (19-44 years)	1383	83.5 (77.2, 89.8)	68.3 (0,128.0)
Age group (years)			
15-18	373	89.4 (80.2, 98.6)	72.4 (30.0, 140.6)
19-30	434	74.6 (65.0, 84.3)	61.9 (0.0, 117.5)
31-44	576	88.5 (78.5, 98.6)	73.4 (18.9, 137.3)
Ethnic group			
Māori	438	89.7 (79.8, 99.6)	72.8 (15.0, 139.1)
Pacific	271	91.2 (80.7, 101.7)	71.4 (35.0, 127.0)
European/Other	674	81.6 (74.0, 89.3)	68.3 (0.0, 128.0)
Neighbourhood deprivation (NZDep2006)			
Quintile1 (least deprived)	148	77.6 (60.0, 95.2)	69.9 (0.0, 130.0)
Quintile 2	220	91.5 (74.4, 108.5)	74.0 (18.9, 148.0)
Quintile 3	218	83.3 (69.3, 97.4)	70.6 (0.0, 126.0)
Quintile 4	324	82.3 (71.5, 93.0)	64.0 (30.0, 121.8)
Quintile 5 (most deprived)	473	81.6 (71.5, 91.6)	68.3 (0.0, 128.0)

Source: 2008/09 Adult Nutrition Survey (Parnell, 2012)
Abbreviation:
IQR Interquartile range

4.3 FOOD CONSUMPTION PATTERNS OF YOUNG CHILDREN

Previous work by FSANZ indicated that young children were the population group most likely to have folic acid intakes in excess of their requirements following the introduction of mandatory fortification. However bread was considered a more suitable vehicle due to the high consumption of milk by young children relative to adults. The fortification of milk was considered likely to cause excessive folic acid intakes for this age group (FSANZ, 2007). We sought to determine if milk continued to be widely consumed by young children and therefore less suitable as a food vehicle.

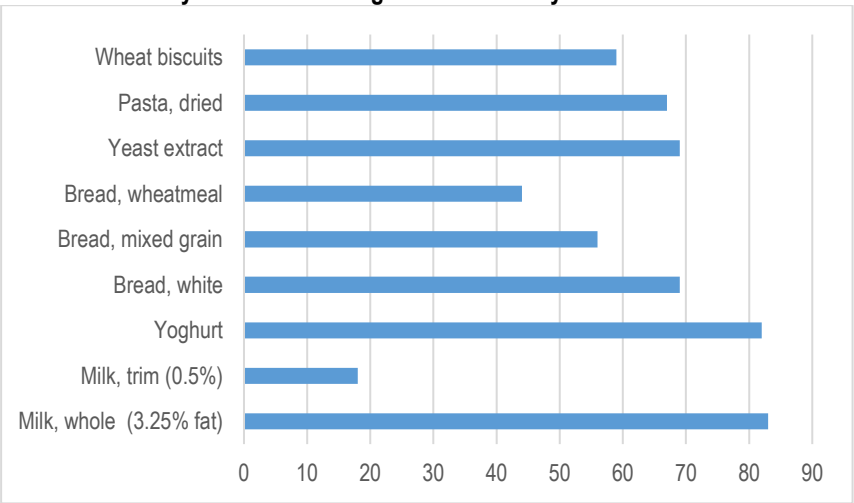
The Eating Assessment in Toddlers (EAT) study investigated the food intake of young children aged 12 to 24 months. The study was conducted between 2011 and 2012 (Mills, 2015) and assessed food intakes by Food Frequency Questionnaire (FFQ) and diet record. Five day diet records were collected on non-consecutive days. The primary aim of the study was to establish the validity of the FFQ.

Participants were recruited from Wellington, Dunedin and Christchurch and were predominately New Zealand European (77%) and higher socioeconomic status. Diet records were completed by 153 caregivers of the young children participants. This was not a national study but did have a large sample size and collected weighed diet records.

The proportion of young children that reported consuming potentially fortifiable foods on one of the five days of diet recording in the EAT study are presented in Figure 4-2. Whole milk and yoghurt were the most commonly consumed foods that are potentially fortifiable (>80%), this was followed by white bread, yeast extract and dried pasta (close to 70%). Wheatmeal bread and mixed grain bread were

consumed by approximately 45% and 55% of young children in the EAT study respectively. This data supports the previous conclusion by FSANZ that due to high consumption of milk by young children relative to adults, milk products are considered a less suitable food vehicle for fortification than bread.

Figure 4-2: Proportion of young children (aged 12 -24 months) reported consuming potentially fortifiable foods on one of the five days of diet recording in the EAT study



4.4 SUMMARY

Appropriate food vehicles for fortification need to be efficacious and effective for the target group, and safe for target and non-target groups. In 2006, FSANZ considered bread to be the most feasible vehicle for mandatory fortification as it was regularly consumed by the target group and technically feasible to fortify (FSANZ, 2006a). High consumption of milk by young children relative to adults, meant milk products were considered less suitable than bread.

MPI New Zealand Food Safety reconsidered feasible fortification vehicles in light of new data from the 08/09ANS (for WCBA) and the 2011/12 EAT study (for young children), particularly to assess whether bread remained a suitable food vehicle (University of Otago, 2011; Mills, 2015). Table 4.3 briefly summarises this analysis against key criteria.

Table 4.3: Summary of the feasibility of potential fortification food vehicles against key criteria

Food vehicle	Regularly consumed by sufficient proportion of the target population	Technically feasible to fortify the food	Permitted to be fortified under the food standards code	Limited risk of over consumption by young children
Bread	✓	✓	✓	✓
Milk	✓	✓	X	X
Fruit juices	X	✓	✓	N/A
Breakfast cereals	X	✓	✓	N/A
Soy beverages	X	✓	✓	N/A
Fruit	✓	X	X	N/A
Vegetables	✓	X	X	N/A
Meat	✓	X	X	N/A

The analysis demonstrated that bread remains the most suitable food vehicle for mandatory fortification for the following reasons:

- bread was most commonly consumed by WCBA; it is consumed in consistent amounts across age, ethnicity and neighbourhood deprivation index; it is technically and economically feasible to fortify and does not pose a significant risk to overconsumption by young children;
- breakfast cereals, fruit juice, and soy products (which are all currently permitted to be voluntarily fortified) are not consumed by a sufficient proportion of WCBA;
- fruit and vegetables are all consumed regularly by sufficient women, but are not feasible to fortify; and

- milk, which is consumed regularly and is technically able to be fortified, is not currently permitted to be fortified in Australia or New Zealand under the Australia New Zealand Food Standards Code. Young children have a high consumption of milk compared to adults and there remains the risk of overconsumption of folic acid by this group if milk was selected as the food vehicle.

This analysis supports FSANZ's previous conclusion that bread remains the most feasible food vehicle for fortification of the food vehicles assessed (FSANZ, 2006a). Fortification of flour and foods made from flour is consistent with international approaches to mandatory folic acid fortification. From this high level analysis it was not possible to assess if fortification of wheat flour would be a feasible alternative. Flour has been a successful vehicle for mandatory fortification in other countries including the United States and Canada.

Based on the conclusions of this analysis it was determined that bread (either as bread or bread making flour) and wheat flour should be further considered as potential food vehicles for mandatory folic acid fortification. Therefore, further analysis was undertaken on five fortification scenarios:

- status quo;
- enhanced voluntary (80% of packaged sliced bread fortified);
- mandatory fortification of:
    - all bread (excluding organic);
    - all bread-making wheat flour (excluding organic);
    - and all wheat flour (excluding organic).

5 Dietary intake assessment for adults and children

The primary objective of the dietary intake assessment is to estimate the impact of the proposed folic acid fortification policies on the dietary intakes of folic acid in the target group (WCBA between 15 to 49 years). Secondary to this is to estimate the dietary intakes of other sub-groups of the New Zealand population, and proportion within each sub-group that may be exposed to excessive intakes of folic acid (i.e. above the UL of intake).

The following fortification scenarios were assessed:

- status quo (current fortification levels);
- enhanced voluntary (80% of packaged sliced bread fortified);
- mandatory fortification of: all bread (excluding organic); all bread-making wheat flour (excluding organic); and all wheat flour (excluding organic).

Organic bread and flour were excluded from the mandatory fortification scenarios because it can no longer be marketed as organic if it contains folic acid. This also allows for some consumer choice for those not wanting to consume folic acid.

Dietary intake assessment of a nutrient requires detailed data on the food consumption patterns of the population matched with the concentration of the nutrient in the consumed foods. Food consumption data from New Zealand national nutrition surveys were used to assess the impact of fortification on the dietary folic acid intakes of adults and children.

A simulated diet approach was used to estimate intakes of folic acid for young children. This approach is aligned with that used for the 2016 New Zealand Total Diet Study (NZTDS) as food consumption data is limited for this age group (MPI, 2018b).

The dietary intake assessment is based on intakes of folic acid from fortified foods only and does not assess intakes of folate from natural food sources nor does it assess the folic acid intakes from dietary supplements. The assessment was limited to folic acid as the focus of this work is to establish the potential change in intakes of folic acid through different fortification scenarios. In addition to this the UL is based only on folic acid.

5.1 THE UPPER LEVEL OF INTAKE OF FOLIC ACID

To assess whether population intakes might be excessive, a comparison of intakes against the UL is conducted. The UL is the highest average nutrient intake likely to pose no adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases (NHMRC, 2006; FSANZ, 2014).

The current UL for folic acid has been set based on safety concerns for high intakes of folic acid from supplements. The UL for adults is set at 1 mg per day based on data that suggests high intake of folic acid (>5mg, five times above the established UL) can potentially conceal vitamin B12 deficiency and delay diagnosis of neurological damage in the elderly (NHMRC, 2006). This fivefold uncertainty factor is conservative and the safety margin is considered to be large. Masking of vitamin B12 deficiency is considered negligible in current medical practice in New Zealand as diagnostic testing of B12 insufficiency is routine practice in the elderly (MPI, 2012c). Table 5.1 lists the ULs for each age and sex sub-group of the population assessed.

Table 5.1: Upper levels of intake (UL) for each age and sex sub-group of the population assessed

Population sub-group	UL (from fortified foods and supplements)
Infants and young children	
0-12 months	Not possible to establish for supplemental folic acid.
1-3 years	300 µg/day as folic acid
Children and adolescents	
4- 8 years	400 µg/day as folic acid
9-13 years	600 µg/day as folic acid
14-18 years	800 µg/day as folic acid
Adults 19 years and older	
Men	1000 µg/day as folic acid
Women	1000 µg/day as folic acid

Source: Adapted from NHMRC (2006)

As there is little direct evidence for other ages, the UL has been set on a relative body weight basis for children and adolescents. It was not possible to set a UL for infants.

Natural food folate is considered safe and no adverse effects have been associated with the consumption of the amounts of folate normally found in fortified foods (NHMRC, 2006; IOM, 1998). As such, the dietary intake assessment was limited to intakes of folic acid from fortified foods and determining the proportion of the population that would be exposed to excessive intakes from this source.

5.2 METHODS

5.2.1 Food consumption data

The most recent New Zealand national nutrition surveys were used to estimate dietary intakes of folic acid for children and adults. These are the 08/09ANS and the 2002 National Children's Nutrition Survey (2002NCNS). These surveys collected nationally representative food consumption and nutrient intake data which was used to model the impact of fortification scenarios in the New Zealand population. Brief summaries of the two surveys are provided below, full details of the survey methodology are available in their respective survey reports (University of Otago and Ministry of Health, 2011; Ministry of Health 2003).

There is no national survey measuring dietary intakes of younger children (<5 years). In order to assess the folic acid intake of toddler's (1-3 years of age), the 14-day simulated typical diet from the 2016 NZTDS was used (MPI, 2018b). A comprehensive literature review was conducted to inform the simulated diets and data from the Eating Assessment in Toddlers (EAT) study was used to inform the NZTDS simulated diet for this age group (Smith, 2017).This study was previously summarised in Section 4.3.

2008/09 Adult Nutrition Survey

The 08/09ANS collected information on the food consumption, nutrient intake and biochemical nutrient levels in New Zealand adults aged 15 years and over. The survey was carried out from October 2008 to October 2009. The survey conducted face-to-face 24-hour food recall interviews with 4721 New Zealanders aged 15 years and above living in private dwellings (Day 1), with 25% of respondents completing a second 24-hour recall (Day 2) (University of Otago and MoH, 2011).

Both days of food consumption data were used for this assessment to estimate 'usual intakes' of folic acid for New Zealanders aged 15 years and above. Usual intakes more accurately reflect longer term nutrient intakes in a population, and are required to enable comparison with nutrient reference values (NRVs) (i.e. the UL) which are established on a long term basis.

Folate status was also assessed as one of the biochemical nutrient components in a sub-set of the surveyed participants.

2002 National Children's Nutrition Survey

The 2002NCNS provides comprehensive information on the dietary patterns of a nationally representative sample of 3,275 New Zealand children aged 5–14 years. The survey was conducted using a 24-hour recall methodology and collected data on dietary supplements as well as foods and beverages. A repeat 24-hour diet recall was obtained from a subsample of 15% of respondents. The survey was carried out from February 2002 to December 2002.

Both days of food consumption data, but not dietary supplement data, were used to estimate 'usual intakes' of folic acid for New Zealand children aged 5-14 years.

Age groups assessed

The folic acid intakes of the population were assessed according to the age groups listed in

Table 5.2. These age ranges reflect the age groups upon which the Australia and New Zealand NRVs are based. As there is no UL for infants (aged 0 to 12 months) this age group was not assessed. The defined target population of WCBA aged is between 15 and 49 years.

Table 5.2: Summary of age groups assessed from the New Zealand Nutrition Surveys and toddler study

Eating Assessment in Toddlers	National Children's Nutrition Survey	Adult Nutrition Survey
12-24 months	5- 8 years 9-13 years 14 years	15-18 years 19-30 years 31-50 years 51-70 years 71 years and above WCBA 15-49 years

5.2.2 Folic acid composition of foods

In order to determine the folic acid intake of the population, up to date food composition data was required to reflect the current availability of folic acid fortified foods. Folic acid composition data was derived for all survey foods reported in the nutrition surveys.

Foods that are currently fortified with folic acid were identified using the most recently collected data in the Nutritrack database (NIHI, 2018). The Nutritrack database collects ingredient and nutrition information panel information from the majority of packaged foods for retail sale in New Zealand supermarkets (NIHI, 2018). A search for all food containing folic acid, as declared in the ingredients list, was conducted on the foods collected in the 2018 annual survey. Folic acid composition data for these foods was then derived from the following sources, listed in order of priority:

1. 2018 data from the Nutritrack database (NIHI, 2018);
2. Nutrition information panel data from the manufacturers website;
3. New Zealand Food Composition Data (Plant and Food Research and Ministry of Health, 2018)
4. 08/09ANS food composition data.

Foods, other than bread, that contained folic acid under voluntary fortification provisions include yeast spreads (e.g. marmite) and some breakfast cereals, fortified orange juice, plant-based milk substitutes, protein supplements, snack bars, meal replacement beverages and therapeutic meal replacements.

5.2.3 Fortification scenarios

Table 5.3 summarises the fortification scenarios assessed. The selection of mandatory fortification scenarios were informed by international approaches and our analysis of suitable food vehicles for fortification in New Zealand in Section 4.

Table 5.3 Summary of folic acid fortification scenarios assessed

Scenario	Folic acid concentration
Status quo (current voluntary fortification)	200 µg/100g bread
Enhanced voluntary fortification (80% packaged sliced bread)	150 µg/100g bread 200 µg/100g bread
Mandatory fortification of all bread (excluding organic)	150 µg/100g bread 200 µg/100g bread 250 µg/100g bread
Mandatory fortification of all bread-making wheat flour (excluding organic)	200 µg/100g flour 300 µg/100g flour
Mandatory fortification of all wheat flour (excluding organic)	200 µg/100g flour 300 µg/100g flour

The fortification concentrations for the status quo, enhanced voluntary and the all bread scenarios were based on the target level of fortification (200 µg per 100 g bread) specified in the NZAB code of practice. The lower concentration of 150 µg/100 g bread was included to accommodate for more widespread fortification under enhanced voluntary and the all bread scenarios. The mandatory fortification of all bread scenario also included the higher concentration of 250 µg/100g bread to align with the maximum amount of folic acid permitted under the current voluntary standard (MPI, 2012a). The concentrations for the mandatory fortification of all bread-making wheat flour and all wheat flour scenarios were aligned with the Australian permissions for the mandatory fortification of bread-making flour in the Australia New Zealand Food Standards Code (no less than 2mg/kg, and no more than 3mg/kg, of folic acid) (FSANZ, 2002).

All scenarios used the same folic acid concentration data for foods, other than bread, that contained folic acid under voluntary fortification (for example breakfast cereals, yeast extracts, breakfast beverages). For the foods that would be impacted by a mandatory fortification scenario, the folic acid composition was amended to reflect the outcome based on the mandatory proposal rather than the folic acid content of the food in 2018. All folic acid concentrations for foods not affected by mandatory fortification policies were retained at the 2018 voluntary fortification level.

Status quo

Under the current voluntary fortification policy 64 varieties of packaged sliced breads are fortified, representing approximately 38% of available breads produced by NZAB, by production volume (Watson, 2018). The industry code of practice stipulates a target level of fortification of 200 µg of folic acid per 100 g of bread (NZAB, 2014). NZAB has previously stated that it produces approximately 90% of packaged sliced bread available in New Zealand.

For the purposes of this assessment the median amount of folic acid declared on the label of fortified breads were used. The 2018 MPI folic acid monitoring report found that the median folic acid concentration declared in the nutrition information panel of fortified breads has remained stable at 200 µg per 100 g from 2014 to 2017 (MPI, 2018a).

The nutrition surveys did not always identify the brand of bread consumed in the survey, therefore it was not possible to accurately identify all survey foods that would be fortified under the current industry code of practice. As such a market share weighted folic acid value was assigned to all non-organic packaged sliced breads reported in the survey to reflect the 34.2% of packaged sliced breads that were fortified[7].

The derivation of folic acid concentrations using a market share model is:
Folic acid concentration = folic acid concentration in bread x market share
= 200 µg folic acid/100 g x 34.2% market share
= 68.4 µg folic acid/100 g

Enhanced voluntary fortification

In this scenario, breads that were identifiable as packaged sliced loaves were required to contain folic acid. Under this scenario two levels of fortification were assessed, fortification at: 150 and 200 µg of folic acid per 100 g of bread.

In order to simulate the impact of 80% of the market share of these products being fortified, all packaged sliced bread products were fortified at 120 and 160 µg of folic acid per 100 g of bread – 80% of the target concentration.

Mandatory fortification of all bread

In this scenario all foods classified as ‘breads’ under the Australia New Zealand Food Standards Code would be required to contain folic acid. The Food Standards Code states that bread is made from cereal flour, is yeast leavened and is baked (Standard 2.1.1-2). Under this scenario three levels of fortification were assessed at: 150, 200 and 250 µg of folic acid per 100 g of bread.

In addition to packaged sliced bread, this scenario included the fortification of: bread rolls, buns, scrolls, gluten-free bread and bread from quick service restaurants. All bread that met the definition, whether reported as consumed or used in a recipe, were fortified at the target level of fortification.

The following products were excluded under this scenario: organic bread, bread mixes, pizzas and pizza bases, non-yeasted breads (e.g. cornbread), pastries, cakes (including panettone, stolen and brioche), biscuits and crackers, bagel crisps, steamed breads, English muffins and crumpets, and homemade bread.

Mandatory fortification of all bread-making wheat flour

Under this scenario all wheat flour for bread-making purposes would be required to be fortified within the range of 200 to 300 µg of folic acid per 100 g of flour. This simulates the impact in New Zealand of the requirements for the mandatory fortification of bread-making flour in Australia, as prescribed in the Food Standards Code (Standard 2.1.1-5(a))

[7] 38% of breads produced by NZAB with NZAB representing 90% of the packaged bread market.

Bread-making flour is made from a wheat that has a medium to high protein content (approximately 10.5-13% protein), and is sometimes referred to as strong flour (NZ Flour Millers Association, 2018). All foods that would be made using a bread-making flour were identified and folic acid concentration amended so that the flour component within the food was fortified. This included both white and wholemeal flours used for bread making.

Some of the products that were fortified in this scenario included: bread, bread rolls, buns, croissants, pizza bases, tortillas, doughnuts, bread mixes. Bread flour that was organic or gluten-free (and products that contain these ingredients) was not fortified under this scenario.

Mandatory fortification of all wheat flour

In this scenario all wheat flour would be required to be fortified within the range of 200 to 300 µg of folic per 100 g of flour. This scenario affects a larger range of products as all wheat flour that is reported as consumed in a recipe is assumed to be fortified at the target level (e.g. wheat flour in batters, cakes, pies, biscuits etc).

5.2.4 Assessment of dietary intakes of folic acid

Assessment of dietary intakes of adults and children

The assessment of dietary intakes of folic acid was conducted by FSANZ. Firstly, folic acid values were generated for each individual food reported as consumed in the nutrition surveys (08/09 ANS, 2002NCNS) at baseline and for each fortification scenario concentration. This included mixed dishes and foods which contained a fortified food vehicle as an ingredient. The new concentrations for mixed dishes, such as sandwiches and crumbed foods, were derived using FSANZ's specially developed hybrid spread sheets[8]. These concentrations were then loaded into FSANZ's custom-developed dietary intake assessment program, Harvest.

Folic acid intakes were calculated for each individual in the nutrition surveys using their individual food consumption records from the dietary survey. The Harvest program multiplied the specified concentration of folic acid for an individual food by the amount of the food that an individual consumed in order to estimate the intake of folic acid from each food. Once this had been completed for all of the foods specified to contain folic acid, the total amount of folic acid consumed from all foods was summed for each individual.

Adjusted nutrient intakes (non-log transformed) were calculated for folic acid. This method determines the within person variation (i.e. the difference between day 1 nutrient intakes and day 2 nutrient intakes for each respondent with two days of data), estimates adjustment factors based on this, and uses these factors to adjust the day 1 population folic acid intake distribution around the mean.

The adjustment is made to each respondent's folic acid intake from the first day of food consumption data from the nutrition survey. The adjustment takes into account several pieces of data including each person's day one nutrient intake, the mean nutrient intake from the group on day one, the standard deviation from the day one sample and the between-person standard deviation from the day two sample. This calculation is described in Equation 1 below. For more information on the methodology of adjusting for second-day nutrient intakes, see the Technical Paper on the National Nutrition Survey: Confidentialised Unit Record File (Australian Bureau of Statistics, 1998).

Equation 1: Calculating adjusted nutrient intakes

$$Adjusted\ value = x + (x1 - x) * \left(\frac{Sb}{Sobs}\right)$$

Where: x is the group mean nutrient intake for the Day 1 sample
x1 is the individual's day 1 nutrient intake
Sb is the between-person standard deviation calculated using day 1 and day 2 nutrient intakes for those respondents surveyed twice (uses a one-way analysis of variance (ANOVA) where person is the independent variable and intake is the dependent variable); and
Sobs is the group standard deviation for the Day 1 sample
Source: (Australian Bureau of Statistics, 1998)

[8] "Hybrid spread sheets" is the commonly used term that refers to the complex spread sheets that are able to recalculate the nutrient concentrations for all relevant foods in a nutrition survey based on changes in nutrient concentrations in certain/selected/key foods, by taking into account where these certain/selected key foods are used in mixed foods using a custom developed set of recipes.

A minimum number (100) of respondents in the second day are needed to generate a robust adjustment factor (i.e. for the parameters of x, Sb and Sobs). To generate the standard deviation values, the adjustment was conducted on the collapsed age-sex groups listed in Table 5.4. While the adjustment factors are calculated for different (collapsed) age-sex groups to ensure a sufficient sample size, these age groups were different to those used for reporting nutrient intakes, which were NRV age-sex gender groups.

Table 5.4: Age-sex groups used to adjust for usual intakes for each survey

2002 NZ NNS		**2008/09 NZ ANS**	
Males	Females	Males	Females
5-9 years	5-9 years	15-30 years	15-30 years
10-14 years	10-14 years	31-50 years	31-50 years
		51-70 years	51-70 years
		71 years and above	71 years and above

After the calculation of adjusted folic acid intakes, population statistics (such as mean and high percentile folic acid intakes) were then derived from the individuals' ranked adjusted intakes.

Not all foods consumed in the nutrition surveys were assigned a folic acid concentration as not all foods are permitted or required to be voluntary fortified. Therefore not all nutrition survey respondents are consumers of folic acid based on day one food consumption records only. However, after folic acid intake adjustments have been made based on a second day of food consumption data, all respondents have a folic acid intake as a function of how the adjusted intakes are calculated. This doesn't mean that there will be 100% of respondents consuming bread over two days. The intake assessments are based on other foods in addition to bread and it is simply a function of the second-day adjustment methodology.

Simulated diet for young children

Due to the limited data available to conduct a dietary intake assessment for young children, it was necessary to assess folic acid intakes of young children using the simulated diet that was developed in the 2016 NZTDS.

Simulated diets are intended to represent an average consumer for a particular age group in the population. The simulated diet included all appropriate foods from the key foods list identified from the EAT study. For a complete list of foods included in the simulated diet, refer to Appendix 3 of the NZTDS report (New Zealand Food Safety, 2018).

The NZTDS simulated diets contain generic foods (e.g. fish cakes, white bread). The foods in the simulated diet for young children were matched to the food composition data used in the dietary intake assessment for adults and children for the various fortification scenarios. The minimum, median and maximum folic acid content of the matched food composition data was determined for each generic food, these are presented in Appendix 2. Dietary intakes of folic acid were calculated by multiplying the folic acid content of each generic food by the amount of that food consumed by young children in the simulated diet.

Infant formula was the only food from the simulated diets which did not have folic acid composition data, as such the folic acid content of this was assumed to be the minimum amount required by the Australia New Zealand Food Standards Code (0.7 µg per 100 g) (FSANZ, 2002).

5.3 RESULTS AND DISCUSSION

The overall aim of any fortification program is to ensure that the distribution of folic acid intakes are increased for the target population of WCBA; whilst minimising excessive intakes for the non-target groups.

5.3.1 Young children (aged 1-3 years)

Folic acid intake estimates for the typical toddler (1-3 years) simulated diet under the different fortification scenarios are presented in Table 5.5. The calculation of dietary intakes is based on the median folic acid concentration in foods, results are also presented on simulated diets using the minimum and maximum concentrations.

Table 5.5: Dietary folic acid intakes for toddlers under different fortification scenarios

	Folic acid dietary intakes (µg per day)				
	Status quo	**Enhanced voluntary** *200 µg/100 g*	**All bread** *200 µg/100 g*	**All bread-making wheat flour** *300 µg/100 g*	**All wheat flour** *300 µg/100 g*
Median[1] (*Minimum, maximum)*	56 *(17,139)*	84 *(17,176)*	111 *(18,211)*	106 *(18,236)*	179 *(30,349)*
% of UL[2] *(UL 300 µg/day)*	20%	30%	40%	35%	60%

Notes:

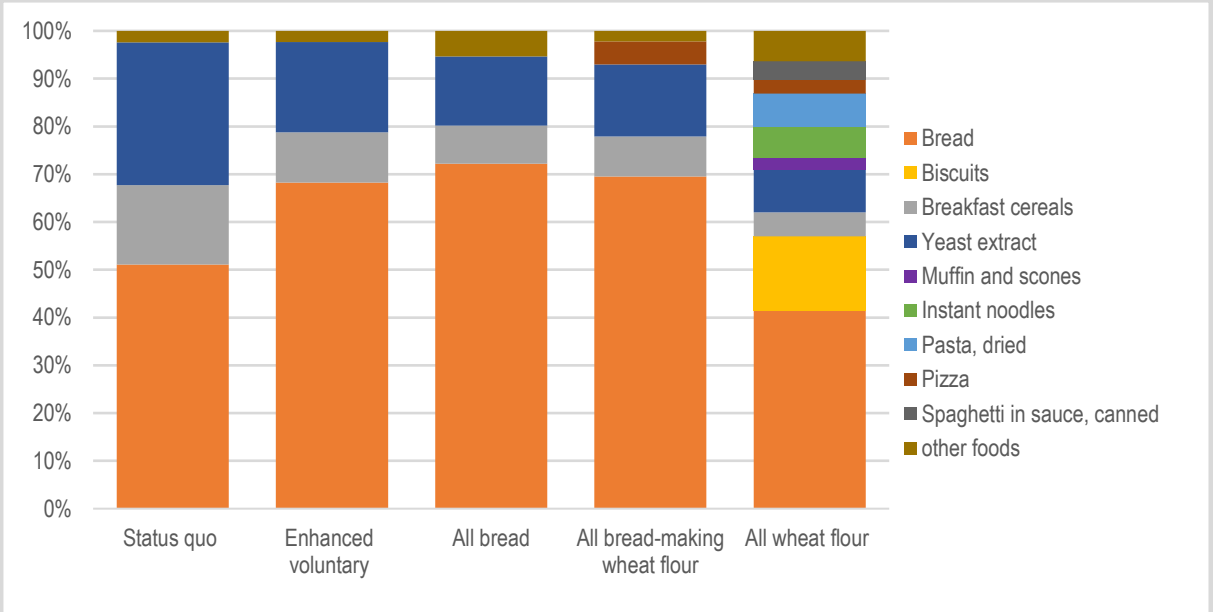
1. Intake based on median folic acid concentration (minimum concentration, maximum concentration)
2. Comparison to UL for folic acid is made with the median intake

The impact of the additional folic acid in the food supply under the different fortification scenarios is evident through comparison to status quo. As expected fortification of all wheat flour delivers the most folic acid to toddlers (179 µg/day) followed by the fortification of all bread (111 µg/day) and all bread-making wheat flour (106 µg/day), which deliver a similar amount of folic acid. Enhanced voluntary fortification delivers more folic acid than the status quo (84 µg vs. 56 µg per day) but less than the other fortification scenarios (106-179 µg per day). There were relatively large differences when the minimum and maximum concentrations were used within each fortification scenario, indicating the variability in products folic acid content.

The median folic acid dietary intake did not exceeded the established UL of folic acid for toddlers (300 µg/day) in any of the fortification scenarios. The only scenario to exceed the UL was the modelling using the maximum concentration of folic acid in the wheat flour fortification scenario (349 µg/day).

The key contributors to dietary folic acid intake in the typical toddler simulated diet are presented in Figure 5-1.

Figure 5-1: Major food contributors to estimated folic acid intake in toddlers' diets under the proposed fortification scenarios



Sources of folic acid in the simulated toddler diet were similar between fortification scenarios. Bread was the largest contributor to folic acid intakes across all fortification scenarios followed by yeast extracts. Breakfast cereals was also an appreciable source of folic acid across all scenarios.

For the all wheat flour scenario, bread made a relatively lower contribution to overall folic acid intake and other flour-based products became appreciable sources of folic acid (e.g. biscuits, pasta, instant noodles) in comparison to the other scenarios.

5.3.2 Adults, adolescents and children

The estimation of dietary folic acid intakes for adults, adolescents and children was undertaken using detailed consumption data from the national nutrition surveys as described in Section 5.1.1.

Estimated mean intakes of folic acid

The estimated mean intake of dietary folic acid for the target population and other age groups of the New Zealand population under each fortification scenario is found in Table 5.7. Following each of the mandatory fortification scenarios there is a notable increase in the folic acid intakes of all population sub-groups.

Mandatory fortification was estimated to lead to an increase in mean dietary intakes of at least 70 µg per day for WCBA under all scenarios modelled. This is considered to be a sufficient increase in folic acid intakes for the target population. The UK FSA set a target that a folic acid fortification program should aim to increase folic acid intakes by an average of 60-100 µg per day in WCBA (Mayer, 2017).

Mandatory fortification of all bread could lead to an increase in mean intakes of 83 to 165 µg per day under the scenarios modelled (target concentrations: 150 and 250 µg per 100 g, respectively). Mandatory fortification of all bread-making wheat flour would yield very similar results to mandatory fortification of all bread at a concentration of 150 and 200 µg per 100 g (estimated increase in mean intakes of 75-132 µg per day, respectively for WCBA).

Mandatory fortification of all wheat flour would result in the largest increase in mean folic acid intakes, with an increase of 143-234 µg per day under the scenarios modelled for WCBA (target concentrations: 200 and 300 µg per 100 g, respectively).

Estimated 5th and 95th percentile folic acid intakes

The intakes of folic acid at the 5th and 95th percentile were used to represent low and high consumers of folic acid within the target population. Generally these percentiles are used as the most appropriate representation of low and high consumers when calculating intakes using 2nd day adjusted methodology. Table 5.6 highlights the dietary intakes of the low and high consumers for the target group and
Figure 5-2 demonstrates how the distribution of folic acid intakes changes for each fortification scenario.

The estimated dietary intakes for low and high consumers of folic acid increase under mandatory fortification scenarios. The mandatory fortification of all bread and all bread-making flour have a similar effect on dietary intakes of WCBA increasing the folic acid intakes of the lowest consumers by approximately 40-70 µg per day. The fortification of all wheat had the greatest impact on dietary intakes increasing the folic acid intakes of the lowest consumers by approximately 100 to 160 µg per day (Table 5.6). Despite the increases in dietary intakes of folic acid, intakes at the 95th percentile remained below the UL of 1000 µg per day.

As fortification becomes more widespread the folic acid intakes increase and the shape of the distribution also changes for the population of WCBA (
Figure 5-2). Fewer women have low intakes and the distribution of folic acid intakes becomes slightly wider under the mandatory fortification scenarios.

Table 5.6 Dietary intakes of low and high folic acid consumers (5th and 95th percentile) for women of childbearing age (µg folic acid per day)

	Concentration (µg/100 g)	Dietary intakes of folic acid (µg per day)		
		Median	5th Percentile	95th Percentile
Status quo	-	60	29	160
Enhanced voluntary	150	83	39	203
	200	104	48	245
All bread	150	140	73	279
	200	178	94	353
	250	216	114	430
All bread-making wheat flour	200	134	69	256
	300	186	96	356
All wheat flour	200	206	129	328
	300	294	188	464

Figure 5-2 Distribution of folic acid intakes in the population of women of women of childbearing age (µg folic acid per day)

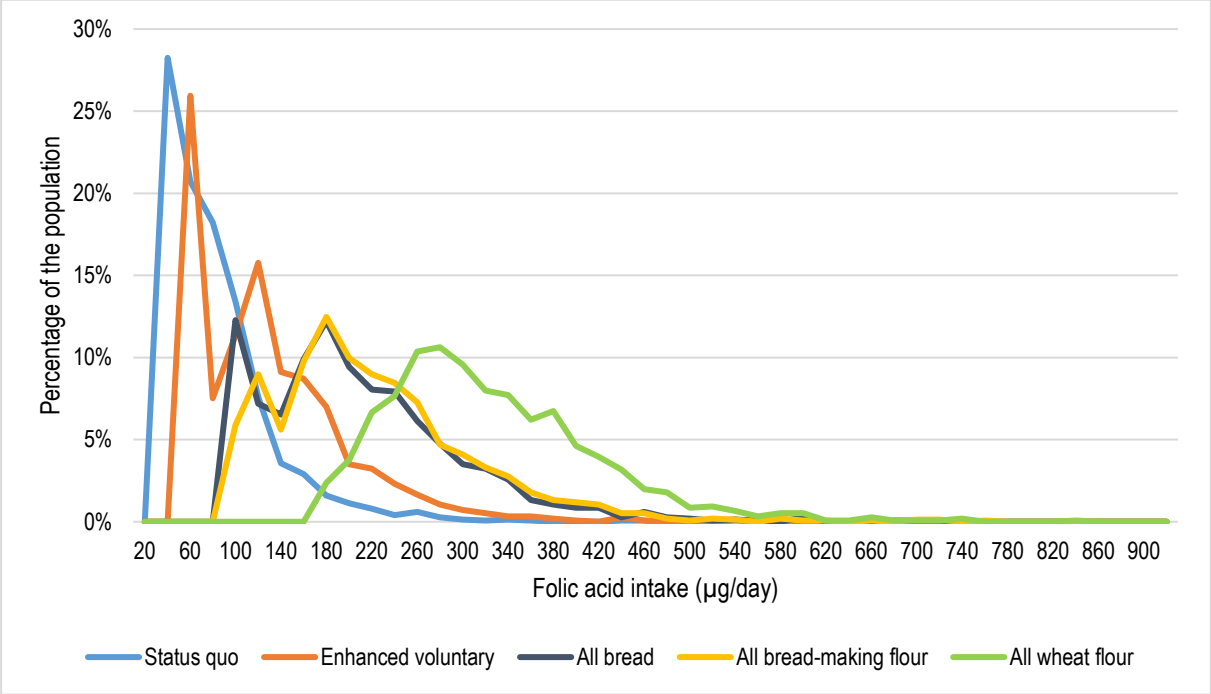


Table 5.7: Mean dietary intakes of folic acid in the target group, women of childbearing age, children, and adults (µg per day)

Population group	Mean dietary folic acid intakes (µg per day)									
	Status quo	Enhanced voluntary		All bread			All bread-making wheat flour		All wheat flour	
		150 µg/100 g	200 µg/100 g	150 µg/100 g	200 µg/100 g	250 µg/100 g	200 µg/100 g	300 µg/100 g	200 µg/100 g	300 µg/100 g
Women of childbearing age (15-49 years)	72	95	116	155	196	237	147	204	215	306
Children (5-14 years)										
5-8 years	97	129	157	196	246	297	189	262	265	376
9-13 years	101	136	167	214	272	329	207	290	297	425
14 years	123	164	201	254	321	388	247	345	344	489
Adolescents										
15-18 years	93	122	149	208	263	318	209	293	293	418
Adults										
19-30 years	83	108	130	187	236	285	185	257	268	382
31-50 years	91	123	151	201	256	311	185	259	262	374
51-70 years	95	127	155	190	240	289	165	227	226	319
71 years and above	96	128	158	183	230	278	158	217	207	290

Table 5.8 Percentage of the population with intakes of folic acid in excess of the UL

Population group	Mean dietary folic acid intakes (µg per day)									
	Status quo	Enhanced voluntary		All bread			All bread-making wheat flour		All wheat flour	
		150 µg/100 g	200 µg/100 g	150 µg/100 g	200 µg/100 g	250 µg/100 g	200 µg/100 g	300 µg/100 g	200 µg/100 g	300 µg/100 g
Women of childbearing age (15-49 years)	0	0	<1	<1	<1	<1	0	<1	0	<1
Children (5-14 years)										
5-8 years	<1	<1	1	1	6	14	1	6	5	36
9-13 years	0	0	<1	<1	<1	3	<1	1	<1	6
14 years	0	0	0	0	0	2	0	0	0	3
Adolescents										
15-18 years	0	<1	<1	<1	<1	<1	<1	<1	<1	2
Adults										
19-30 years	0	0	<1	<1	<1	<1	0	<1	0	<1
31-50 years	0	0	0	<1	<1	<1	0	<1	<1	<1
51-70 years	0	0	0	0	<1	<1	0	0	0	0
71 years and above	0	0	0	0	0	0	0	0	0	0

Estimation of excessive intakes

The proportion of the target and non-target population groups estimated to have exceeded the UL for dietary folic acid is shown in Table 5.8. Under the current voluntary fortification policy, less than 1% of the population exceeded the UL for each sub-group assessed.

Less than 1% of adults, including the target population of WCBA, exceeded the UL under all of the fortification policy scenarios assessed. Children and adolescents were more likely to exceed the UL with a mandatory fortification policy. Mandatory fortification of all wheat flour at the upper bound of 300 µg of folic acid per 100 g of wheat flour was the scenario that resulted in the highest proportion of children and adolescents with excessive intakes. This was followed by mandatory fortification of all bread at the upper limit of 250 µg of folic acid per 100 g of bread. These scenarios led to 36% and 14% of children aged 5-8 years exceeding the UL for folic acid, respectively. Children aged 5-8 years were most likely to exceed the age specific UL of 400 µg/day.

For population nutrient intake assessments, it is assumed that a small proportion of intakes above the UL is generally considered acceptable and indicative of a low likelihood of adverse health effects. In cases where the UL is exceeded, it is common practice to determine whether the proportion above the UL is acceptable on a case-by-case basis. The following are considered by FSANZ in their risk analysis: the extent of exceedances; the affected population groups and the toxicological end point and data used to set the UL (FSANZ, 2014).

Since the UL for folic acid was derived the basis for the toxicological end point has been questioned. The PMCSA report states that a 'recent re-analysis suggests that data originally used to set the UL were incorrectly interpreted, and that the UL therefore lacks a scientific basis (Wald, 2018). After the correct adjustment there was no association between higher doses and the health outcome.'

Although a higher proportion of children exceeded the UL this is not considered a health risk due to the wide safety margin, the uncertainty related to the derived value for the UL and its applicability to children.

Major food contributors to estimated dietary folic acid intake

The key contributors to dietary folic acid intakes for children aged 5-14 years and WCBA under the different fortification scenarios (with the exception of enhanced status quo) are presented below. Percent contributors were calculated from data from a single 24- hour recall.

Dietary sources of folic acid across the status quo and the different fortification scenarios were largely consistent between children and WCBA. Bread was the largest contributor to folic acid intakes under status quo and each fortification scenario for both children and WCBA. Bread contributed the greatest proportion of folic acid in the all bread and all bread-making wheat flour scenarios, and remained a contributor for the all wheat flour scenario. In the all wheat flour scenario other flour based products became key contributors of folic acid (e.g. cakes, muffins, biscuits and pasta). Breakfast cereals were also a key contributor across all scenarios; and yeast extracts (a sub-category of savoury sauces and condiments) were a significant contributor to folic acid intake in status quo.

Although not presented here, the percent contributors to folic acid intake in the other age categories (15-18, 19-30, 31-50, 51-70 and 71+ years) are largely similar to that of WCBA presented above.

Table 5.9 below presents the percent contribution of bread types to folic acid dietary intakes in WCBA. Across all the fortification scenarios, white breads and rolls contributed the greatest proportion of folic acid intake from bread in WCBA, followed by mixed grain then wholemeal breads and rolls. Speciality breads such as flat bread, pita bread, tortillas and pizza bases contributed less than 5% of all folic acid intakes for WCBA across all fortification scenarios.

Figure 5-3: Major food contributors to estimated dietary folic acid intake in children aged 5-14 years

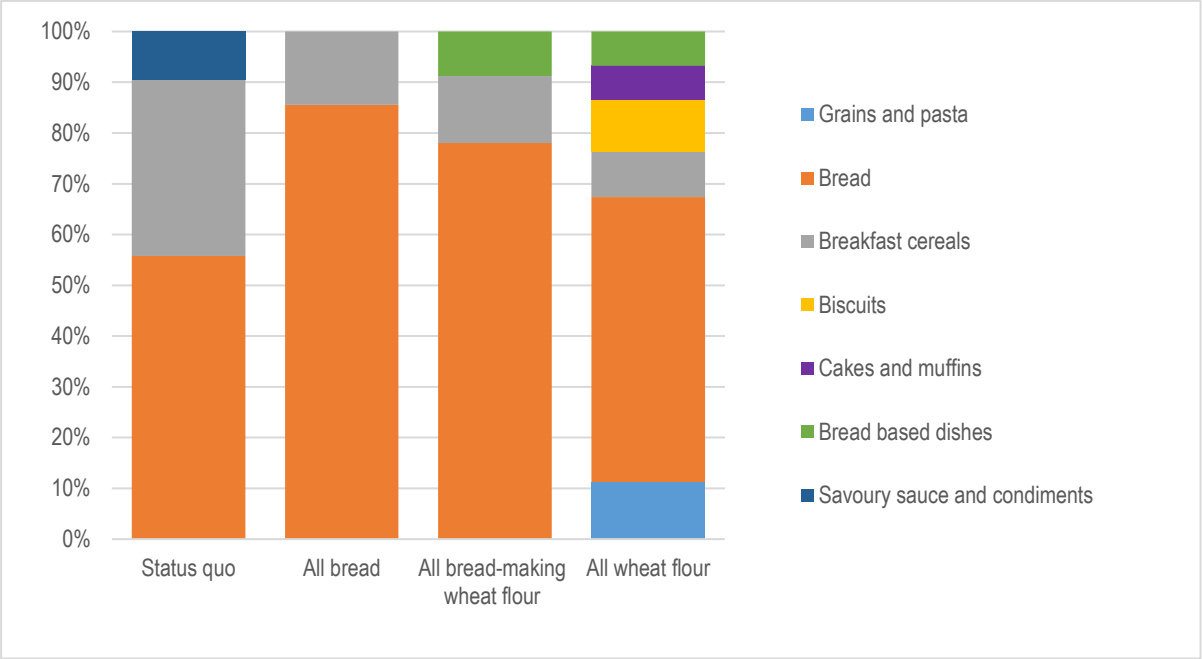


Figure 5-4: Major food contributors to estimated dietary folic acid intake in women of childbearing age

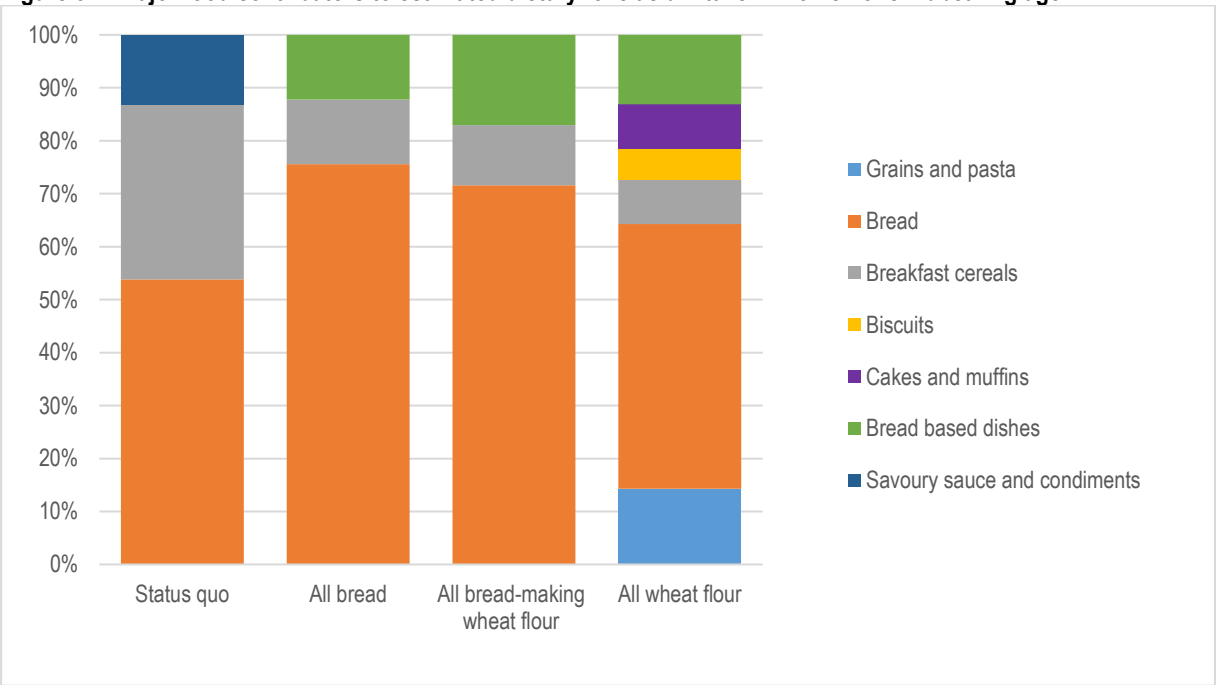


Table 5.9: Percent contribution of bread types to folic acid dietary intakes in women of childbearing age

	Percent contribution to folic acid dietary intakes			
	Status quo	**All bread (200 µg/100 g)**	**All bread-making wheat flour (300 µg/100 g)**	**All wheat flour (300 µg/100 g)**
Bread	**49%**	**68%**	**63%**	**42%**
Regular bread and rolls	49%	62%	55%	37%
White breads and rolls	*20%*	*30%*	*29%*	*20%*
Wholemeal breads and rolls	*8%*	*8%*	*8%*	*5%*
Mixed grain breads and rolls	*19%*	*21%*	*15%*	*10%*
Flat bread, Pita bread, tortillas (plain), pizza bases	0%	<5%	<5%	<5%

5.3.3 Comparison with previous modelling

This work is broadly comparable to previous dietary assessments investigating the impact of mandatory fortification on population intakes of folic acid. Specifically that most of the fortification scenarios can provide folic acid in sufficient amounts to the target population and limit excess intakes in the general population. Comparisons to other dietary assessments need to be interpreted with caution due to different methodologies, data sources, populations and mandatory fortification policies.

The previous dietary intake assessment undertaken by FSANZ in 2006 using New Zealand consumption data from the 1997 NNS estimated that the mean dietary folic acid intake (excluding supplements) under mandatory folic acid fortification of all bread (135 µg per 100 g) would be 198 µg per day for WCBA(16-44 years) (FSANZ, 2006b). It was estimated that very few New Zealand adults would have folic acid intakes exceeding the UL (<1%). Research undertaken by the University of Otago using data from the 2002 NCNS estimated that children aged 5-8 years were the most likely population group to exceed the UL if mandatory fortification of all bread were to be introduced (~3% exceed the UL) (Blakey, 2006).

Dietary assessment modelling estimating the potential impact of fortification of flour with folic acid in the UK was undertaken in 2017 (FSS, 2017). The estimated total population folic acid intake under mandatory bread fortification (using two different bread definitions at 200 µg per 100 g) was 104 to 121 µg per day and all wheat flour (excluding wholemeal at 200 µg per 100 g) was 157 µg per day. At these fortification levels the percentage of the population exceeding the UL was low at 0.4 to 0.5%.

The impact of mandatory fortification of bread and flour with folic acid in Ireland was estimated in 2016 (FSAI, 2016). The estimated total folic acid intake in women aged 18 to 50 years under mandatory bread fortification (at 225 µg per 100 g) was estimated to be 262 µg per day and flour (at 225 µg per 100 g) 265 µg per day. The probability of exceeding the UL for folic acid in older Irish adults (>50 year olds) would remain very low (0.1 to 0.2%) with the fortification scenarios.

Following the introduction of mandatory folic acid fortification of bread-making wheat flour in Australia the mean folic acid intake for women aged 16 to 44 years increase by 145 µg/day, from 102 to 247 µg/day (a 142% increase), greater than predicted (AIHW, 2016). Post-mandatory fortification, very few adults had estimated folic acid intakes that exceeded the UL. For those aged 2 to 3 years, the proportion above the UL increased from 5% to 21%, and for those aged 4 to 8 years from 3% to 15%.

Data from the National Health and Nutrition Examination survey (2007 to 2012) that assess the health and nutritional status of adults in the US, revealed that women in the US with optimal red blood cell folate concentrations (748 -1215nmol/L) reported a mean folic acid intake of 236 µg/100 g (Crider, 2018). This is similar to the predicted mean folic acid intake for the mandatory fortification scenarios.

5.3.4 Limitations of the dietary intake assessment

Dietary modelling based on national food consumption data provides the best estimate of actual consumption of a food and the resulting estimated dietary intake of a nutrient for the population. However, in New Zealand nutrition survey data was collected 10 years ago for adults and 17 years ago for children and changes in dietary patterns and the food supply have likely occurred since this time. Generally, consumption of staple foods such as cereal products do not vary markedly over time, however we are aware that women's bread consumption decreased slightly between the 1997 NNS and the 08/09ANS (Smith, 2015).

New Zealand does not have national consumption data for children under 5 years of age. Therefore the dietary assessment for children aged 12-24 months was based on simulated diets developed for the 2016 NZTDS. This was based on the best available consumption data from the EAT study but is not representative of the entire New Zealand population as participants were predominately New Zealand European and higher socioeconomic status. Simulated diets also only contain the average consumption of generic foods and therefore do not allow us to estimate the proportion of the population who may have intakes in excess of the UL.

The dietary intake assessment did not take into account folic acid intakes from dietary supplements as we did not have sufficient data from the nutrition surveys to calculate intakes. Although only a small proportion of the population are likely to take folic acid supplements they can provide a substantial contribution to the diet. In New Zealand the maximum daily dose of folic acid is 300 µg in a dietary

supplement. However the maximum can be increased to 500 µg folic acid if it has been demonstrated to Medsafe that the supplement is manufactured in a Good Manufacturing Practice certified facility (Medsafe, 2018). Due to the maximum limits on dietary supplements it is unlikely that there would be many in the population exceeding the UL under any of the fortification scenarios assessed. In the adult population intakes of folic acid at the 95th percentile ranged from 300 to 500 µg for the mandatory fortification of bread or bread-making wheat flour; and 300 to 700 µg for the mandatory fortification of all wheat flour.

There are some limitations associated with the folic acid concentration data. Data generated from label values have not been adjusted to take into account potential extra addition of folic acid by manufacturers (overages). For the flour fortification scenarios (i.e. all bread-making wheat flour and all wheat flour) losses in folic acid due to cooking and storage were not accounted for. Another major limitation is the assumption that all wheat flour consumed in New Zealand would be fortified with folic acid under the mandatory fortification of all wheat flour scenario. In reality it is unlikely imported wheat flour-containing foods would be required to be fortified with folic acid but it is difficult to estimate the contribution these products have to wheat flour consumption in New Zealand. Therefore our dietary assessment likely overestimates folic acid intake for this fortification scenario.

5.4 SUMMARY

Undertaking a dietary intake assessment demonstrated that the proposed fortification policies were able to sufficiently increase folic acid intakes in the target population whilst ensuring that the general population was not exposed to excessive intakes. These are two principles that are required to be fulfilled for mandatory fortification in the Policy Guidelines on the Fortification of Food with Vitamin and Minerals (Ministerial Council, 2004):

1. Ensure that the added vitamins and minerals are present in the food at levels that will not result in detrimental excesses or imbalances of vitamin and minerals in the context of total intake across the general population.
2. Ensure that the mandatory fortification delivers effective amounts of added vitamins and minerals with the specific effect to the target population to meet the health objective.

Ensuring intakes will not result in excesses or imbalances in the general population

The likelihood that dietary intakes of folic acid would exceed the UL is very low for adults (<1%) in all scenarios assessed. A higher proportion of children aged 5 to 8 years exceeded the UL in two scenarios: mandatory fortification of all bread at 150 to 250 µg of folic acid per 100 g of bread (1 to 14%) and the mandatory fortification of all wheat flour (5 to 36%).

Although a higher proportion of children exceeded the UL in two scenarios this could be managed through reducing the maximum limit for fortification. Lowering the fortification range for the mandatory fortification of all bread to a maximum of 200 µg of folic acid per 100 g of bread reduced the exceedances of the UL to an acceptable level (6% of children exceeded the UL). Small exceedances of the UL are not considered a health risk for children due to the wide safety margin, the uncertainty related to the derived value for the UL and its applicability to children.

Ensure effective amounts are delivered to the target population

The dietary intake assessment of the proposed scenarios demonstrated that the addition of folic acid to all bread, all bread-making wheat flour or all wheat flour would deliver a sufficient amount of folic acid to the target group, even those with the lowest intakes. The mandatory fortification options could lead to an increase in mean dietary folic acid intakes of at least 70 µg per day for WCBA. This is considered to be a sufficient increase as it meets the UK FSA's requirement that a fortification program should aim to increase folic acid intakes by an average of 60 to 100 µg per day (Mayer, 2017).

6 Modelling the impact of fortification

A stochastic model was developed to assess the impact of folic acid fortification and ensure that the proposed fortification scenarios could deliver effective amounts of folic acid for the reduction of NTD-affected pregnancies. Specifically, the model assessed the impact of the fortification scenarios on the folate status of a simulated population of pregnant women through using a range of values for key variables (in the form of a probability distribution) and how this corresponded to the risk of NTD-affected pregnancies.

The objective was to estimate the impact on the reduction in NTD-affected pregnancies in New Zealand of the current voluntary fortification policy and fortification options to improve WCBA's intakes of folic acid intakes. The fortification options assessed in Section 5 were refined to five feasible policy options each with its own specific fortification concentration (Table 6.1).

Mandatory fortification would require a minimum and maximum limit to be specified in the relevant standard whereas the voluntary fortification approaches rely on setting a target concentration in an industry code of practice.

The fortification concentrations for the status quo was based on the target level of fortification (200 µg per 100 g bread) specified in the NZAB code of practice. A lower concentration of 150 µg/100 g bread was specified for the enhanced voluntary fortification and mandatory fortification of bread options to minimise the proportion of children with intakes above the UL. The concentrations for the mandatory fortification of all bread-making wheat flour and all wheat flour scenarios were aligned with the Australian permissions for the mandatory fortification of bread-making flour in the Australia New Zealand Food Standards Code (no less than 2mg/kg, and no more than 3mg/kg, of folic acid) (FSANZ, 2002).

Table 6.1 Fortification options assessed to model the impact of fortification

Scenario	Fortification concentration
Status quo, current voluntary fortification policy	200 µg/100g bread[1]
Enhanced voluntary fortification of 80% packaged sliced bread	150 µg/100g bread[1]
Mandatory fortification of all non-organic bread	150 µg/100g bread[2]
Mandatory fortification of all non-organic bread-making wheat flour	250 µg/100g flour[2]
Mandatory fortification of all non-organic wheat flour	250 µg/100g flour[2]

Notes:

1. Target folic acid concentration
2. Midpoint of the regulatory range for mandatory fortification (all bread 100 to 200 µg folic acid per 100 g; all bread-making wheat flour and all flour: 200 to 300 µg folic acid per 100 g).

The model is based on the risk of an NTD-affected pregnancy in a simulated population of pregnant women, of which some women take supplements. The first stage in the model is to predict the impact of increased folic acid intakes from fortification on an individual's folate status. The increase in folate status is then used to predict NTD risk for the individual and consequently the population.

6.1 BACKGROUND

The WHO strongly recommends that red blood cell (RBC) folate concentrations should be above 906 nmol/L in WCBA to achieve the greatest reduction in NTDs (WHO, 2015). The evidence that underpins this recommendation is based on two notable studies which provide information on establishing the relationship between folate status and the risk of NTD-affected pregnancies.

The first study to establish the dose-response relationship between blood folate concentrations (RBC folate) and NTDs was a case-control study in Ireland (Daly, 1995). The study was conducted in women who attended their first antenatal clinic assessment at one of the three main Dublin maternity hospitals between 1986 and 1990. Folate status (RBC and serum folate) was measured from stored samples taken at a median gestational age of 15 weeks. Folate status had been prospectively collected from women with a NTD-affected birth and this was matched with women without an NTD-affected birth. A dose-response relationship was established between the risk of having a child with a NTD and folate status. This led to the establishment of a threshold concentration for RBC folate concentrations of 906 nmol/L; at which the risk of NTDs was estimated to be 8 NTD cases per 10,000 births (Daly, 1995). The relationship between a change in serum folate concentrations and the effect on NTD risk was also quantified in a model derived by Wald and colleagues in 2001.

More recently a Bayesian model was developed to estimate the association between RBC folate concentrations at the time of neural tube closure (day 28 of gestation) and the risk of NTDs (Crider, 2014). Data from two population based-studies in China were used to inform the model. The first of which was a prospective community intervention study providing daily 400 µg supplements to prevent NTDs; and the second to evaluate the effect of varying folic acid supplement doses on RBC folate concentrations. It was estimated that RBC folate concentrations of 1180 nmol/L could lead to the lowest risk of NTDs (6 NTDs per 10,000); there was limited additional benefit at concentrations above 1300 nmol/L. These findings are consistent with the Irish case-control study and highlight that this relationship exists in both Irish and Chinese women despite differences in genetic background and diet.

These two publications demonstrate that folate concentrations, particularly RBC folate can be used to predict the prevalence of NTDs in a population.

6.1.1 Previous models

The stochastic models used in this assessment build upon previous work conducted by FSANZ and MPI (FSANZ 2006b; MPI, 2012c). This work uses the latest available data and modelling techniques to assess the range of fortification scenarios under consideration.

In 2006, FSANZ assessed the impact of fortification of bread at a concentration of 135 µg folic acid per 100g bread based on a serum folate status model (FSANZ, 2006b). The relationship between a change in serum folate concentrations and the effect on NTD risk was quantified using the model derived by Wald and colleagues in 2001, based on data from the Irish case-control study (Daly, 1995).

FSANZ used the Wald model (2001) to determine the number of NTD cases prevented at a mean increase in dietary intakes of folic acid of 100 µg (the average increase of folic acid from the mandatory fortification of bread) across the population of WCBA in New Zealand and Australia. At the time this model was developed there was limited New Zealand data available.

In 2012, MPI estimated the impact of fortification on risk of NTDs for a variety of policy options, including voluntary fortification with updated New Zealand specific data. A stochastic model was created to do this based on changes in serum folate concentrations in the population in response to fortification. The Wald model (2001) was used but with modification to the predicted increase in serum folate in response to folic acid intakes. A linear regression equation derived by Quinlivan was used to predict the increase in serum folate in response to folic acid fortification (Quinlivan, 2007).

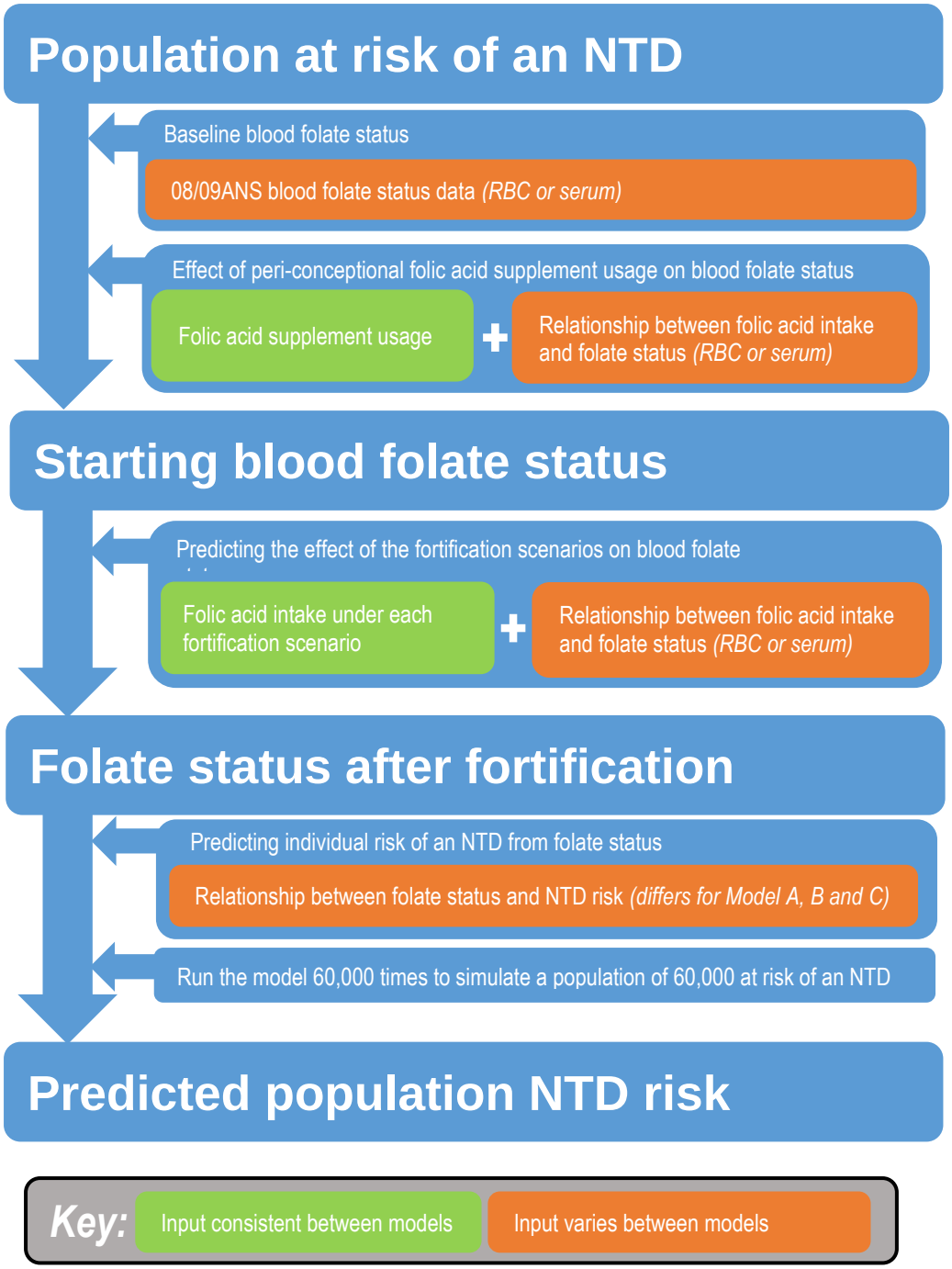
6.2 METHODS

As described in Section 6.1 there are three models that have been published which can be used to predict the risk of an NTD-affected pregnancy based on folate status. Of these published models the Irish case-control study can be used to predict the NTD risk for both serum (Wald, 2001) and RBC folate (Daly, 1995); and the Bayesian model, based on a Chinese population, can be used to predict NTD risk for RBC folate (Crider, 2014). As there was no compelling reason to consider one model as more reliable than the others, the three different models were used to predict the impact of fortification on NTDs:

- Model A: Serum folate Wald model
- Model B: RBC folate Daly model
- Model C: RBC folate Crider model

Figure 6-1 provides an overview of the methodology used to predict the impact of fortification on NTD risk. As outlined in the figure key, green boxes were inputs that were consistent between models and orange boxes were inputs that varied between models. The key differences between the three models were the use of serum or RBC folate and therefore the relationship between folic acid intake and folate status (differs for serum and RBC folate); and the relationship between folate status and NTD risk (as described above this differs for each model).

Figure 6-1: Overview of the methodology used to predict the impact of fortification on NTD risk



6.2.1 Simulated population at risk of an NTD-affected pregnancy

The models were simulated for a population of 60,000 women at risk of a NTD-affected pregnancy. This number represents the average number of live births in New Zealand between 2015 and 2017 (Stats NZ, 2018). Depending on the model, each individual within the simulated population was randomly assigned a blood folate concentration (serum folate and RBC) and whether they were a supplement user (and if so whether they had taken a 400 µg or 800 µg supplement). These two data points were used to establish the simulated population's starting blood folate status.

Blood folate status

The baseline folate status of the simulated population was derived from the distribution of blood folate levels of non-pregnant WCBA (aged 15 to 49 years) from the 08/09ANS (University of Otago and Ministry of Health, 2011). At the time of the 08/09ANS there was relatively low uptake of folic acid

fortification of bread. We could therefore use this as a baseline to model the five proposed fortification scenarios.

The distribution of serum folate and RBC folate of non-pregnant WCBA are presented in Table 6.2 (data extracted by Ministry of Health, January 2019). Serum folate and RBC folate were analysed using the microbiological assay with *Lactobacillus rhamnosus* as the test organism and folic acid as the calibrator (Bradbury, 2014), this method can also be referred to as the Molloy method (Tinker, 2015).

The baseline folate levels were modelled with the @Risk distribution "RiskCumul". @Risk (Palisade) is the software programme that was used. The distribution "RiskCumul" is a cumulative distribution with n points between a minimum and a maximum with cumulative ascending probability p at each point.

Table 6.2: Serum and RBC folate status of non-pregnant women of childbearing age (15 to 49 years) in the 2008/09 Adult Nutrition Survey

Category	Min	1st	5th	10th	25th	50th	75th	90th	95th	99th	Max
Serum folate (nmol/L)	3	6	9	10	14	22	35	51	65	114	575
RBC folate (nmol/L)	14	205	366	434	553	749	982	1317	1564	2777	2937

Usage of periconceptional folic acid supplements

A proportion of women take folic acid supplements prior to conception. A survey by the New Zealand Ministry of Health reports that 8.6% of women take the 800 µg folic acid tablet in the 90 days prior to conception (average of years 2014 and 2015) (see Section 3.2). It was estimated that a further 5.7% of women took a 400 µg folic acid supplement 90 days prior to conception based on the proportion of women taking supplements from the Vitamin and Mineral study *(personal communication 2012, Dr Lisa Houghton).*

The quantity of folic acid (QFA_{Sup}) taken as supplement was modelled as:

QFA_{Sup} = Discrete (0,400,800; 0.8575, 0.057, 0.0855)

Predicting the increase in folate status from folic acid supplements

Through the regular consumption of folic acid supplements, the folate status will increase. The increase in blood folate status corresponding to the amount of folic acid consumed through supplements was calculated for each individual taking a supplement. The revised blood folate status for the simulated population was the baseline folate status and the change in folate status following supplementation. This is referred to as the starting blood folate status for the model and simulates the folate status of the population of pregnant women at the time of conception. The methods for calculating the increase in folate status based on a known amount of folic acid is described in detail below, and they were used to predict the increase in folate status from both fortification and supplementation in the model.

6.2.2 Predicting increase in folate status from fortification

To predict the increase in folate status from increased intakes of folic acid, two approaches were used to reflect the different measures of folate status: serum folate and RBC folate. Folate can be measured in whole blood (RBC folate) and serum (serum folate). Serum folate levels are an indicator of more recent dietary intake of folate and reach a 'steady state' at approximately 90 days; whereas RBC folate is a measure of longer term folate status due to the slower turnover in erythrocytes and take approximately 36 weeks of folic acid intake to achieve a steady-state concentration (Crider, 2019).

Increased folic acid intake through fortification

The increase in folic acid intakes of WCBA from the dietary intake assessment in Section 5 was used to estimate the effect of the fortification scenarios on NTD-affected pregnancies. The status quo scenario demonstrates the increase in folic acid in the food supply since the 08/09 ANS when voluntary folic acid fortification was less widespread. Folic acid concentrations for each fortification scenario were limited to a single concentration that would be aimed for by food producers (

Table 6.3). For mandatory scenarios minimum and maximum requirements would be specified in the relevant food standard so the midpoint of the regulatory range was used; for voluntary standards a code of practice specifies a target concentration for bakers to fortify bread.

Table 6.3 Percentile distribution of folic acid intakes of WCBA

	5th	10th	20th	30th	40th	50th	60th	70th	80th	90th	95th
Status quo	29	31	34	42	53	60	70	83	97	127	160
Enhanced voluntary[1] 150 µg/100 g[2]	39	43	45	57	75	83	93	112	131	167	203
All bread[3] 150 µg/100 g[4]	73	77	92	115	126	140	160	182	205	250	279
All bread-making wheat flour[3] 250 µg/100 g[4]	83	91	116	132	146	160	181	205	230	274	306
All wheat flour[3] 250 µg/100 g[4]	159	173	196	214	230	250	269	290	319	358	396

Notes:

1. Fortification of 80% packaged sliced bread
2. Target folic acid concentration
3. Excludes organic
4. Midpoint of the range of mandatory fortification regulatory minimum and maximum values (all bread 100 to 200 µg folic acid per 100 g; all bread-making wheat flour and all flour: 200 to 300 µg folic acid per 100 g).

Serum folate model

A linear regression equation derived by Quinlivan was used to convert dietary intakes of folic acid to serum folate levels (Quinlivan, 2007). Data from 10 intervention studies using either folic acid or 5-methyltetrahydrofolate were used to determine the relationship between folate interventions and changes in steady state folate concentrations.

The folate intake from these studies were expressed as DFEs. Folic acid is more bioavailable than food folates; as such folic acid is multiplied by 1.7 to convert into DFE (Quinlivan, 2007; NHMRC 2006). To use the regression equation, the additional folic acid intake from the fortification scenarios (Table 6.3) had to be converted to DFEs.

If an individual consumed folic acid there would be a corresponding increase in serum folate from the additional folic acid (either through fortification or supplementation). We used the regression line derived from all intervention studies (excluding the study of van Oort and colleagues) (Quinlivan, 2007) to calculate the increase in serum folate for each individual.

Equation 2: Quinlivan equation to calculate increase in serum folate from intakes of DFEs

$$y = 0.0145x + 0.132$$

NB. Where x is the additional intake of DFEs.

A final serum folate concentration was then calculated for each individual in the simulated population. This was simply the starting serum folate plus the change in serum folate as calculated using the Quinlivan equation. This approach was only used for Model A, the serum folate Wald model.

Red blood cell folate model

A dose-response meta-analysis on the relationship between folic acid intakes and folate status by Duffy and colleagues was used to predict changes in RBC folate in response to folic acid (Duffy, 2014). This review quantified the typical response of RBC folate to a change in folic acid intakes using a random-effects meta-analysis. Overall it was estimated that the exponent to which folic acid intake is raised for RBC folate (*β*^) was 0.4. For an individual with folic acid intakes of 200 µg per 100 g, their corresponding RBC folate was 32% higher than for an individual with an intake of 100 µg per 100 g (Duffy, 2014).

Equation 3: Based on Duffy equation to calculate increase in red blood cell folate from intakes of folic acid

$$y = \left((\frac{x}{200})\text{^}0.4\right) 284$$

NB. Where x is the additional intake of folic acid.

A final RBC folate was then calculated for each individual in the simulated population. This was simply the starting RBC folate plus the change in RBC folate estimated using the data from Duffy and colleagues (Duffy, 2014).

This approach was used for the RBC models: Model B, RBC folate Daly model and Model C, RBC folate Crider model.

6.2.3 Predicting risk of an NTD from folate status

In general the same approach was used for each model, the specific differences for each model are provided in detail. For each of the models the risk of an NTD-affected pregnancy was calculated for each individual within the simulated population based on their folate status following increased folic acid intakes from supplementation and the fortification scenario (final folate status). The risk of an NTD-affected pregnancy was then calculated for the population for the starting folate status in comparison to each of the fortification scenario options. The starting folate status represented the population of WCBA in 2008/09 when there was limited uptake of the voluntary fortification permissions for bread. The median difference between the starting folate status of the simulated population and final folate status of the population was calculated for each fortification scenario. The difference in the median difference for each scenario in comparison to the status quo was then used to compare the impact of enhanced voluntary or mandatory fortification scenarios to the current levels of fortification uptake.

Model A: Serum folate Wald model

The relationship between a change in serum folate concentrations and the effect on NTD risk was quantified in a model derived by Wald and colleagues in 2001 based on the work of Daly and colleagues (1995). Through this work it was estimated that doubling serum folate concentration approximately halved the risk of NTDs. The slope of a regression line, corrected for regression dilution bias, was used to determine the relative odds of an NTD, with the following equation:

Equation 4: Wald equation to calculate the relative odds of an NTD based on serum folate status

$$Relative\ odds = \left(\frac{new\ serum\ folate}{old\ serum\ folate}\right)^{-0.81}$$

This approach previously underpinned the modelling conducted by FSANZ and MPI (FSANZ 2006b, MPI 2012c), and is the model most comparable to previous modelling conduced for the New Zealand population of WCBA.

For a given percentage increase in serum folate, a constant percentage reduction in the risk of an NTD was achieved. In order to estimate the actual risk for the population, the serum folate value for a given NTD risk from the Daly data was required. For the purpose of this work, the risk associated with a serum folate value of 4 µg/L (mid value of 3.0 – 4.9 µg/L) resulting in 1.9 NTDs per 1,000 was used.

A binomial distribution was then used to model whether a pregnancy was affected with an NTD or not. The model was run 60,000 times to model 60,000 pregnancies and the mean risk calculated. The model was run a further 30 times and results were summarised as a median NTD rate per 10,000 births.

Model B and C: RBC folate models

Crider and colleagues developed a risk model to relate the log odds of having an NTD-affected pregnancy with an estimated log RBC folate concentration at the time at which the neural tube closes (Crider, 2014). They derived the predictive equations for both the Irish case-control study (Daly, 1995) and the Bayesian model in the Chinese population in order to compare their results (Crider 2014, Data supplement). Despite the comparability of the two studies to establish an optimal RBC folate concentration, there are differences in the estimates used in prediction equations.

Equation 5: Predictive equations to calculate the log odds of risk of an NTD based on RBC folate status

The predictive equations were based on a logistic regression model where the log odds of risk are linearly related to the natural log of RBC folate:

$$\log(O_i) = \partial_0 + \partial_i * \log(RBCF_i)$$

Where p_i is the probability of subject *i* having a child with a NTD, then:

$$\log(O_i) = \log\left(\frac{p}{1-p}\right)$$

For the Irish case-control study (Daly 1995), Model B, the estimates are: ∂_0=1.6463; ∂_i= -1.2193

For the Bayesian model developed by Crider and colleagues (2014), Model C, the estimates are: ∂_0=4.57; ∂_i= -1.7

We used both predictive equations in our model. These two RBC models were also used in the stochastic modelling conducted for Food Standards Scotland (2017).

The risk of an NTD-affected pregnancy was calculated for each of the 60,000 individuals in the simulated population and the median risk was calculated for the population. The model was run a further 30 times and results were recorded as a median NTD rate per 10,000 births and per year.

6.3 RESULTS AND DISCUSSION

Enhanced voluntary and mandatory fortification scenarios were all effective in further reducing NTDs in New Zealand. As expected, mandatory fortification options were more successful at reducing NTDs and mandatory fortification of all wheat flour was most successful. Enhanced voluntary fortification reduced NTDs by approximately 3 to10%. Mandatory fortification of all bread and all bread making-flour reduced NTDs by approximately 10 to 20%; and all wheat flour by approximately 15 to 30% (Table 6.6).

In terms of the NTD-affected pregnancies that would be prevented each year, the models predicted that each year approximately: 2 to 5 could be prevented with enhanced voluntary fortification; 5 to 9 could be prevented with fortification of all bread or all bread-making wheat flour; 8 to 14 could be prevented with fortification of all wheat flour (Table 6.4).

Table 6.4 presents the predicted number of NTD-affected pregnancies prevented by pregnancy outcome for each of the fortification scenarios and models. As most NTD-affected pregnancies either result in a live birth or termination, reductions in these two outcomes are most greatly impacted by the fortification scenarios.

Table 6.4: Predicted numbers of NTD-affected pregnancies, by pregnancy outcome, prevented per year by the proposed fortification scenarios in comparison to the current fortification levels for models A, B and C

	Total number of NTDs			Live births			Stillbirths			Terminated pregnancy		
	A[1]	B[1]	C[1]	A	B	C	A	B	C	A	B	C
Enhanced voluntary[2]	5.00	2.10	1.80	2.05	0.86	0.74	0.70	0.29	0.25	2.25	0.95	0.81
All bread[3,4]	9.00	5.40	4.80	3.69	2.21	1.97	1.26	0.76	0.67	4.05	2.43	2.16
All bread-making[3,5] wheat flour	8.00	6.30	5.40	3.28	2.58	2.21	1.12	0.88	0.76	3.60	2.84	2.43
All wheat flour[3,5]	13.50	9.60	8.40	5.54	3.94	3.44	1.89	1.34	1.18	6.08	4.32	3.78

Notes:

1. Model A Serum folate (Wald)**;** Model B RBC folate (Daly)**;** Model C RBC folate (Crider)
2. Fortification of 80% packaged sliced bread. Modelled at fortification concentration of 150 µg folic acid per 100 g bread.
3. Excludes organic
4. Modelled at fortification concentration of 150 µg folic acid per 100 g bread, the midpoint of the range of mandatory fortification of all bread
5. Modelled at fortification concentration of 250 µg folic acid per 100 g flour, the midpoint of the range of mandatory fortification of all bread-making wheat flour and all wheat flour

6.3.1 Estimated number of NTDs if mandatory had occurred in 2009

As each scenario was calculated in comparison to a starting folate status representative of WCBA in 2008/09 it is possible to estimate the number of NTD-affected pregnancies that could have been prevented had mandatory fortification of bread-making flour occurred in 2009.

As there has been an increase in the amount of folic acid fortification of bread since 2009 two time points are considered within the ten-year period that mandatory fortification was to take place: October 2009 to 2015; 2015 to 2019. In 2015 the NZAB reported that 30% of their packaged sliced bread was fortified, a level of fortification that has remained fairly steady.

The calculated median difference from the starting folate status and the predicted NTD rates for bread-making flour was used to determine the number of NTDs that could have been prevented in the 6 years from October 2009 to 2015; and the difference between status quo and fortification of bread-making flour was used for the four year period 2015 to 2019.

If mandatory fortification of bread had occurred in 2009, it is estimated that 134 to 180 pregnancies affected by an NTD could have been prevented over the last ten years

Table 6.5: Number of NTD-affected pregnancies that could have been prevented if mandatory fortification was in place from 2009

NTDs prevented	Model A	Model B	Model C
2009 to 2015	102	155	148
2015 to 2019	32	25	21
Total	**134**	**180**	**169**

6.3.2 Comparison in the predictive ability of each model

The predicted NTD prevalence of the current fortification practices ranged from 7.7 to 11.4 NTD-affected pregnancies per 10,000, using Model C (RBC folate Crider) and Model B (RBC folate Daly), respectively (Table 6.6). This aligns well with the most recent New Zealand data, that there were 10.6 NTD-affected pregnancies per 10,000 births in the period 2011 to 2015 (Section 2.4).

Model A (Serum folate, Wald), predicted the largest percentage reduction in NTD-affected pregnancies with increasing coverage of folic acid fortification (Table 6.6). Model A predicted an 11% reduction in NTD-affected pregnancies with enhanced status quo, 19% reduction if all bread was fortified, 17% if all bread-making flour was fortified and 29% if all wheat flour was fortified (Table 6.6).

The two RBC folate models predicted similar reductions in NTD-affected pregnancies (Model B, RBC folate Daly; and Model C RBC folate Crider). Model B predicted that an additional 6.3 NTD-affected pregnancies would be prevented if all bread making flour was fortified (a reduction of 9.2% reduction); compared to preventing an additional 5.4 NTD-affected pregnancies as predicted using Model C (11.7% reduction) (Table 6.6).

Model A and C predicted similar NTD prevalence rates per 10,000 births for each fortification scenario. These models predicted the current NTD prevalence of approximately 7.8 NTD-affected pregnancies per 10,000 births, and that mandatory fortification of all wheat flour could reduce the prevalence of NTD-affected births to approximately 6.0 per 10,000 births (Table 6.6).

Table 6.6: Predicted impact of proposed fortification scenarios on the prevalence of NTDs in comparison to the current fortification using three models

	Current fortification	Enhanced voluntary[1]	All bread[2, 3]	All bread-making wheat flour[2,4]	All wheat flour[2,4]
Predicted median NTD prevalence per 10,000 births (IQR)					
Model A Serum folate (Wald)	7.8 (7.0, 9.3)	7.3 (6.1, 7.8)	6.5 (5.8, 7.5)	6.7 (5.9, 7.5)	6.0 (5.3, 6.5)
Model B RBC folate (Daly)	11.4 (11.4, 11.4)	11.0 (11.0, 11.1)	10.5 (10.5, 10.5)	10.3 (10.3, 10.4)	9.8 (9.8, 9.9)
Model C RBC folate (Crider)	7.7 (7.6, 7.7)	7.3 (7.3, 7.4)	6.8 (6.8, 6.8)	6.7 (6.7, 6.7)	6.2 (6.2, 6.3)
Predicted median difference in NTD prevalence per 10,000 births					
Model A Serum folate (Wald)	Reference	0.8	1.5	1.3	2.3
Model B RBC folate (Daly)	Reference	0.4	0.9	1.1	1.6
Model C RBC folate (Crider)	Reference	0.3	0.8	0.9	1.4
Predicted median number of NTDs prevented per year (% reduction)					
Model A Serum folate (Wald)	Reference	5.0 (10.8%)	9.0 (19.4%)	8.0 (17.2%)	13.5 (29.0%)
Model B RBC folate (Daly)	Reference	2.1 (3.1%)	5.4 (7.9%)	6.3 (9.2%)	9.6 (14.0%)
Model C RBC folate (Crider)	Reference	1.8 (3.9%)	4.8 (10.4%)	5.4 (11.7%)	8.4 (18.2%)

Abbreviations

NTD: neural tube defect; IQR: Interquartile range; RBC: red blood cell

Notes:

1. Fortification of 80% packaged sliced bread; target fortification level of 150 µg folic acid per 100 g of bread
2. Excludes organic
3. Modelled at fortification concentration of 150 µg folic acid per 100 g bread, the midpoint of the range of mandatory fortification of all bread
4. Modelled at fortification concentration of 250 µg folic acid per 100 g flour, the midpoint of the range of mandatory fortification of all bread-making wheat flour and all wheat flour

6.3.3 Comparison with previous modelling

The 2012 MPI stochastic model predicted that the effectiveness of fortification increased as the proportion of population consuming fortified products increased. These findings are consistent with this work, as those food vehicles with more widespread consumption resulted in a larger reduction in NTD-affected pregnancies.

At the time the previous models were conducted for New Zealand population there was a lower uptake of voluntary fortification and higher rate of NTD-affected pregnancies (FSANZ, 2006b; MPI, 2012c). It is expected that comparisons to current fortification would therefore result in fewer reductions in NTDs.

Fortification of all bread in the 2012 MPI model predicted a reduction of 17 NTD-affected pregnancies (95% confidence interval 14, 20). In comparison, Model A predicted that nine NTD-affected pregnancies would be prevented if all bread was fortified in comparison to the current uptake of fortification (status quo). As expected, fewer NTD-affected pregnancies were prevented in this analysis as a third of all bread is now fortified[9].

A direct comparison can be made between the 2012 MPI model and use of the current model using the 2008/09 fortification levels. Using 2008/09 as the baseline, it was predicted that 17 NTD-affected pregnancies could have been prevented each year if all bread had been fortified using Model A, the same number as predicted using the 2012 MPI model. Model A most closely resembles the stochastic model used in 2012 and resulted in the same reduction in NTD-affected pregnancies if all bread was fortified. Models B and C predicted that approximately 25 NTD-affected pregnancies could be reduced in comparison to 2008/09.

By contrast, the 2006 FSANZ model predicted much lower reductions, estimating that only six NTD-affected pregnancies would be prevented if all bread was fortified (FSANZ, 2006b). The main differences in the inputs to the models used by FSANZ and MPI were: the use of the Quinlivan equation to predict the increase in serum folate in response to folic acid fortification and the serum folate data and food consumption data to underpin the model.

The results of the current model also align well with more recent modelling conducted in the United Kingdom and Ireland. The most recent stochastic modelling that was conducted for the UK population presented the results as an estimated percentage reduction in risk (FSS, 2017). It was found that with higher levels of fortification for all non-wholemeal wheat flour (greater than 250 µg/100 g) could lead to a risk reduction of 20 to 25%. Similar reductions in risk were predicted with fortification of all wheat flour at 250 µg/100 g in the current model. Modelling work conducted in Ireland demonstrated that fortification of bread at 120 µg/100 g could reduce the risk of NTD-affected pregnancies by 17% (FSAI, 2016).

As described in Section 3, mandatory fortification has already been implemented in a number of countries and its effect on reductions in NTD-affected pregnancies have been reported. In the USA there was a 28% reduction in NTD rates from 10.6 to 7.6 per 10,000 births between the pre-fortification and post fortification period (1999-2000) (Williams, 2015). Whereas Canada, South Africa, Costa Rica, Chile, Argentina and Brazil have reported declines in NTDs of between 19-55% since the implementation of mandatory folic acid fortification (Crider, 2011). The three models predicted reductions in risk of an NTD-affected pregnancy of 8 to 29% percent if mandatory fortification was introduced. It is reasonable that there would be a range of reductions in risk between countries as the coverage of fortification would vary and the size of the reduction will be lower in countries with a lower baseline prevalence of NTDs (Heseker, 2008). Given the current prevalence rate of NTD-affected pregnancies in New Zealand and the recent increases in voluntary fortification of bread, the predicted reductions in risk from these models seem plausible.

6.3.4 Limitations

Best efforts were taken to develop a robust estimate of the impact of fortification on the prevalence of NTD-affected pregnancies in New Zealand. Three models were developed to calculate this risk to ensure reliability in the estimates calculated. These models have all been used by other researchers and each has its own strengths and limitations. As such it was not considered appropriate to consider any model as 'preferred' or 'most accurate'.

[9] 34.2% of all packaged bread by volume. 38% of breads produced by NZAB with NZAB representing 90% of the packaged bread market.

To date RBC folate is the only biochemical measure of folate recommended to be used as a biomarker for the risk of having a NTD-affected pregnancy (WHO, 2015). As such Models B and C are able to better predict risk at a given RBC folate concentration, however there are some limitations in these models' ability to predict increases in RBC folate concentrations based on a given folic acid intake. We used the dose-response meta-analysis conducted by Duffy and colleagues (Duffy, 2014) but there was significant heterogeneity based on folic acid doses, study duration and assay used. There is limited data available on RBC folate response to folic acid intakes that are of sufficient duration to calculate the response to steady-state conditions and that use the microbiological method. The only meta-analysis to attempt to calculate this could only determine a change in RBC folate concentrations in response to supplements of approximately 400 µg/day (Crider, 2019). Therefore the dose-response meta-analysis conducted by Duffy and colleagues was used, the benefit of using this study is that it aligns well with the coefficients used in the stochastic modelling conducted in the UK (FSS, 2017).

Model A was derived to replicate the previous model used by MPI in 2012. Very recently further work has been done to characterise a dose-response relationship between folic acid intakes and serum folate however this was not available at the time the model was developed (Crider, 2019; Quinlivan, 2007). In addition to this, we used the Quinlivan equation to replicate the 2012 MPI model as closely as possible.

In the Irish case-control study, folate samples were taken at 15 weeks, much later than the time of neural tube closure (Daly, 1995). The authors stated that RBC folate was likely to be a better indicator for folate status at the time of neural tube closure due to the slower turnover in erythrocytes (approximately 36 weeks) (Daly, 1995).

6.4 SUMMARY

Modelling the impact of fortification has demonstrated that enhanced voluntary and mandatory fortification options are all effective in reducing NTD-affected pregnancies. The mandatory fortification options (all bread, all bread-making wheat flour and all wheat flour) were the most successful at reducing NTD-affected pregnancies, with the all bread and all bread making-flour scenarios reducing NTDs by approximately 10-20% and the all wheat flour by approximately 15-30%.

It can therefore be concluded that the mandatory fortification scenarios (all bread, all bread-making wheat flour and wheat flour) can meet the relevant principle required to be fulfilled for mandatory fortification in the Policy Guidelines on the Fortification of Food with Vitamin and Minerals:

- Ensure that the mandatory fortification delivers effective amounts of added vitamins and minerals with the specific effect to the target population to meet the health objective.

Table 6.7 summaries the predicted impact of the fortification scenarios on the prevalence of NTDs.

Table 6.7: Summary of the predicted impact of proposed fortification scenarios on the prevalence of NTDs and comparison to current fortification levels

	Predicted NTD rate (range of predicted rates)	Number of NTDs prevented per year from current fortification levels	% reduction from current fortification levels
Status quo	7.7 – 11.4	-	-
Enhanced voluntary[1]	7.3 – 11.0	2 - 5	3-11%
All bread[2]	6.5 - 10.5	5 - 9	8-19%
All bread-making[2] wheat flour	6.7 - 10.3	5 - 8	9-17%
All wheat flour[2]	6.0 - 9.8	8 - 14	14-29%

Notes

1. Fortification of 80% packaged sliced bread
2. Excludes organic

7 Conclusion

Modelling the impact of fortification has demonstrated that mandatory fortification of bread or bread-making flour are the most suitable fortification scenarios. Under these mandatory fortification scenarios 5 to 9 NTD-affected pregnancies could be prevented each year. These two scenarios can effectively reduce NTD-affected pregnancies without exposing sub-groups of the population to excessive intakes of folic acid.

The modelling demonstrated that enhanced voluntary and mandatory fortification options are all effective in reducing NTD-affected pregnancies. The mandatory fortification options (all bread, all bread-making wheat flour and wheat flour) were the most successful at reducing NTD-affected pregnancies. It can therefore be concluded that the mandatory fortification scenarios (all bread, all bread-making wheat flour and wheat flour) meet the public health objective of reducing NTDs, a principle required to be fulfilled for mandatory fortification (Ministerial Council, 2004). If mandatory fortification of bread-making flour had occurred in 2009 when it came into effect in Australia, it is estimated that 134 to 180 pregnancies affected by an NTD could have been prevented over the last ten years in New Zealand.

Dietary assessment of the proposed scenarios demonstrated that the addition of folic acid to bread, bread-making wheat flour or wheat flour would deliver a sufficient amount of folic acid to the target group, even those with the lowest intakes. The mandatory fortification options led to an average increase of at least 70 µg per day for WCBA. This is considered to be a sufficient increase as it meets the UK FSA's requirement that a fortification program should aim to increase folic acid intakes by an average of 60 to 100 µg per day (Mayer, 2017).

Small exceedances of the UL are not considered a health risk for children due to the wide safety margin, the uncertainty related to the derived value for the UL and its applicability to children. Although a higher proportion of children exceeded the UL in one scenario, this could be managed through reducing the maximum limit for fortification. Lowering the maximum fortification limit for the mandatory fortification of bread to 200 µg of folic acid per 100 g of bread reduced the exceedances of the UL to an acceptable level (6% of children exceeded the UL). If mandatory fortification of all wheat flour was to be considered a preferable policy option, the fortification levels would need to be revised to ensure that less children were exposed to excessive intakes; however in doing so this would also reduce the impact on health benefits. Table 7.1 summarises the fortification options that have been provided to Food Policy to inform the consultation and the impact of each of these options.

Table 7.1: Summary of the predicted impact of proposed fortification scenarios on the prevalence of NTDs in comparison to current fortification levels

Scenario	Fortification Concentration	Predicted NTD rate (range of predicted rates)	Number of NTDs prevented per year from current fortification levels	% reduction from current fortification levels	% children aged 5 – 8 years above the UL
Status quo	Target 200 µg/100g bread	7.7 – 11.4	-	-	<1%
Enhanced voluntary[1]	Target 150 µg/100g bread	7.3 – 11.0	2 - 5	3-11%	<1-2%
All bread[2]	100 to 200µg/100g bread	6.5 - 10.5	5 - 9	8-19%	1 - 6%
All bread-making wheat flour[2]	200 to 300 µg/100g flour	6.7 - 10.3	5 - 8	9-17%	<1 - 6%
All wheat flour[2]	200 to 300 µg/100g flour	6.0 - 9.8	8 - 14	14-29%	5 - 36%

Notes

1. Fortification of 80% packaged sliced bread
2. Excludes organic

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Appendix 1: Total number of live birth, stillbirth, and termination cases associated with NTD-affected pregnancies in New Zealand and their rates

Year	Live births			Stillbirths	Total live and stillbirths			Terminations	Total NTD-affected pregnancies (live birth, stillbirths and terminations)		
	Number	Rate	95% CI	Number	Number	Rate	95% CI	Number	Number	Rate	95% CI
2000	44	7.77	5.64, 10.4	8	52	8.6	6.37,11.37	-	-	-	-
2001	30	5.37	3.62, 7.67	7	37	5.88	4.05,8.26	-	-	-	-
2002	23	4.25	2.69, 6.38	9	32	5.52	3.72, 7.88	-	-	-	-
2003	28	4.98	3.31, 7.20	13	41	6.73	4.76, 9.23	-	-	-	-
2004	29	4.99	3.34, 7.17	21	50	8.03	5.90,10.67	-	-	-	-
2005	31	5.36	3.64, 7.62	18	49	7.92	5.80, 10.56	-	-	-	-
2006	28	4.73	3.14, 6.83	17	45	7.05	5.08, 9.53	-	-	-	-
2007	31	4.84	3.28, 6.87	17	48	6.98	5.09, 9.33	-	-	-	-
2008	33	5.12	3.53, 7.20	13	46	7.09	5.19, 9.46	38	84	12.95	10.33, 16.04
2009	19	3.03	1.82, 4.74	10	29	4.61	3.08, 6.61	28	57	9.05	6.86, 11.73
2010	23	3.59	2.28, 5.40	10	33	5.13	3.53, 7.20	27	60	9.32	7.12, 12.01
2011	33	5.37	3.69, 7.54	17	50	8.09	6.00, 10.60	31	81	13.1	10.40, 16.28
2012	24	3.92	2.51, 5.83	8	32	5.20	3.55, 7.33	28	60	9.74	7.44, 11.35
2013	18	3.06	1.81, 4.84	6	24	4.06	2.60, 6.04	27	51	8.63	6.43, 11.35
2014	30	5.24	3.53, 7.48	9	39	6.77	4.81, 9.25	39	78	13.54	10.70, 16.89
2015	25	4.09	2.65, 6.04	5	30	4.89	3.30, 6.98	19	49	7.99	5.91, 10.56
Total	**449**			**188**	**637**			**237**	**520**		
Average 2011-2015	**26**	**4.3**	**3.6, 5.2**	**9**	**35**	**5.8**	**5.0, 6.7**	**29**	**64**	**10.6**	**9.5, 11.8**

Source: New Zealand Birth Defects Registry, August 2018
Notes: Prevalence rate per 10 000 live births; 95% confidence interval

Appendix 2: Folic acid content of generic foods in the simulated toddler diet

Generic food	Folic acid content (µg/kg)														
	Status quo			Enhanced status quo *2000 µg/ kg*			All bread *2000 µg/ kg*			All bread-making wheat flour *3000 µg/ kg*			All wheat flour *3000 µg/ kg*		
	Min	Median	Max	Min	Median	Max	Min	Median	Max	Min	Median	Max	Min	Median	Max
Biscuits, chocolate	0	0	330	0	0	330	0	0	330	0	0	330	0	947	2144
Biscuit, cracker	0	0	0	0	0	0	0	0	0	0	0	0	0	1903	3282
Biscuit, plain, sweet	0	0	0	0	0	0	0	0	0	0	0	0	0	1066	1454
Bran flake	0	1100	3160	0	1100	3160	0	1100	3160	0	1100	3160	0	1100	3160
Bread, mixed grain	0	684	684	0	1440	1440	0	2000	2000	0	1389	2242	0	1389	2242
Bread, wheatmeal	0	684	814	0	1440	1714	0	2000	2380	0	1906	2250	0	1906	2250
Bread, white	0	684	684	0	1440	1440	0	2000	2000	0	1920	2259	0	1920	2259
Cakes and slices	0	0	380	0	0	380	0	0	380	0	0	380	0	448	1192
Chicken takeaway	0	0	0	0	0	0	0	0	0	0	0	0	0	231	297
Cornflakes	0	1670	3330	0	1670	3330	0	1670	3330	0	1670	3330	0	1670	3330
Fish fingers	0	197	318	0	415	669	0	577	929	0	541	871	0	586.5	871
Fish battered	0	0	0	0	0	0	0	0	0	0	0	0	0	252	524
Hamburger plain	0	0	177	0	0	372	266	585	2000	282	579	2207	282	602	2207
Meat pie	0	0	115	0	0	243	0	0	337	0	0	324	2	460	812
Muesli	0	0	3180	0	0	3180	0	0	3180	0	0	3180	0	0	2220
Muffins and scones	0	0	0	0	0	0	0	0	0	0	0	0	0	924.5	1752
Noodle dish	0	0	17	0	0	35	0	0	48	0	0	45	0	269	1061
Noodle , instant	0	0	0	0	0	0	0	0	0	0	0	0	502	1034	2679
Orange juice	0	0	330	0	0	330	0	0	330	0	0	330	0	0	330
Pasta dried	0	0	0	0	0	0	0	0	0	0	0	0	0	1136	1172
Pizza	0	0	37	0	0	77	0	0	107	0	1033	1918	0	1033	1918
Rice dish	0	0	61	0	0	129	0	0	179	0	0	168	0	0	337
Salad dressing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	59
Sausage	0	0	115	0	0	243	0	0	337	0	0	316	0	0	355
Simmer sauce	0	0	0	0	0	0	0	0	0	0	0	0	0	5	1500
Snack bar	0	0	488	0	0	488	0	0	488	0	0	488	0	0	947
Snacks flavoured	0	0	0	0	0	0	0	0	0	0	0	1913	0	674	1913
Vegetable soup	0	0	69	0	0	145	0	0	201	0	0	225	0	0	497
Soy milk	0	0	350	0	0	350	0	0	350	0	0	350	0	0	350
Spaghetti in sauce canned	0	0	8	0	0	16	0	0	22	0	0	19	544	625	629
Wheat biscuit, cereal	0	0	2200	0	0	2200	0	0	2200	0	0	2200	0	0	2200
Yeast extract	8000	8000	20000	8000	8000	20000	8000	8000	20000	8000	8000	20000	8000	8000	20000

Appendix 3: Summary of inputs to the stochastic model

Summary of inputs for Model A - serum folate Wald model

Variable	Description	Distribution, formula or value	Unit	Source
BSF_{nmol}	Baseline serum folate (nmol / L)	Cumul(3,575,{6,9,10,14,22,35,51,65,114},{0.01, 0.05,0.1,0.25,0.5,0.75,0.9,0.95, 0.99})	nmol / L	2008/09 New Zealand Health Survey
$CF_{nmol \rightarrow \mu g}$	Conversion nmol to µgram	2.265	Factor	
$BSF_{\mu g}$	Baseline serum folate (µg / L)	$BSF_{nmol} / CF_{nmol \rightarrow \mu g}$	µg / L	
QFA_{Sup}	Quantity of folic acid consumed from supplements	Discrete({0,400,800},{0.8575, 0.057,0.0855})	µg FA	Ministry of Health, 2018 Vitamin and Mineral study, 2011
$CF_{FA \rightarrow DFE}$	Conversion folic acid to dietary folate equivalents	1.7	Factor	IOM, 1998 NHMRC, 2006
QDFE	Quantify of dietary folate equivalents consumed	$QFA * CF_{FA \rightarrow DFE}$	µg DFE	
ISF_{Sup}	Increase in serum folate	(0.0145 x QDFE) + 0.132, but if QDFE = 0, then $ISF_{Sup} = 0$	µg / L	Quinlivan and Gregory, 2007
SSF	Starting serum folate	$SSF = BSF_{\mu g} + ISF_{Sup}$	µg / L	
Additional intake of folic acid from fortification policies				
QFA_{SQ}	1. Status quo (2018 fortification levels) (µg folic acid per day)	Cumul(0,526,{ 29,31,34,42,53,60,70,83,97,127,160}, {0.05,0.1,0.20, 0.3,0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with current fortification permissions
QFA_{VF}	2. Enhanced voluntary fortification of bread (µg folic acid per day)	Cumul(0,1081,{39,43,45,57,75,83,93,112,131,167,203},{0.05,0.1,0.2,0.3, 0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with proposed fortification scenario
QFA_{MBr}	3. Mandatory fortification of bread at 150 µg/100 g (µg folic acid per day)	Cumul(0,1081,{ 73,77,92,115,126,140,160,182,205,250,279}, {0.05,0.1,0.20, 0.3,0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with proposed fortification scenario
QFA_{MBrFl}	4. Mandatory fortification of bread making flour at 250 µg/100 g (µg folic acid per day)	Cumul(0,1005,{ 83,91,116,132,146,160,181,205,230,274,306}, {0.05,0.1,0.20, 0.3,0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with proposed fortification scenario

QFA_{MWhFl}	5. Mandatory fortification of all wheat flour at 250 µg/100 g (µg folic acid per day)	Cumul(0,1013,{159,173,196,214,230,250,269,290,319,358,396}, {0.05,0.1,0.20, 0.3,0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with proposed fortification scenario
QFA_{Fort}	Quantity of folic acid from the fortified food vehicle	Quantity of dietary folic acid intakes per day from one of the five simulated fortification.	µg FA/day	
QDFE	Quantify of dietary folate equivalents consumed	$QFA_{Fort} * CF_{FA \rightarrow DFE}$	µg DFE	
ISF_{Fort}	Increase in serum folate after fortification	(0.0145 x QDFE) + 0.132, but if QDFE = 0, then $ISF_{Fort} = 0$	µg / L	
FSF	Final serum folate	$SSF + ISF_{Fort}$	µg / L	
Predicting NTD risk				
D_{Conc}	Daly serum folate concentration	Factor = 4 µg / L		Daly, 1995
D_{NTD}	Daly NTD rate	Factor = 1.9 NTD per 1000		Daly, 1995
$ChPr_{SSF}$	Changed probability of SSF	$ChPr_{SSF} = (SSF/ D_{Conc})^{\wedge -0.81}$		Wald, 2001
Pr_{NTD_SSF}	Probability of NTD for starting serum folate (SSF)	$Pr_{NTD\_SSF} = (ChPr_{SSF} * D_{NTD}) / 1,000$		
Bin_ Pr_{NTD_SSF}	NTD or not	Binomial (1, Pr_{NTD_SSF})	Yes/No 1/0	
$ChPr_{FSF}$	Changed probability of Final serum folate (FSF)	$ChPr_{FSF} = (FSF/SSF)^{\wedge -0.81}$		Wald, 2001
Bin_ Pr_{NTD_FSF}	NTD or not	Binomial (Bin_ Pr_{NTD_SSF} , $ChPr_{FSF}$)	Yes/no, 1/0	

Summary of inputs for the Red Blood Cell folate model

Variable	Description	Distribution, formula or value	Unit	Source
BRBCF	Baseline RBC folate (nmol / L)	Cumul(14,2937,{205,366,434,553,749,982,1317,1564,2277},{0.01, 0.05,0.1,0.25,0.5,0.75,0.9,0.95,0.99})	nmol / L	2008/09 New Zealand Health Survey
QFA_{Sup}	Quantity of folic acid consumed	Discrete({0,400,800},{0.8575, 0.057,0.0855})	µg FA	Ministry of Health 2018
$IRBCF_{Sup}$	Increase in RBC folate	$((QFA_{Sup}/200)^{0.4}) \times 284$	nmol/L	Duffy 2014
SRBCF	Starting RBC folate	SRBCF = BRBCF+ $IRBCF_{Sup}$	nmol/L	
Additional intake of folic acid from fortification policies				
QFA_{SQ}	1. Status quo (2018 fortification levels) (µg folic acid per day)	Cumul(0,526,{29,31,34,42,53,60,70,83,97,127,160}, {0.05,0.1,0.20, 0.3,0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with current fortification permissions
QFA_{VF}	2. Enhanced voluntary fortification of bread (µg folic acid per day)	Cumul(0,1081,{39,43,45,57,75,83,93,112,131,167,203},{0.05,0.1,0.2,0.3, 0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with proposed fortification scenario
QFA_{MBr}	3. Mandatory fortification of bread at 150 µg/100 g (µg folic acid per day)	Cumul(0,1081,{73,77,92,115,126,140,160,182,205,250,279}, {0.05,0.1,0.20, 0.3,0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with proposed fortification scenario
QFA_{MBrFl}	4. Mandatory fortification of bread making flour at 250 uµ/100 g (µg folic acid per day)	Cumul(0,1005,{83,91,116,132,146,160,181,205,230,274,306}, {0.05,0.1,0.20, 0.3,0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with proposed fortification scenario
QFA_{MWhFl}	5. Mandatory fortification of all wheat flour at 250 µg/100 g (µg folic acid per day)	Cumul(0,1013,{159,173,196,214,230,250,269,290,319,358,396}, {0.05,0.1,0.20, 0.3,0.4,0.5,0.6,0.7,0.8,0.9,0.95})	µg FA/day	FSANZ dietary modelling of 08/09ANS dataset with proposed fortification scenario
QFA_{Fort}	Quantity of folic acid from the fortified food vehicle	Quantity of dietary folic acid intakes per day from one of the five simulated fortification.	µg FA/day	
$IRBCF_{Fort}$	Increase in RBC folate after fortification	$((QFA_{fort} /200)^{0.4}) \times 284$	nmol/L	Duffy, 2014
FRBCF	Final RBC folate	SRBCF + $IRBCF_{fort}$	nmol/L	

Model B: RBC folate Daly model				
Predicting NTD risk				
LOR_{SRBCF}	Log odds of risk SRBCF	$\log\frac{p}{1-p} = A - B\log SRBCF$ *A* = 1.6463; *B* = 1.2193	Risk of NTD per 1,000 births	Crider 2014 FSS 2017
LOR_{FRBCF}	Log odds of risk FRBCF	$\log\frac{p}{1-p} = A - B\log FRBCF$ *A* = 1.6463; *B* = 1.2193	Risk of NTD per 1,000 births	Crider 2014 FSS 2017

Model C: RBC folate Crider model				
Predicting NTD risk				
LOR_{SRBCF}	Log odds of risk SRBCF	$\log\frac{p}{1-p} = A - B\log SRBCF$ *A* = 4.57; *B* =1.7	Risk of NTD per 1,000 births	Crider, 2014 FSS, 2017
LOR_{FRBCF}	Log odds of risk FRBCF	$\log\frac{p}{1-p} = A - B\log FRBCF$ *A* = 4.57; *B* = 1.7	Risk of NTD per 1,000 births	Crider, 2014 FSS, 2017