The effectiveness and cost-effectiveness of mandatory folic acid and iodine fortification

Final Report

COAG
HEALTH COUNCIL

The effectiveness and cost-effectiveness of mandatory folic acid and iodine fortification.

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Food Fortification Initiative (FFI)

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Abbreviations

Abbreviation	*Description*
1995 NNS	1995 National Nutrition Survey
ACT	Australian Capital Territory
AE	adverse effect
AHMAC	Australian Health Ministers Advisory Council
AIHW	Australian Institute of Health and Welfare
ANCNPAS	Australian National Childrens Nutrition and Physical Activity Survey
ANS	(New Zealand) Adult Nutrition Survey
ANZFRMC	Australia New Zealand Food Regulation Ministerial Council
APHDPC	Australian Population Health Development Principal Committee
AR-DRG	Australian refined diagnostic related groups
ASEAN	Association of Southeast Asian Nations
AT	Assistive Technology
ATSI	Aboriginal and Torres Strait Islander
$AUD	Australian dollar
CAT	chronic autoimmune thyroiditis
CATI	computer-assisted telephone interviewing
CBA	cost-benefit analysis
CDAH	Child-Determinants of Adult Health (survey)
CEA	cost-effectiveness analysis
CHERE	Centre for Health Economics Research and Evaluation
CI	confidence interval
CUA	cost-utility analysis
DFE	dietary folate equivalent
DIAMOND	Dietary Modelling of Nutritional Data
DNA	deoxyribonucleic acid
EAR	estimated average requirement
€EUR	Euro
FDA	Food and Drug Administration
FFI	Food Fortification Initiative
FFQ	food frequency questionnaires
FRSC	Food Regulation Standing Committee
FSANZ	Food Standards Australia New Zealand
FT	full time
£GBP	British pound
GDP	gross domestic product
GP	general practitioner
HIV	human immunodeficiency virus
HT	Hashimoto’s thyroiditis
ICCIDD	International Council for Control of Iodine Deficiency Disorders
ICER	incremental cost-effectiveness ratio

Abbreviation	*Description*
IDD	iodine deficiency disorder
IGN	Global Iodine Network
IQ	intelligence quotient
IQR	interquartile range
LY	life years
MBS	Medicare Benefits Schedule
MPI	Ministry for Primary Industries (New Zealand)
MUIC	median urinary iodine concentration
NA	not applicable/not available
NHMRC	National Health and Medical Research Council
NHMS	National Health Measures Survey
NINS	(Australian) National Iodine Nutrition Survey
NLSY79	National Longitudinal Survey of Youth 1979
NND	neonatal death
NNPAS	National Nutrition and Physical Activity Survey
NNS	neonatal survivor
NR	not reported
NRV	nutrient reference values
NSW	New South Wales
NTD	neural tube defect
$NZD	New Zealand dollar
NZDep	New Zealand deprivation index
NZHS	New Zealand Health Survey
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
PBS	pharmaceutical benefits schedule
PGA	pteroylmono-glutamic acid
PPM	parts per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PT	part-time
QALY	quality-adjusted life year
RBC	red blood cell
RCT	randomised controlled trials
RDI	recommended daily intake
RNA	ribonucleic acid
RR	relative risk
SACN	Scientific Advisory Committee on Nutrition
SB	stillbirth
SD	standard deviation
SES	socio-economic status
Tg	thyroglobulin
TgAb	thyroglobulin antibodies

Abbreviation	***Description***
TOP	termination of pregnancy
TPOAb	thyroperoxidase auto-antibodies
TSH	thyroid stimulating hormone
UIC	urinary iodine concentration
UK	United Kingdom
UL	upper level (of intake)
USA	The United States of America
$USD	US Dollar
WHO	World Health Organization
WLS	Wisconsin Longitudinal Study of Social and Psychological Factors in Aspiration and Attainment
WTP	willingness to pay

Symbols

Symbol	*Description*
%	per cent
g	gram
kg	kilogram
L	litre
mg	milligram
mL	millilitre
ng	nanogram
nmol	nanomole
pmol	picomole
µg	microgram

1 Executive Summary

In 2009, mandatory folic acid fortification was introduced in Australia to reduce the incidence of neural tube defects (NTDs), and mandatory iodine fortification was introduced in both Australia and New Zealand to address the re-emergence of iodine deficiency.

This Report describes and evaluates the effectiveness of the mandatory folic acid fortification initiative in Australia, and the mandatory iodine fortification initiatives in both Australia and New Zealand.

1.1 Background (Section 2)

NTDs are serious birth defects that result in significant morbidity and mortality. A proportion of NTDs are preventable with a sufficient intake of folic acid, ideally started before conception.[1]

Iodine is an essential element for growth and development, and adequate iodine status is important in pregnancy for the neurodevelopment of the fetus. Iodine deficiency is the largest preventable cause of mental impairment in the world.[2]

The fortification initiatives require the mandatory addition of folic acid to wheat flour used in bread making (in Australia only), and the mandatory replacement of non-iodised salt with iodised salt in bread (in both Australia and New Zealand). These requirements came into effect as part of Standard 2.1.1 *Cereals and Cereal Products* (the Standard) of the Australia New Zealand Food Standards Code (the Code).[3]

The Standard (for iodine):

- required the mandatory replacement of non-iodised salt with iodised salt in bread, with the salt iodisation level to be in the range of 25-65 milligrams (mg) of iodine per kilogram (kg) of salt. Bread represented as organic was exempt from this requirement[4]; and
- allowed for iodine in already iodised salt and reduced sodium salt to be retained, at the current range of 25-65 mg per kg, to be consistent with the mandatory requirement.[4]

The Standard (for folic acid):

- required the addition of 2-3 mg of folic acid per kg of wheat flour for making bread in Australia.[5] Bread represented as organic was exempt from this requirement.[3]

In agreeing to the implementation of the mandatory fortification initiatives, the then Australia New Zealand Food Regulation Ministerial Council (ANZFRMC), now the Australia and New Zealand Ministerial Forum on Food Regulation (the Forum) agreed that a comprehensive and independent review of mandatory fortification (the Review) be conducted two years after implementation. The purpose of the Review, as outlined by Ministers, was to undertake an informed assessment of:

- the health impacts of folic acid and iodine fortification;
- the effectiveness of the mandatory fortification initiatives;
- the cost impacts on the food industry; and
- the adequacy of the monitoring framework.

The independent Review was undertaken in three stages:

- Stage 1: The 2015 *Review of compliance with, and enforcement impacts of, the mandatory fortification of bread with folic acid and iodine* (Catalyst report)[6];
- Stage 2: The 2016 Australian Institute of Health and Welfare (AIHW) report, *Monitoring the health impacts of mandatory folic acid and iodine fortification* (AIHW report)[7] and updated iodine data from the New Zealand Ministry for Primary Industries (MPI), *Mandatory iodine fortification in New Zealand: Supplement to the Australian Institute of Health and Welfare 2016 report for Monitoring the health impacts of mandatory folic acid and iodine fortification* (MPI companion report)[8]; and
- Stage 3: An independent evaluation of the effectiveness of the mandatory fortification initiatives (this Report).

This Report builds upon the outcomes of the previous stages of the Review, as presented in the Catalyst report,[6] AIHW report,[7] and MPI companion report.[8] The Catalyst report[6] concluded that compliance was satisfactory in the food industry and that there were sufficient quality assurance mechanisms in place. The costs of introducing the mandatory fortification initiatives were less than expected.[6] The AIHW[7] and the MPI companion[8] reports assessed the population health impacts of the mandatory fortification initiatives and found that initiatives resulted in increased levels of iodine and folic acid in the food supply. There were subsequent increases in the nutrient intakes and an improvement in the nutrient status of the population.[7,8]

This Report used the monitoring framework agreed to by the Australian Health Ministers Advisory Council (AHMAC) in 2007 to undertake the Stage 3 evaluation. This monitoring framework formed part of introducing mandatory folic acid fortification in Australia,[9] and mandatory iodine fortification in Australia and New Zealand[5,10] in 2009.

The framework was based on a progression from the policy intervention (introducing the regulation for mandatory fortification) to the policy objective (a change in health outcomes). It involved consideration of any undesirable outcomes (adverse health effects). The monitoring framework was based on five main components: food composition and food industry compliance; nutrient intake; nutrient status; health benefits, and adverse health effects.

The policy objectives were specific for each micronutrient. For folic acid fortification, the objective was to reduce the incidence of NTDs. For iodine fortification, the objective was to address the re-emergence of iodine deficiency in Australia and New Zealand.

This Report's evaluation of each of the mandatory fortification initiatives consisted of:

- an evaluation of each initiative's implementation using the monitoring framework;
- an evaluation of whether each initiative satisfied pre-determined criteria of effectiveness, equity, efficiency, certainty, feasibility and sustainability in achieving the policy objective; and
- an evaluation of each initiative's value for money.

Prior to the introduction of the mandatory fortification initiatives, a series of policies and interventions existed, such as education, voluntary fortification and supplementation for both folic acid and iodine. There was an intensive voluntary iodine fortification program present in Tasmania that was effective in combating the re-emergence of iodine deficiency in that state.[11]

For folic acid, interventions did not cease with the introduction of mandatory fortification. Therefore, mandatory fortification was an additional complementary policy, not a substitute for the policies that existed prior to mandatory fortification. For iodine, education and supplementary policies continued. However, the mandatory fortification of bread replaced the previous voluntary bread fortification initiative.

The evaluations in this Report compare the pre-mandatory fortification suite of policies (the alternative of no mandatory fortification including education, supplementation and voluntary fortification) to the post-mandatory fortification suite of policies (the alternative of mandatory fortification including mandatory fortification, voluntary fortification, education and supplementation).

1.2 Mandatory folic acid fortification in Australia (Section 3)

1.2.1 Achievement of policy objective (Section 3.5)

The NTD rate reduced following the introduction of mandatory folic acid fortification; therefore, the policy objective was achieved. It was estimated that a statistically significant 14.4% reduction in the NTD rate occurred after the introduction of mandatory folic acid fortification.[12] There was a 74% decline in the NTD rate for babies of Indigenous mothers and a 55% decline for babies of teenage mothers.[12]

The modelling showed that approximately 32 fewer NTDs per year occur in the post-mandatory folic acid fortification period than in the pre-mandatory folic acid fortification period noting NTDs were declining in the pre-mandatory fortification period. Approximately 14 NTDs (of the 32) were estimated to be directly attributable to the introduction of mandatory folic acid fortification, assuming the pre-mandatory fortification declining trend in NTDs continued at the same rate after the introduction of mandatory fortification.

1.2.2 Evaluation of implementation (Section 3.4)

The evaluation of the implementation of mandatory folic acid fortification in Australia was conducted against the outcomes used to assess the five components (food composition, nutrient intake, nutrient status, health benefits and adverse health effects) of the monitoring framework. Implementation, for each component of the monitoring framework, was successful if the expected change occurred.

The level of folic acid in bread increased by more than the expected 120 micrograms (µg) per 100 grams (g) (from 20-29 µg/100g to 134-200 µg/100g of bread). Folic acid intake in women aged 16-44 years, increased by 145 µg/day (which was also greater than the expected increase of 100 µg/day). Folic acid intake in women aged 16-44 years also increased by more than expected (145 µg/day increase, the expected increase was 100 µg/day). Folic acid intake was calculated based on a 1995 nutritional survey for adults updated with post-mandatory fortification folic acid values for bread.

The nutrient status of women aged 16-44 years could not be compared between the pre-mandatory fortification and post-mandatory fortification periods because of the use of different analytical tests. The 14.4% reduction in the NTD rate was based on a sub-national dataset (excluding Victoria, Tasmania and Australian Capital Territory) and was comparable to the 4-14% decrease predicted.

Adverse effects in the Australian population were not directly estimated. The proportion of the population that exceeded the upper level of intake was estimated to be less than 1% of adults. However, the calculation was based on a 1995 nutrition survey and did not include consideration of supplements. Twenty-one per cent of children aged 2-3 years were estimated to exceed the upper level of intake; this was based on a 2007 nutrition survey and included supplements.

In general, the implementation of mandatory folic acid fortification was mostly demonstrated to have occurred. Although the lack of comparable national data before and after the introduction of mandatory folic acid fortification, and a reliance on earlier nutrition surveys weakened the conclusions.

1.2.3 Evaluation of effectiveness, equity, efficiency, certainty, feasibility, and sustainability (Section 3.5)

Mandatory folic acid fortification was more effective than the pre-mandatory fortification suite of policies. As expected, the addition of mandatory folic acid fortification did not meet the intake requirements for pregnant women or women intending to become pregnant. Folic acid supplementation before and until three months into pregnancy is the current recommendation and should be maintained.

Mandatory folic acid fortification demonstrated improved equity in outcomes. In particular, it reduced the disparity that existed in rates of NTDs for babies of teenage mothers and for babies of Indigenous mothers.

This Report estimated mandatory folic acid fortification to be efficient compared to the alternative of no mandatory folic acid fortification. Further follow-up is required to confirm this.

Mandatory folic acid fortification increased the certainty of providing folic acid in the diet. Feasibility of achieving the policy objective was demonstrated, as there was a reduction in the NTD rate. Demonstration of the feasibility of implementation (for example folic acid status) was limited by data availability.

The sustainability of mandatory folic acid fortification was not assessed because of the short follow-up period. Nonetheless, it is likely to be superior to the pre-mandatory fortification suite of policies that existed before its introduction.

There are limitations to the evaluation as discussed above. In addition to the short follow-up period, the annual variability in NTD rates and lack of a national dataset limit the certainty of the conclusions.

1.2.4 Evaluation of value for money (Section 3.6)

This Report estimated mandatory folic acid fortification as value for money. The mandatory folic acid fortification initiative, over a period of several years, was found to be health producing and cost saving. This is mainly due to the high cost and high morbidity of NTDs. Mandatory folic acid fortification yields approximately 500 additional quality-adjusted life years (QALYs) and saves $AUD 2million per year, each year it is in place. When discounted at 5% per annum, mandatory folic acid fortification yields 131 additional QALYs and saves $AUD 350 000 each year it is in place. The difference between the discounted and undiscounted estimates is because most of the savings and several of the benefits are realised in the future.

1.3 Mandatory iodine fortification in Australia (Section 5)

1.3.1 Achievement of policy objective (Section 5.5)

In Australia, mandatory iodine fortification successfully addressed the re-emergence of mild iodine deficiency.[7] In this Report, mandatory iodine fortification was compared to both the intensive voluntary fortification strategy in Tasmania and the pre-mandatory fortification suite of policies in other jurisdictions.

1.3.2 Evaluation of implementation (Section 5.4)

The evaluation of the implementation of mandatory iodine fortification in Australia was conducted against the outcomes used to assess the four components of the monitoring framework (for iodine, the nutrient status is the health outcome of interest).

Iodine in bread increased by more than the 46 µg/100g bread expected (From <2 µg/100g to 53-70 µg/100g of bread). Iodine intake in women aged 16-44 years (51 µg/day) and children aged 2-3 years (37 µg/day) increased as expected. Iodine intake was calculated based on a 1995 nutritional survey for adults and a 2007 nutritional survey for children updated with post-mandatory fortification iodine values for bread.

The iodine status of women aged 16-44 years could not be compared between the pre-mandatory fortification and post-mandatory fortification periods because of a lack of pre-mandatory fortification data. The iodine status of children aged 8-10 years increased from mild iodine deficiency to adequate iodine status.

Less than 1% of adults were estimated to exceed the upper level of intake. However, this was based on a 1995 nutrition survey and did not include consideration of supplements. Twenty per cent of children aged 2-3 years were estimated to exceed the upper level of intake; this was based on a 2007 nutrition survey and included supplements.

The implementation was mostly, but not completely demonstrated. A lack of comparable national data on iodine status in the period before and after the introduction of mandatory iodine fortification limited the ability to demonstrate that all components of implementation occurred as expected. Reliance on earlier national nutrition surveys (food consumption data) also placed a degree of uncertainty on estimates of iodine intake.

1.3.3 Evaluation of effectiveness, equity, efficiency, certainty, feasibility, and sustainability (Section 5.5)

The effectiveness of the mandatory iodine fortification initiative was superior to pre-mandatory fortification suite of policies. Both mandatory iodine fortification and the intensive voluntary iodine fortification program present in Tasmania were effective in combating the re-emergence of iodine deficiency. Mandatory iodine fortification does not satisfy the iodine requirements of pregnant and lactating women and supplementation of these subgroups will be required to continue.

Equity improved as measured in the post-mandatory fortification period by population iodine status.

Mandatory iodine fortification on an Australia-wide basis was more efficient than the intensive voluntary iodine scheme of Tasmania.

Mandatory iodine fortification increased the certainty of providing iodine in the diet. Feasibility of achieving the policy objective was demonstrated; however, the feasibility of implementation was only partially demonstrated, being limited by data availability.

This Report found that the sustainability of the mandatory iodine fortification initiative may be superior to the pre-mandatory fortification suite of policies, but a longer period of follow-up is required for a conclusive result.

1.3.4 Evaluation of value for money (Section 5.6)

The mandatory iodine fortification initiative cost approximately $AUD 60 000 per million persons moved from below the World Health Organization (WHO) threshold, to either meeting or exceeding the threshold, as measured by urinary iodine concentration (UIC). The initiative led to iodine sufficiency at the population level.

The productivity increase associated with mandatory iodine fortification was unable to be assessed accurately for Australia. A small increase in productivity would, however, outweigh the costs of mandatory iodine fortification.

There was a lack of pre-mandatory iodine fortification data, and no data was collected on adverse effects or health benefits of the Australian population. This limited the certainty of the conclusions in this Report.

1.4 Mandatory iodine fortification in New Zealand (Section 6)

1.4.1 Achievement of policy objective (Section 6.5)

Mandatory iodine fortification in New Zealand achieved the policy objective and addressed the re-emergence of mild iodine deficiency. Prior to mandatory iodine fortification, the adult population of New Zealand had mild iodine deficiency and insufficient intake.

1.4.2 Evaluation of implementation (Section 6.4)

Mandatory iodine fortification in New Zealand resulted in an increase of iodine levels in bread from a mean of <2 µg/100g to a median of 28-49 µg/100g (46 µg/100g was expected). Iodine intakes increased by 9% in women aged 16-44 years and by 107% in children.[7] For adults, this result was based on a small sample, and the increase was less than expected.

The median urinary iodine concentration (MUIC - a population measure of iodine status) in women aged 16-44 years increased from 48 µg per litre (L) to 104 µg/L. The MUIC for all adults increased from 53 µg/L to 103 µg/L. Iodine status of children improved from mild iodine deficiency to adequate iodine status.

The proportion of adults and children estimated to be above the upper level of intake was less than 1%.

The implementation was partly demonstrated. Adequate iodine status was well demonstrated in adults but not in children for whom a nationally representative survey was not undertaken post-mandatory fortification. Due to data limitations, particularly regarding changes in nutrient intakes, several of the intermediate outcomes were not demonstrated to have occurred, including changes in nutrient intake.

1.4.3 Evaluation of effectiveness, equity, efficiency, certainty, feasibility, and sustainability (Section 6.5)

Mandatory iodine fortification was superior in effectiveness, compared to the pre-mandatory fortification suite of policies.[8]

Mandatory iodine fortification does not satisfy the iodine requirements of pregnant and lactating women and supplementation of these groups should continue.

The equity impacts are complicated. Elderly women, New Zealand women of European origin, and women who reside in areas with less relative socio-economic deprivation, as groups, did not move to adequate iodine status as a result of mandatory iodine fortification. Other groups (for example men), however, did.

Mandatory iodine fortification increased the certainty of providing iodine to the New Zealand population. Feasibility of achieving the policy objective was demonstrated. Feasibility of implementation was only partially demonstrated. The sustainability of mandatory iodine fortification was likely to be superior to the pre-mandatory fortification suite of policies, but a longer follow-up period is required for a conclusive result.

1.4.4 Evaluation of value for money (Section 6.6)

The mandatory iodine fortification initiative cost approximately $NZD 100 000 per million persons moved from below to above the WHO threshold, as measured by UIC.

The productivity increase associated with mandatory iodine fortification was unable to be assessed accurately for New Zealand. A small increase in productivity would, however, outweigh the costs of mandatory fortification.

No data were collected on adverse effects or health benefits of the New Zealand population. This limited the certainty of the conclusions in this Report.

1.5 Updated review on safety, consumer acceptance and the international experience of mandatory fortification

1.5.1 Safety

The 2006 safety review of folic acid by Food Standards Australia New Zealand (FSANZ) identified several hypothesised risks without evidence of harm at the levels of folic acid intake anticipated to occur with mandatory folic acid fortification.[9] Meta-analysis of trials involving supplementation (higher doses) of folic acid has not demonstrated a statistically significant increase in cancer risk for the population.[13]

The issue of masking of B_{12} deficiency due to increased folic acid intake is likely to be restricted to the elderly or those with poor diets.[14] There is no robust evidence to suggest this is a problem with levels of intake of folic acid expected with the mandatory folic acid fortification initiative, without folic acid supplementation. The evidence base is low grade and inconclusive. Monitoring may be required to confirm or refute hypothesised risks.

A 2014 WHO systematic review and meta-analysis of salt iodisation concluded that there was no evidence of an association between iodine fortification and hypothyroidism.[15] The WHO review also concluded that there was an inconsistent association with hyperthyroidism. There was, however, a positive relationship between iodised salt and the development of anti-thyroid antibodies (see section 8.8). The literature since the WHO review is consistent with the findings of the WHO meta-analysis.[15]

1.5.2 International experience

An increasing number of countries had introduced mandatory fortification of food products with folic acid and iodine. There is an international awareness that programs of salt reduction may affect salt iodisation programs. This may require coordination of these programs and alterations to salt iodisation programs if salt intake decreases.

A systematic review found that mandatory folic acid fortification (as opposed to voluntary fortification) is associated with a lower prevalence of live births with spina bifida.[16] Some countries, for example, the United States, have broadened the range of foods that are fortified in order to reach specific high-risk groups.[17]

International experience suggests the re-emergence of iodine deficiency is not limited to Australia and New Zealand. There is international recognition that robust monitoring systems are required to ensure that the gains achieved by eliminating iodine deficiency at a population level are maintained.[18] Internationally, there has been a decrease in the proportion of the world population who are iodine deficient. The iodisation of salt is credited with achieving this trend.[19]

1.5.3 Consumer acceptance

There is a lack of knowledge among consumers about the mandatory fortification initiatives in both Australia and New Zealand. A FSANZ survey indicated that almost half the surveyed population supported mandatory fortification when the potential benefits were explained to them.[20] The importance of the loss of choice associated with mandatory fortification was acknowledged.[21-23] The majority of peer-reviewed literature focuses on the knowledge among pregnant women of the importance of folic acid/folate and iodine intake.

1.6 Recommendations (Section 7)

Recommendation 1: Robust ongoing monitoring should occur to determine the continued effectiveness of the mandatory fortification initiatives.

The monitoring framework was logical and consistent with the evaluation of the implementation. Robust ongoing monitoring is, however, required to:

- ensure adequate folic acid and iodine status in the population and in subgroups;

- assess whether mandatory fortification continues to be the most appropriate strategy; and

- develop epidemiological evidence of potential adverse effects.

There were significant limitations in the data when applying the monitoring framework. Data on the impact of fortification on the incidence of potential adverse effects and other health effects (e.g. reduction in iodine deficiency disorders) in Australia or New Zealand were not available. Data limitations constrained the certainty of the conclusions in this Report.

The analysis in this Report was conducted using a pre-post framework. As there was limited information about potential confounders and no control group, there was limited adjustment for other potential causes of change. It is possible some improvement will have been due to other factors, such as changes in diet or the use of supplementation. Future evaluations should consider these limitations when designing their monitoring frameworks.

Recommendation 2: The mandatory folic acid initiative should be reviewed with a complete national NTD data set, and with a longer follow-up period.

The assessment of mandatory folic acid fortification's effectiveness was based on a short period of review, with considerable annual variability in NTD rates, and from a subset of Australian jurisdictions. Its value for money depends on the modelled effectiveness. In addition, this initiative's sustainability is uncertain due to an inadequate follow-up period.

If the rate of NTDs is reducing independently of mandatory folic acid fortification, then the value of this initiative would also decrease over time. Accordingly, it is recommended that, following a longer period, the initiative should be reviewed using a complete national NTD data set.

Other recommendations, including those relating to future research and evidence collection, are outlined in Section 7 of this Report.

2 Introduction

In 2009, mandatory folic acid fortification was introduced in Australia to reduce the incidence of neural tube defects (NTDs), and mandatory iodine fortification was introduced in both Australia and New Zealand to address the re-emergence of iodine deficiency.

NTDs are serious birth defects that result in significant morbidity and mortality. A proportion of NTDs are preventable with a sufficient intake of folic acid, ideally started before conception.

Iodine is an essential element for growth and development, and iodine sufficiency is of particular importance in pregnancy for the neurodevelopment of the fetus.[24] Iodine deficiency is considered the largest preventable cause of mental impairment in the world.[2]

This Report describes and evaluates the effectiveness of the mandatory folic acid fortification initiative in Australia, and the mandatory iodine fortification initiative in both Australia and New Zealand.

2.1 Background

In agreeing to the implementation of the mandatory fortification initiatives, the then Australia New Zealand Food Regulation Ministerial Council (ANZFRMC), now the Australia and New Zealand Ministerial Forum on Food Regulation (the Forum) agreed that a comprehensive and independent review of mandatory fortification be conducted two years after implementation (the Review). The purpose of the Review, as outlined by Ministers, was to undertake an informed assessment of:

- the health impacts of folic acid and iodine fortification;
- the effectiveness of the mandatory fortification initiatives;
- the cost impacts on the food industry; and
- the adequacy of the monitoring framework.

The independent review was undertaken in three stages:

- Stage 1: The 2015 *Review of compliance with, and enforcement impacts of, the mandatory fortification of bread with folic acid and iodine* (Catalyst report)[6];
- Stage 2: The 2016 Australian Institute of Health and Welfare (AIHW) report, *Monitoring the health impacts of mandatory folic acid and iodine fortification* (AIHW report)[7] and updated iodine data from the New Zealand Ministry for Primary Industries (MPI), *Mandatory iodine fortification in New Zealand: Supplement to the Australian Institute of Health and Welfare 2016 report for Monitoring the health impacts of mandatory folic acid and iodine fortification* (MPI companion report)[8]; and
- Stage 3: An independent evaluation of the effectiveness of the mandatory fortification initiatives (this Report).

The Centre for Health Economics Research and Evaluation (CHERE) was commissioned by the Australian Government Department of Health on behalf of the Australian Health Ministers Advisory Council (AHMAC) to complete the final stage of the Review, following a tender process.

This Report reviewed the effectiveness of the mandatory iodine fortification initiatives in both Australia and New Zealand and the mandatory folic acid fortification initiative in Australia only. It required an examination of whether the benefits of mandatory fortification exceed the costs (through a cost-benefit analysis), and an assessment of any unexpected impacts.

The results reported in this Report have built upon the outcomes of the previous stages of the Review, as presented in the Catalyst report,[6] the AIHW report[7] and the MPI companion report.[8] These reports were developed in accordance with the monitoring framework. The Catalyst report[6] assessed the compliance with, and the impact on the food industry and enforcement agencies of, mandatory fortification. The AIHW report[7] and the MPI companion report[8] assessed the population health impacts of mandatory fortification.

This work was funded by AHMAC and a joint Food Regulation Standing Committee (FRSC)/ AHMAC Working Group (the Working Group) chaired by the Australian Government Department of Health have overseen the work.

AHMAC agreed to a monitoring framework in 2007, following consultation and as part of introducing mandatory folic acid fortification (in Australia), and mandatory iodine fortification in Australia and New Zealand.[5] The framework was based on a logical progression from the policy intervention (introducing the regulation for mandatory fortification) to the policy objective (a change in health outcomes). It involved consideration of any undesirable outcomes (adverse health effects).

The policy objectives were specific for each micronutrient. For folic acid fortification, the objective was to reduce the incidence of NTDs. For iodine fortification, the objective was to address the re-emergence of iodine deficiency in Australia and New Zealand.

The policy mechanism to address the re-emergence of iodine deficiency was a change in regulations, based on Food Standards Australia New Zealand's (FSANZ) Proposal P230 (New Zealand) and Proposal P1003 (amending the New Zealand-only Standard to become a joint Standard for both Australia and New Zealand, whereby the mandatory iodine fortification requirements took effect in September 2009 in New Zealand and in October 2009 in Australia).

The Standard:

- required the mandatory replacement of non-iodised salt with iodised salt in bread, with the salt iodisation level to be in the range of 25-65 milligrams (mg) of iodine per kilogram (kg) of salt. Bread represented as organic was exempt from this requirement[4]; and
- allowed for iodine in already iodised salt and reduced sodium salt to be retained, at the current range of 25-65 mg per kg, to be consistent with the mandatory requirement.[4]

The policy mechanism to reduce the incidence of NTDs was also a change in regulations. The requirement for mandatory folic acid fortification was based on the final assessment report from FSANZ on the consideration of mandatory folic acid fortification (Proposal P295).[9] The Standard:

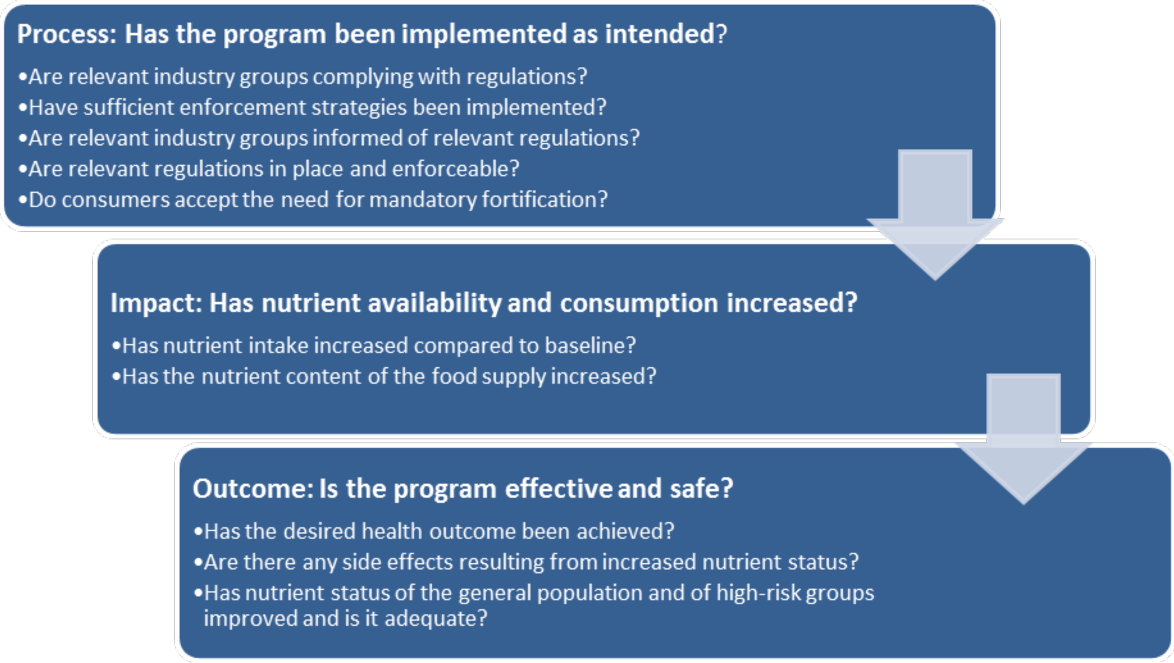
- required the addition of 2-3 mg of folic acid per kg of wheat flour for making bread in Australia, with the requirements coming into effect in September 2009.[5]

The definition of bread and the exemptions (such as bread represented as organic) is reproduced in Section 8.1.3.

2.2 Monitoring framework

Figure 1 describes the generic monitoring framework agreed by AHMAC before the standards development work commenced. The framework moved from information about the process, to impact on the food supply and consumption through to health outcomes (both positive and negative).

Figure 1: Proposed monitoring framework



Source: Adapted from Figure 1 Attachment 12 of P295 Final Assessment Report for Consideration of Mandatory Fortification with Folic Acid[9]

Subsequently, expert groups within the FRSC developed individual frameworks for mandatory folic acid and mandatory iodine fortification monitoring. The baseline and follow-up reports produced by the AIHW used these monitoring frameworks as a basis for reporting.[7,25,26]

The generic monitoring framework was based on five main components:

1. Food composition and food industry compliance;
2. Nutrient intake;
3. Nutrient status;
4. Health benefits; and
5. Adverse health effects.

The AIHW identified specific monitoring questions and gave an assessment the quality of the data.[26] These are considered for folic acid in Section 3 and for iodine in Section 5 and 6 of this Report. For both mandatory iodine fortification and mandatory folic acid fortification, the subgroup of women of childbearing age was highlighted as a target population. The health benefit associated with mandatory folic acid fortification is a decrease in the incidence of neural tube defects. The health benefit related to mandatory iodine fortification is adequate iodine nutrition (addressing the re-emergence of iodine deficiency).

2.3 Pre-specified outcomes

The Review had pre-specified outcomes to be included in this Report, specifically to:

- Evaluate the outcomes of the program implementation consisting of:
    - changes in food composition (nutrient availability) and compliance;
    - changes in nutrient intakes for target populations;
    - changes in biomedical measures; and
    - impact on rates of NTD (for folic acid);
- Evaluate whether the program has been effective in meeting its policy objectives;
- Assess the mandatory fortification initiatives against the objectives, using the monitoring framework, including a commentary on the overall policy objectives relating to effectiveness, equity, efficiency, certainty, feasibility and sustainability of the public health initiatives; and
- Undertake a cost-benefit analysis.

The reports prepared for the previous stages of the Review were provided to CHERE and required to be used to inform the outcomes of this Report. At the time of finalising this Report, the AIHW[7] and MPI companion[8] reports had been publicly released in 2016, but the 2015 Catalyst report[6] had not been published. The MPI companion report[8] was published in 2016 by the New Zealand Ministry for Primary Industries, and a pre-publication version was provided to the authors.

Also provided were pre-publication versions of a report by Hilder titled *Neural Tube Defects in Australia 2007-2011*,[12] and the FSANZ reports on the monitoring of dietary intake of iodine and folic acid.[27,28] These reports were made publicly available in 2016.

Material in the public domain was also provided to CHERE including expert public health advice recommending mandatory fortification as the preferred strategy,[29] a meta-analysis of selected cancers, all-cause mortality and folic acid supplementation,[13] FSANZ consumer awareness reports,[20,23] the various FSANZ proposals (P230, P295 and P1003)[4,9,10] and the AIHW baseline monitoring reports.[25,26,30] CHERE was required to utilise this material.

The supplied material was supplemented and replaced with existing material within the public domain if it was considered more informative than the information contained in the AIHW and Catalyst reports (see Section 8.2).

2.4 Structure of this Report

Wherever feasible, data from the AIHW report[7] and the Catalyst report[6] were used to maximise consistency within the Review process. If this was not appropriate or possible, alternative information was used and justification provided. The MPI companion report[8] and the study published by Jones et al.[31] was used to assess the New Zealand iodine health impacts, rather than the New Zealand iodine health impacts information contained in the AIHW report.[7] This was because the MPI companion report[8] and Jones et al.[31] data were superior to those included in the AIHW report[7] (see 8.2.4.for a discussion of this issue).

This Report is divided as follows:

- Section 3: mandatory folic acid fortification in Australia;
- Section 4: an introduction to iodine;
- Section 5: mandatory iodine fortification in Australia;
- Section 6: mandatory iodine fortification in New Zealand;
- Section 7: the adequacy of the monitoring frameworks and observations for the future; and
- Section 8: contains supporting material and literature reviews

Section 4 is a discussion about the importance of iodine, dietary requirements and measurement. It is useful material before reading Section 5 or Section 6. To avoid duplication, the modelling approach and assumptions are described once, in Section 5, and cross-referenced in Section 6.

These sections are supplemented with supporting material (Section 8) and references (Section 9).

Alternative text for the figures in the document is presented in Section 10.

3 Mandatory folic acid fortification in Australia

3.1 Introduction

Section 3 of this Report evaluates the implementation and impact of mandatory folic acid fortification, especially in meeting the policy objective of reducing the incidence of NTDs in the Australian population.

Mandatory folic acid fortification of wheat flour for bread making was introduced to reduce the incidence of preventable NTDs by increasing folic acid intakes of women of childbearing age (16-44 years). Folic acid is important for preventing NTDs.[32]

NTDs are serious birth defects resulting from a disruption of the development of the spinal cord and brain.[33] This disruption occurs early in pregnancy (by 22 to 28 days).[9] NTDs can result in stillbirths and babies born with NTDs are at a high risk of infant mortality. Moreover, survivors often suffer a decrease in health-related quality of life and require lifelong health care and social care.[30] Spina bifida is one type of NTD.[12]

Folate is a B vitamin naturally found in food, such as green leafy vegetables, cereals, grains and fruit.[7,9] Folic acid or pteroylmono-glutamic acid (PGA) is the synthetic form of folate used in supplements (such as multivitamins and prenatal tablets) and fortification. It is rarely found in nature and is more stable than naturally occurring folate.[32] (see Section 8.1.4: Folic acid metabolism and measurement for more information).

Folate is necessary for several biochemical pathways (as well as preventing NTDs) including DNA synthesis (required for dividing cells) and the methylation cycle.[32] A deficiency in folate can result in anaemia.[34]

The dietary folate equivalent (DFE) combines the different forms of folate into a single measure. Folate intake can be difficult to measure in food as it is present in different forms so food databases can be inaccurate.[32]

1 microgram (µg) of DFE is equivalent to:

- 1 µg food folate; or
- 0.5 µg folic acid on an empty stomach; or
- 0.6 µg folic acid with meals.[7]

Different amounts of folate are required at various stages of life. There are also different reference values for the intake of folate, termed nutrient reference values (NRV).[32]

The most commonly used nutrient reference values in this Report are:

1. Estimated average requirement (EAR), a daily nutrient level estimated to meet the requirements of half the healthy individuals in a particular life stage and gender group;
2. Recommended daily intake (RDI), the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group; and

3. Upper level of intake (UL), the highest average daily nutrient intake level likely to pose no adverse health effect to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.[32]

The NRVs for folate increase with adulthood and the EAR and RDI also increase at times of increased demand, such as during pregnancy and breastfeeding (Table 1). The NRVs do not include consideration of the extra requirements to prevent NTDs in pregnancy.[32] The EAR for folate, expressed as DFEs, can be used to examine the prevalence of inadequate intakes in the population.[32]

Table 1: Folate requirements by age and life stage

Age and life stage	EAR (Dietary Folate Equivalent)	RDI (Dietary Folate Equivalent)	Upper Level of Intake (Folic Acid)
1-3 years	120 µg/day	150 µg/day	300 µg/day
4-8 years	160 µg/day	200 µg/day	400 µg/day
9-13 years	250 µg/day	300 µg/day	600 µg/day
14-18 years	330 µg/day	400 µg/day	800 µg/day
> 19 years	320 µg/day	400 µg/day	1 000 µg/day
Pregnant	520 µg/day	600 µg/day	1 000 µg/day[a]
Lactation	450 µg/day	500 µg/day	1 000 µg/day[a]

a UL is slightly lower for 14-18-year-olds who are pregnant or lactating
Abbreviations: EAR, estimated average requirement; RDI, Recommended daily intake
Source: NHMRC and NZ MoH 2006.[32]

Red blood cell (RBC) folate is considered the most robust measure of folate status.[35] It is less sensitive to dietary fluctuations than serum folate and therefore more representative of folate status.[7]

The World Health Organization (WHO) recommends, given the limitations of the evidence, that in women of childbearing age the RBC folate level is kept above 400 nanograms (ng) per millilitre (mL). It also recommends that the portion of the population with a red cell folate level below 400 ng/mL be regarded as a measure of folate insufficiency at a population level.[36]

A relationship between folate/folic acid and NTDs was recognised in the 1960s meaning that NTDs are potentially a preventable form of morbidity and mortality which can be mitigated by the use of folic acid.[33] Estimates of the portion of preventable NTDs range from 50% to over 70%.[37]

Since the early 1990s, Australian women have been advised to increase their intake of folic acid and folate before and during pregnancy. As the critical time for preventing NTDs is before 28 days into the pregnancy, folic acid supplementation should ideally commence before one month before conception.[1,38]

Before the introduction of the mandatory scheme, education campaigns were conducted, and voluntary fortification of food was encouraged. These initiatives had been successful, but despite the decrease in NTDs, concerns remained about the completeness of protection, particularly considering the distribution of NTDs. Mothers at the extremes of reproductive age, women from geographical areas of relative disadvantage and Indigenous women were more likely to have pregnancies impacted by NTDs.[30]

The voluntary fortification of some food products was introduced in 1995, which saw a subsequent decrease in NTDs.[30,39] Additionally, long-standing Australian recommendations existed about the requirements for folic acid supplementation before and during pregnancy.[38]

After consultation and consideration of the options, mandatory fortification of wheat flour for bread making with folic acid was selected as the preferred option to address this public health issue.[9]

From September 2009, Australia mandated the use of folic acid in wheat flour for making bread (except for bread represented as organic). (See Section 8.1.2 for a definition of bread).

3.2 Monitoring framework for folic acid

The monitoring framework developed by FRSC and the specific questions identified by the AIHW were used to assess the changes that occurred in food composition, nutrient intake, nutrient status, health benefit and adverse effects from the pre-mandatory folic acid fortification period to the post-mandatory folic acid fortification period.[7] The monitoring framework is discussed in Section 2.2

The monitoring framework was designed as an outcome hierarchy where each step represents an achievement required before the next step can be attained. For example, folic acid had to be included in bread before the increased intake of folic acid occurs. Women of childbearing age (16-44 years) were the subgroup of interest. The key monitoring questions for mandatory folic acid fortification commenced with changes in the composition of food and concluded with the health benefits of reduced incidence of NTDs (Table 2). The health benefit for mandatory folic acid was also the policy objective.

Table 2: Key mandatory folic acid fortification monitoring questions

Framework Component	Monitoring question
Food composition and industry compliance	Has the level of folic acid in our food supply increased? Is the food industry adequately complying with the mandatory fortification standards?
Nutrient intake	Have folic acid intakes in women of childbearing age increased?
Nutrient status	Has the folate status of women of childbearing age improved?
Health benefits	Has the incidence of NTDs decreased?
Adverse health effects	Does mandatory folic acid fortification result in adverse health effects for the population?

Abbreviations: NTD, Neural Tube Defect
Source: AIHW Baseline report for monitoring 2011[26]; Table S.1

The AIHW report,[7] which used the monitoring framework concluded that most, but not all, of the desired outcomes were achieved (Table 3). The assessment was conducted by answering the monitoring questions, mostly by comparing data for different indicators in pre-mandatory fortification and post-mandatory fortification periods.

The objective of reducing NTDs was achieved. There was estimated to be a 14.4% reduction in the NTD rate between the pre-mandatory fortification and post-mandatory fortification periods.

Two outcomes were not able to be demonstrated. First, improvement in the folate status of women of childbearing age was not assessed because of a lack of comparable data between the pre-mandatory fortification and post-mandatory fortification periods. The lack of comparable data was due to the use of different analytical tests for folate status between the periods. Second, the question of mandatory folic acid fortification resulting in adverse effects was assessed as not applicable, as no increase in cancer or all-cause mortality was directly associated with increased folic acid intakes in adults. There was an increase in the proportion of children who exceeded the UL of intake, but this was considered likely not to pose a health risk because of the fivefold safety margin based on adults.[7] The safe upper intake limit for folic acid of 1 mg was set with this issue in mind, being one-fifth of the 5 mg level. Therefore, it is argued,[7] the upper intake limit was set with a large margin of safety (see Section 8.9 for a discussion of the safety of folic acid fortification). However, the estimates for the portion of adults exceeding the UL were based on earlier nutrition surveys that did not include the use of supplements and, therefore, are likely to be an underestimate.

Table 3: Key mandatory folic acid fortification outcomes in Australia

Monitoring Question	**Measure**	**Pre-mandatory fortification**	**Post-mandatory fortification**	**Outcome**
Has the level of folic acid in our food supply increased?	Mean folic acid level of bread	20–29 µg/100g	134–200 µg/100g	Desired outcome achieved
Are the food industries adequately complying with the mandatory fortification standards?	Are the food industries adequately complying with the mandatory fortification standards?	Not applicable	Mills and baking businesses have systems in place to ensure compliance.	Desired outcome achieved
Have folic acid intakes of women of childbearing age increased?	Mean folic acid intakes in women aged 16–44 years	102 µg/day	247 µg/day	Desired outcome achieved
Has the folate status of women of childbearing age improved?	Mean red blood cell and serum folate	Serum folate data available for limited assessment. No adequate red blood cell folate baseline data are available.	<u>Red blood cell folate</u> All women aged 16–44 years: 1647 nanomole (nmol) per litre (L) Pregnant women aged 16–44 years: 1958 nmol/L Breastfeeding women aged 16–44 years: 1775 nmol/L	Not applicable
Has the incidence of neural tube defects (NTDs) decreased?	NTD incidence per 10 000 conceptions that resulted in a birth	<u>Total study population</u> All women: 10.2 Indigenous women: 19.6 Teenagers: 14.9 <u>Population omitting NSW residents</u>	<u>Total study population</u> All women: 8.7 (14.4% decrease) Indigenous women: 5.1 (74.2% decrease) Teenagers: 6.7 (54.8% decrease) <u>Population omitting</u>	Desired outcome achieved

Monitoring Question	Measure	Pre-mandatory fortification	Post-mandatory fortification	Outcome
		All women: 12.8 Indigenous women: 22.8 Teenagers: 18.6	NSW residents All women: 11.2 (12.5% decrease) Indigenous women: 4.5 (80.2% decrease) Teenagers: 7.0 (62.6% decrease)	
Does mandatory folic acid fortification result in adverse health effects for the population?	Proportion of the population with folic acid intakes above the UL	Women aged - 16–44 years: 0% 19 years and over: 0% Children aged - 4–8 years: 3% 2–3 years: 5%	Women aged - 16–44 years: 0% 19 years and over: <1% Children aged - 4–8 years: 15% 2–3 years: 21%	Not applicable
Does mandatory folic acid fortification result in adverse health effects for the population?	Cancer and all-cause mortality	Not applicable	No increase in cancer or all-cause mortality can be directly associated with increase in folic acid intakes in adults	Not applicable

Note: The study population for NTDs was not national; Population omitting NSW was used as a sensitivity analysis
NTD incidence reported from the NTD rates in Hilder 2016[12]
Abbreviations: NSW, New South Wales; NTD, Neural Tube Defect; UL, upper level (of intake)
Source: AIHW Report 2016[7]; Table O.1

The AIHW report[7] is critiqued in Section 8.2.4 of this Report. A lack of comparable data in the pre-mandatory fortification period, a reliance on pre-mandatory fortification nutrition surveys and a lack of nationally representative datasets, including for NTDs, were among the limitations identified.

3.3 Evaluation components

For the purposes of this Report, the outcomes of mandatory folic acid fortification were compared to those achieved using the suite of policies that existed before it was introduced (the pre-mandatory fortification suite of policies). These policies consisted of a combination of education, voluntary fortification and supplementation. All these policies continued alongside the mandatory folic acid fortification initiative meaning that mandatory fortification did not replace these policies but rather complemented them.

The evaluations conducted in this Section relate to:

1. Implementation of mandatory folic acid fortification;
2. Achievement of the policy objective (NTD reduction); and
3. Value for money of mandatory folic acid fortification.

For the purposes of this Report, the implementation of mandatory folic acid fortification was required to be assessed using the following outcomes as outlined in the monitoring framework (Section 3.4):

- changes in food composition;
- changes in nutrient intakes;
- changes in nutrient status (biomedical measures); and
- impact on rates on NTDs.

The evaluation criteria against which the overall policy objective (NTD reduction) was required to be assessed were effectiveness, equity, efficiency, certainty, feasibility and sustainability (Section 3.5). This assessment was both comparative (against the pre-mandatory fortification suite of policies) and absolute. This framework was extended beyond the policy objective to other aspects of the monitoring framework, such as nutrient intake and nutrient status.

The question of whether the mandatory folic acid fortification initiative represents value for money was assessed using a cost-benefit analysis (CBA) (Section 3.6).

3.4 Evaluation of implementation

3.4.1 Methodology

This Report assessed the implementation of mandatory folic acid fortification using the monitoring framework. The outcomes of changes in food composition, changes in nutrient intakes, changes in nutrient status (biomedical measures) and the impact of rates on NTDs were assessed.

Success was considered to have been achieved if the increase or change in magnitude estimated was at least as large as expected according to the proposal for mandatory folic acid fortification.[9]

Each outcome was also required to be assessed between two nationally representative datasets that allowed valid comparison. The complete success of the initiative's implementation required the demonstrated successful implementation of all outcomes.

3.4.2 Results

The implementation of the mandatory fortification initiative for folic acid in Australia was mostly but not completely demonstrated to be successful.

The level of folic acid in the food supply (bread) increased, estimated folic acid intake increased, the folate status of the subgroup of women of childbearing age increased (although the magnitude of the increase is uncertain and therefore cannot be considered to have been successfully demonstrated) and the rate of NTDs decreased in line with expectations. However, some concerns exist about the nationally representative nature of some of the datasets, notably those used for the estimation of nutrient intake and the estimation of NTD reduction (Table 4). There are also concerns with the estimation of NTD reduction considering the year-to-year variability in NTD rates combined with the short study period.

Table 4: Assessment of implementation of mandatory folic acid fortification

Implementation area	Measurement	Estimated difference expected in proposal	Actual estimated difference	Nationally representative data used in comparison	Assessment
Food composition	Mean folic acid level of bread	From 20-29 µg/100g to 120 µg/100g bread	From 20-29 µg/100g to 134-200 µg/100g bread	Yes	Demonstrated to be successful
Nutrient intake	Mean folic intake in women aged 16-44 years	100 µg/day increase	From 102 µg/day to 247 µg/day 145 µg/day increase	Uncertain	Demonstrated (with caveats)
Nutrient status	Mean red blood cell folate level	-	Not calculable	No	Not demonstrated
Health outcomes	NTD incidence	4-14%	14.4% decrease in NTD rate	No	Not demonstrated using a national dataset

Source: AIHW Report 2016[7]

3.4.3 Folic acid in the food supply

The implementation step of changing the food composition of bread was successfully achieved as fortified bread contained the expected level of folic acid. The mean folic acid level in the post-mandatory fortification bread samples exceeded the expected 120 µg per 100g of bread and was 134-200 µg per 100g of bread.[7] This achievement was demonstrated by two analytical surveys with random bread selection. The method is appropriate.

3.4.4 Folic acid intake

Folic acid intake was estimated using the updated values of folic acid in bread in the FSANZ dietary monitoring program (Dietary Modelling of Nutritional Data (DIAMOND)). Except for the folic acid content of bread, the data for food consumption in the post-mandatory fortification period was not sourced from the post-mandatory fortification period (2009 or after).

Instead, information from the 1995 National Nutrition Survey (1995 NNS) and the 2007 Australian National Childrens Nutrition and Physical Activity Survey (ANCNPAS) was used to model intake in both the pre-mandatory fortification and post-mandatory fortification periods. The AIHW report[7] argued that this was the best available data at the time of the assessment, and thus was unlikely to make a major difference. The AIHW reported that FSANZ conducted further validation work and concluded it was representative.[7] The estimated increase in folic acid exceeded the expected increase of 100 µg/day.

However, the lack of use of contemporary food composition data from the 2011-2012 National Nutrition and Physical Activity Survey (NNPAS) is a limitation. A decrease was observed in the percentage of female consumers aged 16-44 years who consumed bread in the 1995 NNS (74.6%)

and the 2011-2012 NNPAS (58.2%).[28] Therefore, it is uncertain that the methodology employed was representative of the post-mandatory fortification population.

Therefore, the expected increase has been demonstrated, but the data used may not accurately represent women of childbearing age in the post-mandatory fortification period.

Supplement use was not considered in the 1995 NNS, and this is a weakness in assessing the difference in folic acid/folate intake over time.[27] This may result in overestimating the proportion of women with an intake under the EAR. This may also result in underestimating the proportion of adults who exceed the folic acid intake UL.

The calculated increase in intake can be inferred to be the change attributable to mandatory folic acid fortification as essentially all other variables have been held constant in the modelling. The portion of women who are modelled to be under the relevant EAR levels decreased (Table 5). For pregnant women and lactating women, this may be an overestimate, as it does not include supplements or the impact of dietary adjustment with pregnancy.

Table 5: Proportion of women (16-44 years) with folic acid intake below EAR

Life stage	EAR (DFE)	Pre-mandatory fortification	Post-mandatory fortification	Difference
Non-pregnant	320	11%	1%	10%
Pregnant	520	64%	22%	44%
Lactating	450	46%	10%	36%

Abbreviation: DFE, dietary folate equivalents; EAR, estimated average requirement
Source: AIHW Report 2016[7]; FSANZ 2016[27]; Table 8

3.4.5 Folate status of women of childbearing age

The folate status of women of childbearing age was assessed using different surveys for the pre-mandatory fortification and post-mandatory fortification periods. Different analytical methods were used, and the results are not directly comparable.[36] Therefore, a difference between the pre-mandatory fortification and post-mandatory fortification periods was not calculated.[7] The implementation of the change in folate nutrient status was not demonstrated.

The pre-mandatory fortification results were sourced from the Child-Determinants of Adult Health (CDAH) study between 2004 and 2006, from a subgroup that was not nationally representative. Blood samples were taken from 996 non-pregnant women, a sub-sample of the original study population who were recruited as children. Only 25% of the original study participants contributed to the blood samples sub-study, and they were better educated and smoked less. Therefore, they may not have been nationally representative of the population. The study used a chemiluminescent microparticle binding protein assay. The post-mandatory fortification information came from the National Health Measures Survey (NHMS) from 2011-2012. The NHMS is a nationally representative survey, but the analytical method used to evaluate folate status was different (chemiluminescent immunoassay), and the results are not comparable between studies.[7]

3.4.6 Rate of NTDs (health impact)

The mandatory folic acid initiative was expected to prevent 26 (95% Confidence Interval [CI] 14-49) NTDs per year against the background of 340 (range 300-350) NTD affected pregnancies in Australia,[9] an anticipated reduction in NTD rates of 4% to 16%.

The health impacts resulting from a reduction in NTDs reported in the AIHW report[7] are described more fully in Hilder (Table 6).[12] Two measures were used to report the results in Hilder, the NTD rate, and the birth prevalence. The NTD rate is the number of babies with NTD among pregnancies that ended in a birth or a termination of pregnancy for congenital anomaly in a defined population divided by the number of total births (live births and stillbirths) in that population.[12] Birth prevalence of NTD is the proportion of all babies born in a defined population who have NTD.[12] Incidence is not usually estimated for NTDs because it cannot be measured. This is because a portion of NTD-affected pregnancies results in spontaneous miscarriage or a termination for other reasons.[30]

Following the mandatory folic acid initiative, there was a 14.4% (95% CI 0.7%-26.2%) decrease in the NTD rate. The decrease was concentrated in teenagers (55% [95% CI 4.8%-78.5%] reduction) and younger mothers but is consistent with the 14% decrease in NTDs expected from the combination of mandatory and voluntary fortification, and supplementation initiatives.

Although the start date for mandatory folic acid fortification was September 2009, some millers and bakers started before that date.[12] Therefore, the data on NTDs was broken into three periods, a baseline from October 2006 to December 2007, a transition period from Jan 2009 to October 2009 (consisting of those whose pregnancy might be partially impacted by the implementation of folic acid fortification) and post-mandatory fortification period (September 2009 to 2011).

There was a significant decrease in the rate of NTDs for babies of Indigenous mothers of 74.2% (95% CI 45.1%-87.9%) between the pre and post-mandatory fortification periods.

Table 6: NTD rate during pre and post-mandatory fortification (Indigenous)

Population or subgroup	Pre-mandatory fortification NTD rate (NTDs per 10 000 births)	Transition NTD rate (NTDs per 10 000 births)	Post-mandatory fortification NTD rate (NTDs per 10 000 births)	RR	Lower bound of 95% CI of RR	Upper bound of 95% CI of RR
Total	10.2	9.4	8.7	0.86*	0.74	0.99
Indigenous	19.6	14.3	5.1	0.26*	0.12	0.55
Non-Indigenous	9.3	8.8	8.5	0.91	0.78	1.06

Per 10 000 total births
Note: Baseline (October 2006 to December 2008), Transition (January 2009 to September 2009) and Standard (October 2009 to March 2011); The study population in Hilder was not national
Abbreviations: 95% CI, 95% confidence interval; NTD, neural tube defect; RR, relative rate *, relative rate reduction is statistically significant at 5% level
Source: Hilder 2016[12]; Table F4, Table F3

Table 7: NTD rate during pre and post-mandatory fortification by maternal age

Population or subgroup by maternal age	Pre-mandatory fortification NTD rate (NTDs per 10 000 births)	Transition NTD rate (NTDs per 10 000 births)	Post-mandatory NTD rate fortification (NTDs per 10 000 births	RR	Lower bound of 95% CI	Upper bound of 95% CI
Total	10.2	9.4	8.7	0.86*	0.74	0.99

Population or subgroup by maternal age	Pre-mandatory fortification NTD rate (NTDs per 10 000 births)	Transition NTD rate (NTDs per 10 000 births)	Post-mandatory NTD rate fortification (NTDs per 10 000 births	RR	Lower bound of 95% CI	Upper bound of 95% CI
<20 years maternal age	14.9	13	6.7	0.45*	0.22	0.95
20-24 years maternal age	11.5	11	8.2	0.71	0.49	1.04
25-29 years maternal age	9.5	7.5	7.9	0.83	0.62	1.12
30-34 years maternal age	8.7	8.9	8.1	0.93	0.70	1.24
35+ years maternal age	7.6	9.2	9	1.19	0.85	1.66

Per 10 000 total births
Note: Baseline (October 2006 to December 2008), Transition (January 2009 to September 2009) and Standard (October 2009 to March 2011); The study population in Hilder was not national
Abbreviations: 95% CI, 95% confidence interval; NTD, neural tube defect; RR, relative rate *, relative rate reduction is statistically significant at 5% level
Source: Hilder 2016[12]; Table F4, Table F3

Data about NTDs was included in the analysis from New South Wales, Queensland, Western Australia, South Australia and Northern Territory (excluding Victoria, Australian Capital Territory [ACT] and Tasmania). New South Wales data about NTDs was known to be less complete. It has had a lower rate (approximately half) of notified NTDs, and this may be because of the passive notification system from health service providers.[12] The relative rate of NTDs between New South Wales (NSW) and the other states had not changed over time and therefore it was included in the analysis. The relative ascertainment of NTDs in NSW (compared to other states) was 51.2% in the period 2004-2008 and 43.4% in the period of 1999-2003.[12]

A second analysis was conducted excluding New South Wales. If the New South Wales data was excluded, there was a 12.5% (95% CI -4.7%-28.9%) reduction in the rate of NTDs per 10 000 births.[12] Without the inclusion of the NSW data, the decrease was not statistically significant.

In summary, there are caveats on the estimated decrease in NTDs because of the lack of a national dataset. The results from the analysis of a complete dataset would be more compelling. The short study period post-mandatory fortification and the year-to-year variability in NTD rates (due to the relative rarity of NTDs) also contribute to the uncertainty of these results. Because the dataset was not national, excluding Victoria, ACT and Tasmania, the criterion of using nationally representative data has not been achieved.

3.4.7 Review of other studies and discussion

The implementation of mandatory folic acid fortification was mostly but not completely demonstrated. Most aspects of its implementation had limitations due to lack of nationally representative data, a reliance on earlier nutrition surveys or a lack of comparable data.

Compared to a more robust design, such as an interrupted time series analysis, a pre-post structure for evaluation results in low internal validity.[40] The use of different groups or surveys in each period lowers the internal validity even further. Thus, nationally representative datasets are preferred for the pre-post comparison periods in evaluating implementation.

However, the intake of folic acid and the nutrient status of folic acid in specific subgroups have been assessed using non-nationally representative population samples. These published studies, conducted in a hospital laboratory in Sydney and Indigenous communities in Western Australia and New South Wales, have demonstrated an improvement in folic acid status associated temporally with the introduction of mandatory folic acid fortification.

Brown et. al.[39] presented de-identified results from April 2007 and April 2008 and the period from April 2009 to April 2010 of RBC folate samples analysed at Royal Prince Alfred Hospital in Sydney. The samples were from both outpatients and inpatients, and all samples were analysed using the same type of analyser. After the introduction of mandatory folic acid fortification red cell folate levels rose, and the prevalence of low folate levels fell. The prevalence of high serum and red cell folate levels also rose. These differences were all statistically significant. The comparability of the populations being studied would not be representative of the Australian population because tests were requested for a specific medical reason and the potential differences between the pre and post-mandatory fortification periods were not discussed. When the anaylsis was restricted to sample from women aged between 15 and 50 years, the portion of women with a low folate level recorded in samples fell. In April 2010 only one sample from women aged between 15-50 years was low (n=609 samples).[39]

Black et. al.[41] conducted a pre-post analysis in three Indigenous community controlled health centres in NSW. Children were the population studied. Two interventions occurred- the mandatory folic acid fortification initiative and the availability of subsidised fruit and vegetables (alongside nutritional education). RBC folate levels were collected a year apart, and 125 children had blood taken at both times. Different analysers were used at different sites so the results could not be combined. Mean RBC folate level increased significantly at two sites but not at a third. The combination of interventions means the observed differences cannot be confidently attributed to mandatory folic acid fortification.

Bower et. al. used identical methods at two time points to establish folic acid intake and red cell folate in the Indigenous population aged 16-44 years at two sites in Western Australia before and after mandatory folic acid fortification.[42] The sample size was small (81 before fortification and 95 after fortification). There was a statistically significant increase in RBC folate and dietary folate intake for both men and women.

These subgroup analyses show a consistent trend of increasing dietary folate intake and increasing RBC folate level associated with mandatory folic acid fortification. In summary, other published research suggested that implementation occurred.

3.5 Evaluation of policy objective (NTD reduction)

3.5.1 Background to evaluation of policy objectives

The evaluation criteria were pre-specified in the 2005 expert public health advice,[29] and Box 2 from the expert public advice is replicated in Table 8: Evaluation criteria for mandatory fortification schemes. Regarding equity, specific issues of education/socio-economic status and Indigenous status were discussed in the expert public health advice.

There were differences in NTD rates between Indigenous and non-Indigenous women prior to mandatory fortification. Women of Indigenous background were twice as likely as non-Indigenous women to have a baby with spina bifida or encephalocoele between 1980-2000 in Western Australia.[43]

Table 8: Evaluation criteria for mandatory fortification schemes

Assessment criteria	Questions
Effectiveness	Can nutrient requirements be met by the proposed strategy? Has the strategy been shown to work elsewhere?
Equity	Does the strategy reach the population equally? Specifically, those most at risk?
Efficiency	Can the strategy be implemented efficiently considering opportunity costs?
Feasibility	Can the strategy be practically implemented? Are there technical barriers to implementation?
Certainty	Can a proposed strategy deliver adequate quantities of a nutrient to those who need it most?
Sustainability	Can ongoing implementation of the strategy be guaranteed?

Source: Adapted from Box 2 of Expert Public Health Advice 2005[29]

The 2005 expert public health advice assessed the relative usefulness of each of the potential strategies for folic acid. These strategies included mandatory fortification, voluntary fortification, supplements, dietary education and the status quo. The strategy of mandatory folic acid fortification was considered the most effective public health strategy (Table 9).

Table 9: Assessment of public health strategies to increase folic acid intake

Criteria	Mandatory fortification	Voluntary fortification	Supplements	Dietary education	Maintaining status quo
Effectiveness	Yes	Yes	No[a]	No	No
Equity	Yes	No	No	No	NA
Efficiency	Yes	No[b]	Unsure	No	NA
Certainty	Yes	No	Yes[c]	No	NA
Feasibility	Yes	Yes	Yes	Yes	NA
Sustainability	Yes	No	No	No	NA

a Required early in pregnancy but a large percentage is unplanned.
b Ongoing Implementation costs.
c Although supplements vary in dose.
Source: Adapted from Box 4 of Expert Health Policy Advice 2005[29]

Mandatory folic acid fortification was not expected to satisfy the requirements for folic acid in pregnancy but, for completeness sake, this was included in the indicators of effectiveness. Not fortifying to the level required for pregnancy was because the risk assessment was against the nutrition needs of the entire population. Not increasing folic acid intake above the UL for the non-target population was a consideration in setting the level of mandatory folic acid fortification.[5,9] Women of childbearing age are the subgroup of interest for mandatory folic acid fortification.

It should be appreciated that the majority of this Report's comparative evaluation was undertaken as part of a pre-post design. A pre-post design is weak in terms of internal validity. This limits the confidence that can be placed in the results of an assessment of evaluation criteria.

This Report's assessment of the evaluation criteria was supplemented by the results of other research (which was not nationally representative), which is included in the discussion.

3.5.2 Methodology

Indicators were developed for each of the criteria. Some indicators were absolute, that is, without a comparative element. Others were comparative against the pre-mandatory fortification suite of policies. The estimation of comparative differences required two results (one for pre-mandatory fortification and one for post-mandatory fortification) that are valid for comparison. Within this Report's value for money evaluation, effectiveness was altered by adjusting for an observed decrease in the rate of NTDs before mandatory fortification (see Adjustment for NTD rates in Section 3.6.8). For each of the indicators, a pre-determined data set and threshold for success was applied. A conclusion was reached in this Report about the success of each of the indicators.

This Report was required to assess the pre-determined criteria against the policy objective of reducing NTD rates. This Report also undertook additional evaluations of food composition and nutrient intake for completeness (Table 10).

Table 10: Evaluation criteria and indicators for mandatory folic fortification

Criteria	Question/indicator	Absolute or comparative	Threshold for success (data source) Table number in this Report (if appropriate)
Achievement of policy objective (also included in measures of effectiveness)	Was mandatory folic acid fortification effective at reducing NTDs compared to pre-mandatory fortification?	Comparative	Was a statistically significant reduction (5%) in the incidence of NTD between pre-mandatory fortification and post-mandatory fortification periods for Australia demonstrated? (Hilder[12]) (Table 6)
Effectiveness	Were nutrition needs satisfied by mandatory folic acid fortification?	Absolute	Was the folic acid nutrient status of all women of childbearing age satisfactory by comparison to WHO guidelines? (AIHW report[7]) Was the folic acid intake of women of childbearing age satisfactory? (AIHW report[7]) (Table 5) Was the folic acid intake of pregnant women satisfactory? (AIHW report[7]) (Table 5) Was the folic acid intake of lactating women satisfactory? (AIHW report[7]) (Table 5)
Effectiveness	Was mandatory folic acid fortification more effective at satisfying the nutrition needs than the alternative?	Comparative	A reduction in the portion of the women of childbearing age with inadequate folic acid intake from the pre-mandatory fortification period to the post-mandatory fortification period (AIHW report[7]) (Table 5)
Effectiveness	Was mandatory folic acid fortification effective at	Comparative	Was a statistically significant reduction (5%) in the incidence of

Criteria	Question/indicator	Absolute or comparative	Threshold for success (data source) Table number in this Report (if appropriate)
	reducing NTDs compared to pre-mandatory fortification?		NTD between pre-mandatory fortification and post-mandatory fortification periods for Australia demonstrated? (Hilder[12]) (Table 6)
Effectiveness	Was the reduction in NTD attributable to mandatory folic acid fortification?	Comparative	Adjusting for continuing reduction in NTD, is the impact of the strategy estimated to be positive? (this step was conducted in the economic evaluation in section 0)
Equity	Did the population have access to foods fortified with folic acid with mandatory folic acid fortification?	Absolute	Was the folic acid in the fortified food at the required level? (AIHW report[7]) (Table 4)
Equity	Was there equity in the distribution of folic acid status between socio-economic groups?	Absolute	Was there no statistically significant difference between folic acid status between SES? (AIHW report[7])
Equity	Were there inequities in the distribution of folic acid nutrient status between Indigenous and non-Indigenous populations?	Absolute	Was there no statistically significant difference between folic acid status between Indigenous and non-Indigenous populations? (AIHW report[7]) (Table 6)
Equity	Has access to foods fortified with folic acid improved?	Comparative	Has there been an increase in the level of folic acid in bread? (AIHW report[7]) (Table 4)
Equity	Has the inequity between socio-economic status been reduced?	Comparative	Was a reduction in the difference in rate of NTDs between socio-economic status demonstrated (AIHW report[7])
Equity	Has the inequity between Indigenous and non-Indigenous status been reduced?	Comparative	Was a reduction in the difference in the rate of NTDs between Indigenous and non-Indigenous populations demonstrated? (AIHW report[7]) (Table 6)
Efficiency	Has the strategy been implemented efficiently?	Absolute	Did the Catalyst report demonstrate any avoidable or excess costs? (Catalyst report[6])
Efficiency	Was the strategy the most efficient means of achieving the outcome demonstrated, the reduction in NTDs?	Comparative	Only estimated if efficiency is equal between options- Is the strategy the lowest cost alternative in the economic evaluation to achieve the outcome? (Section 3.6)
Feasibility	Was the strategy be successfully implemented?	Absolute	Were all the implementation outcomes demonstrated to be achieved as assessed in the implementation section? (Section 3.4)

Criteria	Question/indicator	Absolute or comparative	Threshold for success (data source) Table number in this Report (if appropriate)
Feasibility	Was the policy objective demonstrated to have been achieved?	Absolute	Was a statistically significant reduction (5%) in the incidence of NTD between pre-mandatory fortification and post-mandatory fortification periods for Australia demonstrated? (Hilder[12]) (Table 6)
Feasibility	Were there sufficient quality assurance procedures in place?	Absolute	Were sufficient quality assurance procedures in place in the Catalyst report? (Catalyst report[6])
Certainty	Has the introduction of mandatory folic acid fortification delivered folic acid to those who need it most?	Comparative	Assumed to have increased because of increased certainty about folic acid in diet
Sustainability	N/A	Absolute	Assumed to have not been demonstrated because of the limited post-mandatory fortification period

Abbreviation: NTD, neural tube defect; SES, socio-economic status; WHO, World Health Organization

3.5.3 Results

In this Report, the policy objective was achieved, with a reduction in the rate of NTDs demonstrated between the pre and post-mandatory fortification periods in Hilder[12]. However, it was demonstrated with the use of a sub-national dataset.

The absolute indicators for effectiveness were not completely demonstrated. Mandatory folic acid fortification was not demonstrated to satisfy the nutrient requirements of the population, notably pregnant women. The nutrient requirements of the target group of women aged 16-44 years were estimated to be satisfied. This suggests mandatory folic acid fortification achieved its policy-relevant nutrient objective (Table 11).

Table 11: Absolute indicators for effectiveness of mandatory folic acid fortification

Question	Indicator	Result	Conclusion
Was the folic acid nutrient status of all women of childbearing age satisfactory?	At the population level, red blood cell folate concentrations should be above 400 ng/mL (906 nmol/L) in women of reproductive age, to achieve the greatest reduction of NTDs[36]	Not able to be assessed, folate levels that used the chemiluminescence method could not be compared to threshold	Not able to be demonstrated. Microbiological assay is recommended as the most reliable choice to obtain comparable results for red blood cell folate across countries[36]
Was the folic acid intake of women of childbearing age sufficient?	Proportion of women aged 16-44 years with DFE below the EAR for non-pregnant women	1% of women (16-44 years) (Table 5)	Demonstrated
Was the folic acid intake of pregnant women	Proportion of women aged 16-44 years with DFE	22% of women (16-44 years) (Table 5)	Not able to be demonstrated

Question	Indicator	Result	Conclusion
sufficient	below the EAR for pregnant women		
Was the folic acid intake of lactating women sufficient?	Proportion of women aged 16-44 years with DFE below the EAR for lactating women	10% of women (16-44 years) (Table 5)	Not able to be demonstrated

Abbreviations: DFE, dietary folate equivalent; EAR, estimated average requirement; NTD, neural tube defect
Source: AIHW report 2016[7]; WHO 2015[36]

In this Report, mandatory folic acid fortification was demonstrated to be relatively effective compared to the pre-mandatory fortification suite of policies, given the limitations of the data (Table 12). All the indicators improved with mandatory folic acid fortification.

Table 12: Relative indicators for effectiveness for mandatory folic acid fortification

Question	Indicator	Result	Conclusion
Was mandatory folic acid fortification more effective at satisfying the nutrition needs than the alternative?	Comparison between the portion of women aged 16-44 years who are below the EAR	A reduction from 11% to 1% (Table 5)	Comparative effectiveness demonstrated
Was mandatory folic acid fortification effective at reducing NTDs compared to pre-mandatory fortification?	Reduction in NTDs Australia wide with a 95% confidence interval that excludes zero	14.4% decrease (95% CI 0.7%-26.2%) (Table 6)	Comparative effectiveness partially demonstrated- a complete Australian dataset was not available
Was the reduction in NTD attributable to the strategy?	Was the calculation of reduction in NTDs greater than zero when including adjustment for background rate (See Section 3.6.8)	14 fewer NTDs were estimated to have occurred with mandatory folic acid fortification	Comparative effectiveness demonstrated (subject to limitations)

Abbreviations: EAR, estimated average requirement; NTD, neural tube defect
Source: AIHW Report 2016[7]; Hilder 2016[12]; FSANZ 2016[27]

Absolute indicators for equity demonstrated that mandatory folic acid fortification was mostly but not completely equitable (Table 13).

Table 13: Absolute indicators for equity of mandatory folic acid fortification

Question	Indicator	Result	Conclusion
Does the population have access to foods fortified with folic acid?	Was the folic acid in the fortified food at the required level?	The folic acid level of bread was at the required level (Table 4)	Absolute increase in access to folic acid demonstrated
Was there equity in the distribution of folic acid status between socio-economic groups?	No statistically significant difference between folic acid status between SES?	There were only small differences between groups[7]	Mandatory folic acid fortification was demonstrated to be equitable
Was there equity in the distribution of folic acid nutrient status between Indigenous and non-	Was there no statistically significant difference between folic acid status between Indigenous and	Mean serum folate levels were lower for Indigenous people by 14-24%[7]	Mandatory folic acid fortification was not demonstrated to result in equitable outcomes

Question	Indicator	Result	Conclusion
Indigenous populations?	non-Indigenous populations? Was a minimally important difference between the groups excluded?		

Abbreviation: SES, socio-economic status
Source: AIHW Report 2016[7]; Figure 2.13; Figure 2.17

The performance of mandatory folic acid fortification, with regard to equity, was superior to the pre-mandatory fortification suite of policies. Inequity in NTD rates based on socio-economic status was not able to be assessed in this Report because of data limitations.

Table 14: Relative indicators for equity of mandatory folic acid fortification

Question	Indicator	Result	Conclusion
Has access to foods fortified with folic acid improved?	Difference in folic acid content of bread	The folic acid level increased in bread (see Section 3.4)	Improvement in equity of access
Has the inequity between socio-economic status been reduced?	Difference in NTD rate by socio-economic status	Not assessed in Hilder[12] or AIHW report[7] No post-mandatory fortification peer-reviewed literature found by socio-economic status	Not demonstrated
Has the inequity between Indigenous and non-Indigenous status been reduced?	Decrease in NTD rate for Indigenous versus non-Indigenous	Decrease in NTD rates for non-Indigenous by 9.1% versus decrease in Indigenous by 74.2% (Table 6)	Improvement in equity demonstrated, but significant limitations

Abbreviation: NTD, neural tube defect
Source: AIHW 2016[7], Hilder 2016[12]

The Catalyst report[6] (see Section 8.2.2: Catalyst report) reported the costs of implementation of mandatory folic acid fortification to be less than expected. As the outcomes of mandatory folic acid fortification were estimated to be superior for the purposes of the economic evaluation, the conclusion reached in this Report is that mandatory folic acid fortification was efficient.

The feasibility of mandatory fortification was mostly but not completely demonstrated by the evaluation of its implementation (see Section 3.4: Evaluation of implementation). Limitations in the available data meant the changes in nutrient status and health outcomes were not demonstrated. The Catalyst report[6] concluded that quality assurance was sufficient. The feasibility of achieving the policy objective was demonstrated, albeit with a dataset that was not national.

Certainty was assumed to have improved because of the increase in the folic acid content of bread.

Sustainability was assumed not to have been demonstrated due to the short period after mandatory fortification.

3.5.4 Discussion of whether policy objectives (reducing NTDs) achieved

Mandatory folic acid fortification reduced the NTD rate by 14.4%; therefore, the policy objective was achieved. However, the estimation was based on a subset of Australian jurisdictions. This limits the strength of the conclusions.

In general, mandatory folic acid fortification was found in this Report to be comparatively superior in achieving an NTD reduction to pre-mandatory fortification suite of policies. That is, mandatory folic acid fortification was relatively superior to the alternative of no mandatory folic acid fortification when considering equity, effectiveness and efficiency.

The lack of comparability of the pre-mandatory fortification estimates of nutrient status of folic acid/folate made it difficult to draw firm conclusions about the relative effectiveness, equity, feasibility and efficiency of mandatory folic acid fortification.

This issue was compounded by a lack of a nationally representative data in several key areas, including the health outcome of reducing NTDs. The short follow-up time made a demonstration of sustainability impractical; in a relatively rare event such as an NTD, it made the statistical examination of the outcome subject to wider confidence intervals. The lack of a national dataset of NTDs was a significant limitation in this Report's evaluation of mandatory folic acid fortification against the stated policy objective.

As expected, the introduction of mandatory folic acid fortification was not demonstrated to satisfy the nutrient intake requirements for pregnant women. Mandatory folic acid fortification is required to be combined with other policies (notably supplementation) to ensure that folic acid intake requirements are met for pregnant women.

The results presented were subject to significant limitations and hence the applicability of the calculated results to populations of interest was limited. The lack of information about supplement use in the calculation of EAR could be considered a limitation.[27]

The estimates of the target population that had an inadequate intake of folate (and folic acid) fell. This result would be more compelling if a more contemporary food composition survey was used.[27] However, comparatively, mandatory folic acid fortification was more effective than the alternative of no mandatory folic acid fortification.

Mandatory folic acid fortification improved equity outcomes compared to the pre-mandatory fortification suite of policies. There was a substantial fall in the NTD rate for births of Indigenous mothers; the point estimate is now lower than for births of non-Indigenous mothers (5.1 versus 8.5 per 10 000 total births [Table 6]). However, some absolute equity differences continue to exist in nutrition status: Indigenous Australians had a lower folate level than the general population after the introduction of mandatory folic acid fortification. The importance of the differences in folate levels will need to be considered in the context of the lower NTD rate measured in the post-mandatory fortification period; in the future, the results need to be confirmed. Mandatory fortification improved equity in relation to access to fortified foods. Voluntary fortification may result in product differentiation, and fortified foods may be more expensive than unfortified foods.

The peer-reviewed research concluded mandatory fortification improved the nutrient status of disadvantaged populations. Bower et al.,[42] after re-sampling two areas in Western Australia, found an improvement in the folate status for Indigenous males and females in those areas.[42] Black et al.[41] also demonstrated an increase in red cell folate status for Indigenous children in

NSW with the introduction of mandatory folic acid fortification. However, this finding is confounded by the introduction of a concurrent second intervention (discounted fruit and vegetables). There was no consistent trend in terms of folic acid nutrient status by socio-economic status. A difference was observed by geographic location with those living in outer regional areas having the lowest folate levels. There were also differences by state, with NSW, South Australia and Tasmania having the highest folate levels.

Mandatory folic acid achieved its objective of reducing NTDs for those with a higher probability of risk. The distribution of the relative improvements in NTD rates was higher in babies of teenage mothers (54.8% reduction) and babies of Indigenous mothers (74% reduction). These results show the potential equity impacts of mandatory fortification. As both groups are at a higher risk for NTDs, mandatory folic acid fortification has been pro-equity in reducing the impact of NTDs in the populations with the highest burden. The dramatic fall of NTDs in babies of Indigenous mothers will need to be confirmed over a longer period, due to the small numbers in these groups and the variability in NTD rates year-to-year.

The reduction of NTDs to babies of Indigenous mothers was also found by Bower et al.[42] The authors found a 68% drop in the rate of NTDs comparing the pre-mandatory fortification period (1980-2009) to the post-mandatory fortification period (2010-2014). This difference was statistically significant, but the confidence interval was wide (Prevalence ratio 0.32 [95% CI 0.15-0.69]).[42]

A potential inequity exists because folic acid is delivered to a large proportion of the community who are not the intended targets of the initiative (women of childbearing age). Arguments can be made about the impact of folic acid fortification on the non-target population. For example, a reduced proportion of the non-target population estimated to be folate deficient can be presented as an increase in equity. However, if there is the potential for exposure to a risk of adverse effects, this would produce a negative impact on equity. As discussed in Section 8.9, there is no conclusive evidence of adverse effects occurring in the population in relation to mandatory folic acid fortification. However, the large number of persons exposed relative to those who are the intended targets suggests that evidence of benefit and harm needs to be periodically revisited as more evidence is produced.

As modelled in the cost-effectiveness analysis, mandatory fortification was less expensive and produced more health than the pre-mandatory fortification suite of policies (see Section 3.6.19). Therefore, mandatory fortification was more efficient than the alternative of no mandatory fortification. This remains subject to the assumption that effectiveness has been correctly estimated in the economic evaluation.

The feasibility of the implementation of mandatory folic acid fortification has been mostly, but not completely, demonstrated by the evaluation of the outcomes of implementation. This is discussed in Section 3.4: Evaluation of implementation. The reduction in the NTD incidence provides some reassurance that the earlier implementation steps may have been satisfied even if they could not be demonstrated by a comparison between nationally representative pre-mandatory fortification and post-mandatory fortification datasets. The feasibility of achieving the policy objective was demonstrated.

Compared to the pre-mandatory fortification suite of policies, there is increased certainty about the folic acid content of bread. It is more certain that folic acid will be delivered to the target group as a result of mandatory fortification. This conclusion remains subject to limitations. The delivery is dependent on the consumption of fortified foodstuffs as part of the initiative. The consumption of folic acid fortified food will need to be monitored into the future and may require adjustment.

The sustainability of mandatory folic acid fortification is yet to be demonstrated. The identification of high-risk subgroups may be important in continuing to reduce the burden of NTDs in Australia. The sustainability of mandatory fortification is potentially greater than the pre-mandatory fortification suite of policies, as it does not require the food industry to decide to fortify products that have a wide consumption in the key target group.

Additionally, if it is assumed that the trend of a reduced rate of NTDs continues, then the additional NTDs prevented by mandatory fortification *may* decrease over time. In this circumstance, the value of mandatory folic acid fortification would also decrease over time. For this reason, continued evaluation of the impact of mandatory folic acid fortification may be required to ensure its benefits outweigh the opportunity costs.

3.6 Evaluation of value for money

This Report assessed the value for money of the mandatory folic acid fortification initiative using a CBA. The initiative was considered to be value for money if the CBA was positive or the cost-utility analysis (CUA) had a cost per quality-adjusted life year (QALY) of less than $AUD 50 000. This Report also conducted a cost-effectiveness analysis and CBA of folic acid mandatory fortification comparing mandatory fortification with no mandatory fortification.

The purpose of a CBA is to ascertain if the community is better off with one scenario rather than an alternative scenario.[44] A CBA allows the consideration of all costs and benefits rather than making decisions based on selected outcomes.[44]

Additional information on conducting and interpreting a CBA is found in Section 8.5.

3.6.1 Assumptions

In undertaking the CBA, some assumptions were necessary due to the pre-post nature of the evaluation and a lack of information about potential costs and benefits. Three key assumptions made in this Report's CBA concerned the pre-post nature of the data (concerning changing NTD rates and sunk or one-off costs), the loss of value of choice with mandatory fortification, and the assessment of adverse effects. These assumptions were tested in sensitivity analyses.

3.6.2 Assumptions inherent in pre-post structure

The pre-post structure informed the initiative's assessment. This approach meant the same information was used to consider the success or failure of the initiative and the economic evaluations, ensuring the results were concordant.

Assessing the magnitude of change in the outcomes is an inappropriate assumption if other policies or behaviours are also changing. The background trend rate of decreasing NTDs over time is an example of this. If this trend continues, the pre-post approach undertaken would overestimate the benefit associated with changing to mandatory folic acid fortification. The background trend rate of NTDs was included and was assumed to capture changes in supplement use and other confounders relating to NTD incidence not associated with demographics.

Some confounders, such as demographic changes, can be controlled for by using a reference population. This reduces the confounders associated with changes in maternal age. For this evaluation, a reference population of Australia in 2014 was used.

Another issue that arises with the pre-post structure is that of start-up/one-off /sunk costs. Sunk costs such as those due to a write-off in packaging costs were incurred as a result of in the change from the pre-mandatory fortification suite of policies to the post-mandatory fortification suite of policies.

While it may be appropriate to consider potential sunk costs when estimating the change from one set of initiatives to another, these are not included in the base case evaluation undertaken in this Report. Rather, the comparison is made between the situation in 2014 with mandatory folic acid fortification compared to the situation in 2014 if mandatory folic acid fortification had not been introduced. The base case did not include one-off or sunk costs in either alternative.

The decision not to include such costs was made because their inclusion would create a status quo bias. Before mandatory folic acid fortification, start-up costs make the status quo of the set of policies without mandatory folic acid fortification potentially less expensive. After its introduction, it would make mandatory fortification potentially less expensive than the alternative of changing to the alternative of no mandatory fortification because the one-off costs would be incurred again.

This assumption was tested in the scenario analysis with start-up costs on one alternative and then the other.

3.6.3 Model structure

Economic evaluation type

This economic evaluation used a decision analytic framework to assess the benefits and costs of mandatory folic acid fortification compared to no mandatory fortification. A cohort approach was taken, using Australia's population in 2014. As no data for 2014 NTD rates were available, the NTD rates measured in 2011 were applied to the 2014 population numbers. The impacts of the estimated NTD affected pregnancies in 2014 were extrapolated over the lifetime of those affected.

The economic evaluation conducted is a cost-utility analysis. That is, health impacts (positive and negative) were measured (or quantified) as quality-adjusted life years (QALYs). Costs for the health system, the population, government, and manufacturers were valued in dollars.

The CUA was extended to a CBA, where the health benefits were monetarised in Section 3.6.17.

3.6.4 Population, modelled alternatives and outcomes of interest

The population for the modelling was that potentially impacted by mandatory fortification. This population is all people in Australia. The policy objective for mandatory folic acid fortification was to reduce NTDs.[7,29] Therefore, pregnant women and neonates (and the corresponding rates of NTDs in these populations) were included explicitly in the modelling.

The two alternatives considered in the economic evaluation were:

- Australia with mandatory folic acid fortification – mandatory fortification (including the pre-mandatory fortification suite of policies); and
- the counterfactual of Australia without mandatory folic acid fortification – no mandatory fortification (retaining the pre-mandatory fortification suite of policies).

The outcomes of interest identified were the changes in the expected number of NTDs and the costs of fortification. A societal perspective was used for the economic evaluation. The benefits and costs quantified are described in Table 15.

Table 15: Economic Evaluation outcomes, measurement and valuation

Identified cost or benefit	Health outcome measurement	Health services cost	Productivity changes and other costs
Babies born with NTDs.	QALY.	Health service related cost. Assistive technology.	Decrease in carers' employment. Decrease in patients' employment.
Terminations for NTD.	Maternal utility decrement measured as QALY. Increased QALY associated with birth.	Health service related cost.	No change.
Stillbirth with NTD.	Maternal utility decrement measured as QALY. Increased QALY associated with birth.	Health service related cost.	No change.
NTD affected pregnancy.	QALY loss.	Health service related cost.	No change.
Adverse effects.	QALY loss.	Health service related cost.	No change.
Costs of fortification.	N/A	N/A	Cost to: • industry of providing fortification. • government of monitoring fortification

Note: Costs and consequences differ between stillbirths, alive at birth (neonatal deaths and neonatal survivors)
Abbreviations: NTD, neural tube defect; QALY, quality-adjusted life year

Initially, a base case was calculated. This base case used the modelled difference in the AIHW report[7] adjusted for the background decrease in NTDs and did not include the start-up costs of fortification, adverse effects, the maternal utility decrement associated with terminations or the potential loss in consumer surplus. Subsequently, a series of scenarios, which included adverse effects, termination utility decrements, and start-up costs, were developed. The potential loss of consumer surplus was considered as a threshold analysis.

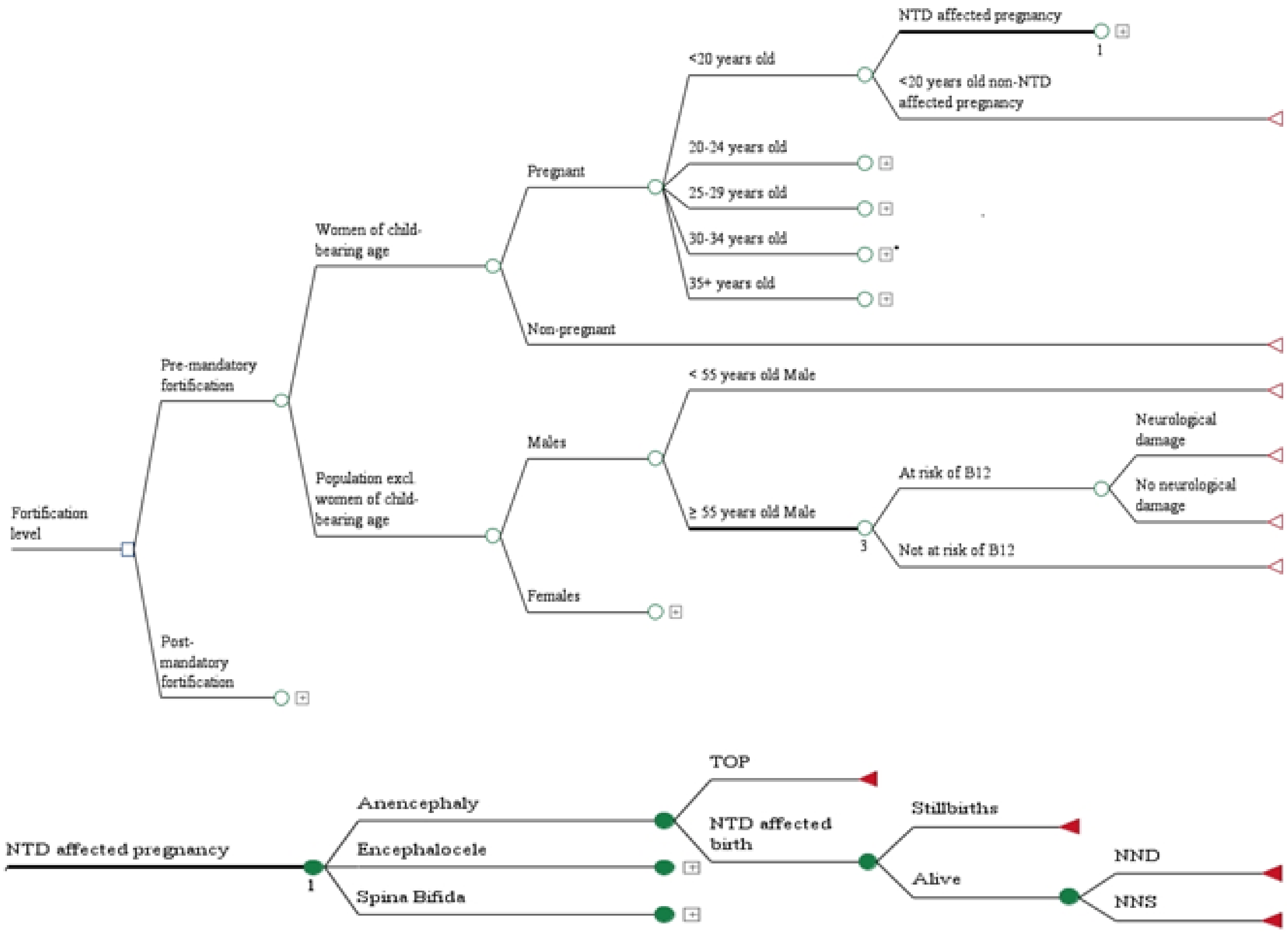
3.6.5 Decision analytic framework

The decision tree is presented in Figure 2. Essentially the population was divided into two main groups: women of childbearing age (16-44 years) and the remaining population.

Women of childbearing age include women that are pregnant and non-pregnant. For those that are pregnant, the pregnancy can be impacted by an NTD. If impacted by an NTD the severity is determined, and a portion of pregnancies is terminated. The change in the NTD rate between the two alternatives results in a change in terminations as well as live births. If not impacted by an NTD the pregnancy progresses as normal with a normal expected life expectancy.

The remainder of the population was divided into an older and a younger group. The older group was used for considering adverse effects, such as the development of neurological abnormalities from a B_{12} deficiency that may be exacerbated by folic acid fortification.

Figure 2: Folic acid fortification economic evaluation decision tree



Note: NND, neonatal death; NNS, neonatal survivor; TOP, termination of pregnancy

3.6.6 Model assumptions

The following assumptions were used:

1. The model included Australia's population in 2014 and the births that occurred in 2014. That is a population of 23 610 906 persons, including 298 453 pregnancies.

2. The model used a lifetime horizon for those included in the cohort. Pregnancies were included in the cohort of the index year.

3. Spina bifida occulta, as opposed to spina bifida, was not included in the monitoring framework and was not included in the scope of the AIHW report.[7] Therefore, it was not included in this model.

4. NTD rates per 10 000 births differed by maternal age and were adjusted for isolated NTD cases. Isolated NTDs have either no co-existing congenital anomalies or only have co-existing anomalies directly related to the NTD. The model assumed that the proportion of the type of isolated NTD was the same, regardless of maternal age.

5. Pre-mandatory fortification NTD case rates were based on 'Baseline' (October 2006 to December 2008) and Post-mandatory fortification NTD case rates were based on 'Standard' (October 2009 to March 2011). These timeframes were based on the analysis performed in Hilder.[12]

6. The outcome of an NTD affected pregnancy is either birth (stillbirth or live birth) or termination of pregnancy (TOP). The base case assumed that TOP occurred at the same rate regardless of NTD type (42.8%). The model assumed TOP does not alter the eventual family size and, after two years, the costs and outcomes of a non-NTD affected pregnancy were included.

7. For NTD-affected pregnancies that are not terminated, the outcome could be stillbirth or live birth (neonatal death and neonatal survivor). The outcomes focus on neonates for survival and utility. QALYs were calculated.

8. Included costs were for the health care of the neonate to adulthood (specifically for treatment of NTD); the cost of delivery; the cost of carers and the cost of ongoing fortification for government and industry;

9. A discount rate of 5%;

10. No adverse effects in the base case; and

11. No loss of consumer surplus due to a reduction in choice.

3.6.7 Model inputs

Health outcomes

NTDs are relatively rare. There was a short study period post-mandatory fortification in the AIHW report.[7] This decreases the confidence in the point estimate in Hilder.[12] These results were based on a subset of national data. The results in Hilder[12] were extrapolated to the entire country.

NTD outcomes

The model relied on the NTD data provided in the AIHW report[7] and Hilder.[12]

The NTDs estimated comprise three distinct conditions: anencephaly, spina bifida and encephalocoele. Spina bifida occulta is a mild form of NTD and was not included in the AIHW baseline monitoring report[30] in 2011 or the AIHW report[7] in 2016.

The descriptions of the different types of NTDs are;

- anencephaly, a congenital anomaly characterised by the total or partial absence of the cranial vault, the covering skin, and the brain. Remaining brain tissue may be very much reduced in size;
- spina bifida, a congenital anomaly characterised by a failure in the closure of the spinal column and by herniation or exposure of the spinal cord and/or meninges through the incompletely closed spine;
- encephalocoele, a congenital anomaly characterised by herniation of the brain and/or meninges through a defect in the skull; and
- spina bifida occulta, a mild form of NTD and not obvious at birth.

NTDs were categorised in Hilder[12] as isolated NTDs if there were either no co-existing congenital anomalies or only co-existing anomalies that occurred as a consequence of NTD. Isolated NTDs are considered to be more strongly associated with folate insufficiency.[12] These proportions were used in the model (Table 16).

Table 16: NTD cases by subtype

Cases, n (%)	Anencephaly	Encephalocoele	Spina bifida	Total
NTD[a], n (%)	400 (39)	115 (11)	515 (50)	1 030 (100)
Isolated NTD, n (%)	351 (43)	74 (9)	400 (48)	825 (100)

[a]. This is a hierarchical system that allocates each baby to one NTD group. Anencephaly takes precedence over all other NTD conditions, and spina bifida takes precedence over encephalocoele.
The study population in Hilder was not national
Abbreviation: NTD, neural tube defect
Source: Hilder 2016[12]; Table 3; Table E.5.

Table 17 presents the proportions of NTD outcomes by NTD classification. If the pregnancy is NTD-affected, it can be terminated before birth. If an NTD-affected pregnancy results in birth, a stillbirth could result. If the neonate is born alive, it can either die within the first 28 days, which is classified as a neonatal death (NND), or, it survives, this is a neonatal survivor (NNS). It should be noted that the sample size for encephalocoele persons is small (n=27). Hence, the estimated proportions should be interpreted with caution.

Table 17: NTD birth outcomes by NTD classification

NTD Birth outcomes	Anencephaly	Encephalocoele	Spina bifida	Total
Stillbirths, n (%)	85 (68)	27 (38)	179 (46)	291
Alive at birth[a], n (%)	40 (32)	44 (62)	209 (54)	293
Total[b], n	125	71	388	584

NTD Birth outcomes	Anencephaly	Encephalocoele	Spina bifida	Total
Alive at birth, NTD-affected Neonatal deaths, n (%)	40 (100)	8 (18)	43 (21)	91
Alive at birth, NTD-affected Neonatal survivors, n (%)	0	36 (82)	166 (79)	202

a Alive at birth outcomes comprises of neonatal deaths (NND) plus neonatal survivors (NNS) (NND + NNS)
b NTD birth outcomes comprise stillbirths (SB), neonatal deaths (NND) and neonatal survivors (NNS)
The study population in Hilder was not national
Abbreviations: NTD, neural tube defect
Source: Hilder 2016[12]; Table 7, p.30

3.6.8 Incidence of NTDs

NTD rates before mandatory folic acid fortification

The rate is the number of NTD-affected babies from birth (live births and stillborn) or TOP for congenital anomaly regardless of pregnancy gestation divided by the number of total babies born.

In 2008, the rate of NTDs was 10.7 (95% CI 8.9–12.5) NTDs per 10 000 total births.[30] The average annual decline in the rate of NTDs between 1998 and 2008 averaged 0.2 per 10 000 births and was more evident for spina bifida, with no appreciable change in the occurrence of either anencephaly or encephalocoele.[12]

NTD rates after mandatory folic acid fortification

Hilder[12] provided details of the incidence of NTDs (NTD incidence per 10 000 conceptions that resulted in birth). Data were available from New South Wales, Queensland, Western Australia, South Australia and the Northern Territory.

Analysis omitting New South Wales from the total study population was undertaken as a sensitivity analysis to address the potential bias of missing data from this state (see Section 3.4.2). The analysis showed that inclusion of New South Wales data provided a much larger population and improved the study's power. For consistency, where possible, the model used the full data set in the base case and included the results omitting NSW in a sensitivity analysis.

Hilder[12] measured NTD rates for conception that occurred at Baseline (October 2006 to December 2008), Transition (January 2009 to September 2009) and Standard (October 2009 to March 2011). The Standard period is used as the estimate of the period after fortification (post-mandatory fortification) as pregnancies occurring during this period had the benefit of mandatory fortification from conception onwards. The Baseline period is used to estimate the rates occurring during the period when the pre-mandatory fortification suite of policies was in place.

In the period October 2009 to March 2011, NTD rates had fallen by 14.4% (95% CI 0.7%-26.2%) compared to October 2006 to December 2008. This decrease was statistically significant (Relative Risk [RR] 0.86 [95% CI 0.738-0.993]).[12] When the population omitted NSW residents, the reduction was 12.5% (95% CI -4.7%-28.9%) and non-statistically significant.[12] This accorded with the estimated reduction between 4 to 16%.[12]

Maternal age

Higher NTD rates were reported among babies of teenagers (mothers aged < 20 years) in the baseline period.[12] In the post-mandatory fortification period, NTD rates declined in babies of teenage mothers (mothers aged <20 years) by 54.8% in the total study population, and by 62.6% in the population of babies of teenage mothers (mothers aged < 20 years) omitting NSW residents. Both these results were statistically significant. The NTD rate rose in mothers aged 35 years or older in the post-mandatory fortification period, but this difference was not statistically significant.

In the model, the rates in the 'control' arm refer to the pre-mandatory (baseline) fortification cases (per 10 000 births). These were converted to probabilities. The relative rates were taken from Hilder[12] (regardless of statistical significance). Based on those reported rates provided, odds ratios were calculated.

The odds ratio was applied to calculate the probability of an event after folic acid mandatory fortification.

Based on this analysis, the NTD rates were lower in the post-mandatory fortification period in all age groups, except for women aged 35+ years where the odds ratio was 1.15 indicating that this group of women had higher odds of having a baby with an NTD (Table 18). These odds ratios were not statistically significant.

Table 18: Calculation of NTD during pre and post-mandatory fortification

Age of mother	Calculated OR (95% CI)	R_C/N_C (probability)	R_T/N_T (95%CI)
<20 years	0.4350 (0.1747 - 1.0829)	0.0013	0.0013 (0.0005 - 0.0002)
20-24 years	0.6903 (0.2817 - 1.6916)	0.0010	0.0010 (0.0007 - 0.0003)
25-29 years	0.8053 (0.3133 - 2.0702)	0.0008	0.0008 (0.0006 - 0.0003)
30-34 years	0.9018 (0.3462 - 2.3490)	0.0007	0.0007 (0.0007 - 0.0003)
35+ years	1.1474 (0.4367 - 3.0145)	0.0006	0.0006 (0.0007 - 0.0003)

Per 10 000 total births, unadjusted
Abbreviations: NTD, neural tube defect; OR, odds ratio

Adjustment for NTD rates

In the model, two adjustments were made to the NTD rates provided in the Hilder[12] and, Macaldowie and Hilder.[30] These were:

- adjustment for isolated cases only[12] and;
- adjustment for the previously noted downward trend in overall prevalence of NTDs since 1998 in the scenario analysis.[30]

Isolated cases are likely to be more amenable to the provision of sufficient levels of folic acid than non-isolated cases. It was assumed the rate of non-isolated cases was not impacted by mandatory fortification.[12] This assumption is conservative, potentially reducing the measured impact of folic acid mandatory fortification.

The odds ratio was adjusted to assess the effectiveness of mandatory folic acid fortification on NTD rates. The adjustments included;

- the average rate of non-isolated across baseline, transition, standard periods out of total cases, per 10 000 births was 1.5667 (being the average of baseline 1.5, transition 1.8 and standard 1.4);

- the proportion of non-isolated cases in the baseline period was 0.1536;
- the proportion of non-isolated cases in the transitional period was 0.1667; and
- the proportion of non-isolated cases in the standard period was 0.1801.[12,30]

In 1998, the overall prevalence of NTDs was 13.3 (95% CI 11.1–15.5) per 10 000 births. The lowest overall prevalence was recorded in 2008 when there were 10.7 (95% CI 8.9–12.5) NTDs per 10 000 births. An average annual fall in overall prevalence of 0.2 per 10 000 was observed between 1998 and 2008 with a positive test for linear trend [line of best fit shown has the formula y=14.2–0.23x].[30] In addition to this, it was stated that "between 1998 and 2008 the average annual decline in the overall prevalence of NTDs was 0.22 NTD per 10 000 births per year" [p.vii, Macaldowie 2011].[30] The 95% confidence interval was not reported by Macaldowie but was calculated from the information in Table A6.1, the 95% confidence interval for the decreasing prevalence was -0.42 to -0.04 per year, it was also statistically significant at a 5% level. The decrease in prevalence was applied to the rates of NTDs.

The reduction in rate trend was adjusted for time by assuming the midpoint of each period, i.e. Baseline to Transition (13 months, December 2007) and Transition to Standard (8.5 months, June 2010). This difference was converted into an annual rate (2.58 years * 0.23). The annual background rate reduction in NTD rates was applied in the model to the pre-mandatory fortification NTD arms (assuming the fall would be the same across all maternal age groups) in the base case. The rate difference was calculated between the two time points, not extrapolated out to 2014. This was done because the comparison is between pre-mandatory fortification and post-mandatory fortification periods as estimated in Hilder.[12] The results were not extrapolated to the 2014 population; they were applied to the 2014 population.

Adverse health effects of excess folic acid

The AIHW report[7] did not demonstrate that the Australian population experienced any adverse effects. Based on these findings the base case did not include any adverse effects (see Section 8.2).

However, in the scenario analysis, specific at-risk populations were considered, and the implications of adverse effects included in estimating health benefits and health costs. The adverse effect chosen was neurological dysfunction associated with B_{12} deficiency exacerbated by an increase in folate/folic acid, which is the basis for the establishment of the UL for folic acid.

There were two sources of uncertainty in this analysis: the proportion of the population at risk, and the proportion of the at-risk population that experienced the adverse effect. For example, the AIHW report[7] suggested the at-risk population consisted of those whose folic acid intakes exceeded the UL of intake. Different definitions of 'at risk' populations and the proportion at risk are used (Table 19), indicating that there are a number of possible definitions and estimates. The majority of studies have focused on the proportion of the population who consume over 1 mg per day of folic acid (UL) as the measure of those at risk. The AIHW report[7] estimated that less than 1% of the population would be at risk.

Table 19: At-risk populations for adverse effects of excess folic acid intake

Population	'At-risk' population	Source	Adverse effect	Portion of population "at-risk"	Portion of 'at risk' that experience adverse effect
All adults	Intake > 1mg daily.	AIHW report[7]	Not specified	<1%	Not specified

Population	'At-risk' population	Source	Adverse effect	Portion of population ''at-risk''	Portion of 'at risk' that experience adverse effect
			(Neuropathy)		
Adults aged over 55 years	B_{12} deficient, Intake> 1 mg daily.	Rabovskaja[45]	Neuropathy	23%	33%
Australian population	Low B_{12} (<150 picomole [pmol] per litre)	ABS microdata	Not specified (Neurology)	2.2%	Not specified
	B_{12} (<250 pmol/L)	ABS microdata	Not specified (Neurology)	21%	Not specified
Adults aged 15-44 years	Probability of > 1 mg folic acid intake and pernicious anaemia.	Bentley[46]	Neuropathy	-	0.012-0.029/100 000 person years
Adults aged 45-64 years	Probability of > 1mg intake and pernicious anaemia.	Bentley[46]	Neuropathy	-	0.078-0.185/100 000 person years
Adults > 65 years	Probability of > 1mg intake and pernicious anaemia.	Bentley[46]	Neuropathy	-	0.0181-0.427/100 000 person years

Epidemiology

Table 20 presents epidemiology statistics of the total and the pregnant Australian population in 2014, the year used as the cohort year.

The model is split between women of childbearing age (16-44 years) (20%) and the remainder of the population. The total number of mothers in 2014 aged between 16 to 44 years was 298 453, and the total Australian population was 23 610 906 .[47] The remainder of the population (excluding women of childbearing age) was split between those aged less than 55 years, and 55 years and older, to assess for adverse effects for potential excessive folate levels in the extended base case. This was because older individuals are potentially more prone to the adverse neurological effects of excessive folic acid intake (see Section 8.9)

Table 20: Australian population statistics (2014)

Population	Persons, n (%)
Australian population	23 610 906(100)
Women of childbearing age, age 16-44 years	4 738 756(20)
Pregnant women of childbearing age	298 453(6)
Non-pregnant women of childbearing age	4 440 303(94)
Population excluding women of childbearing age	18 872 150(80)
Males	11 743 253(62)
Females	7 128 897(38)
Males, <55 years	8 773 826(75)
Males, ≥55 years	2 969 427(25)
Females, <55 years	2 303 568(32)
Females, ≥55 years	4 825 329(68)

Source: ABS 3101.0 - Australian Demographic Statistics Jun 2015[48]

The main population of interest was women of childbearing age and pregnant women. The outcome for NTD-affected pregnancies are neonates, and the ratio of males to females for births in 2014 was 105.1.[47]

The distribution of maternal age in 2014 was applied to the pregnant population in the model.

Table 21: Australian population birth statistics

Birth gender and maternal age	Persons, n (%)
Birth gender male	153 592 (51.2)
Birth gender female	146 105 (48.8)
Persons	299 697 (100)
Maternal age <20 years	8 873 (3)
Maternal age 20-24 years	38 558 (13)
Maternal age 25-29 years	82 741 (28)
Maternal age, 30-34 years	102 336 (34)
Maternal age≥ 35 years	65 945 (22)
Maternal age, 16-44 years	298 453

[a] Calculated using data from ABS, 3301.0: Table 8.1 Births, Nuptiality and age of mother, Australia–2014
Source: ABS 3301.0 - Births Australia 2014[47]

Utilities

The utilities of the various population subgroups and health states in the economic model were sourced from the literature (Table 22). The Tufts University Cost-Effectiveness Analysis Registry[1] was used to identify utility weights. In the base case, pregnancies resulting in a termination were assumed to have a utility of 0. It was also assumed that stillbirths would have a utility of 0.

A Tufts utility review identified literature on maternal utilities for TOP.[49-51] The model used the estimated disutility from Harris et al.,[49] the utility of testing, elective abortion (future unaffected birth) had a utility of 0.836 and that for 'normal test result, unaffected birth was 0.923. This resulted in a disutility of -0.087 (-0.22-0).[49] These were applied in the scenario analysis. It was assumed that the utility decrement applied to TOP was the same for stillbirths.

Table 22: Results of literature review on utility values for termination of pregnancy

Health State	Utility value (range)	Year	Method and population	Source
Second-trimester loss after amniocentesis, with unaffected child from a future birth	0.93 (0.76 - 0.97)	1994	Standard gamble 72 women presenting to the prenatal diagnosis centres Location: USA	Musci (2005)[50] Kuppermann (1999)[52]
False positive screening test (First-trimester test, uncertain results, second-trimester test)	0.96 (0.93 - 0.99)	1994	Standard gamble 72 women presenting to the prenatal diagnosis centres Location: USA	Musci (2005)[50] Kuppermann (1999)[52]

[1] URL: Tufts registry. Accessed 11 February 2016

Health State	Utility value (range)	Year	Method and population	Source
Second-trimester therapeutic abortion/ termination of pregnancy	0.92 (0.76 - 0.96)	1997-1998	Standard gamble 72 women presenting to the prenatal diagnosis centres Location: USA	Musci (2005)[50] Kuppermann (1999)[52]
Testing, elective abortion, future unaffected birth	0.836 (0.4 - 1)	1997-1998	Time trade-off 534 pregnant women aged 16-47 years presenting to obstetric clinics and practices Location: USA	Harris (2004)[49] Kuppermann (2000)[53]
Testing, elective abortion, no future birth	0.692 (0.13 - 1)	1997-1998	Time trade-off 534 pregnant women aged 16-47 years presenting to obstetric clinics and practices Location: USA	Harris (2004)[49] Kuppermann (2000)[53]
Testing, normal results, unaffected birth	0.923 (0.62 - 1)	1997-1998	Time trade-off 534 pregnant women aged 16-47 years presenting to obstetric clinics and practices Location: USA	Harris (2004)[49] Kuppermann (2000)[53]
Fetal loss	0.9 (NA)	NR	Assumption, not explicitly stated	Partridge (2012)[51]
Intact survival	1 (NA)	NR	Assumption, not explicitly stated	Partridge (2012)[51]
Disutility for fetal loss	-0.1 (NA)	NR	Assumption, not explicitly stated	Partridge (2012)[51]

Table 23: Results of literature review on utility values for neuropathy adverse effect

Health State	Utility value (range)	Year	Population	Source
Severe neuropathy	0.588 (0.20, 0.92)	1999	Patients aged 65 years were recruited from a primary care practice-based research network in Oklahoma QoL measure: Not explicitly stated: either SF-36, QWB-SA or HUI-3 Location: USA	Mold et al. (2004)[54]
Neuropathy	-0.358 (-0.535, -0.18)	2006	Persons with diabetes QoL measure: EQ-5D-3L Location: Norway	Solli et al. (2010)[55]
Neuropathy	0.63 (NA)	-	-	Fonseca et al. (2013)[56]
Neuropathy	–0.24 (NA)	-	-	Attard et al. (2014)[57]

Health State	Utility value (range)	Year	Population	Source
Neuropathy	0.87 (0.8, 0.95)	-	-	Bendavid et al. (2011)[58]
Neuropathy	0.63 (NA)	-	-	Samyshkin et al. (2012)[59]
Neuropathy	-0.0243 (NA)	-	-	Brown (2014)[60]

Table 24: Utility values included in folic acid economic evaluation

Category	Population	Utility	Source
General population	Neonates	1	Assumption
General population	Children	0.94	Mittman et al. (1999)[61]
General population	Adults, all	0.766	Norman et al. (2013)[62]
General population	Adults, all	0.87	Clemens et al. (2014)[63]
NTD-affected pregnancies	Termination of pregnancy	0	Assumption
NTD-affected pregnancies	Stillbirth	0	Assumption
NTD-affected pregnancies	Anencephaly	0	Assumption
NTD-affected pregnancies	Encephalocoele	0.45	Tilford et al. (2005)[64]
NTD-affected pregnancies	Spina bifida: Sacral lesion	0.61	Tilford et al. (2005)[64]
NTD-affected pregnancies	Spina bifida: Lower lumbar lesion	0.54	Tilford et al. (2005)[64]
NTD-affected pregnancies	Spina bifida: Thoracic lesion	0.45	Tilford et al. (2005)[64]
NTD-affected pregnancies	Spina bifida: all	0.55	Tilford et al. (2005)[64]
AE	Neuropathy	-0.358	Solli et al. (2010)[55]
TOP/SB	Testing, normal results, unaffected birth minus Testing, elective abortion, future unaffected birth	0.923-0.836=-0.087	Harris et al. (2004)[49]

Utility value used is the thoracic lesion for spina bifida from Tilford et al. (2005)[64]
Abbreviations: AE, adverse effect, NTD, neural tube defect; SB, stillbirth; TOP, termination of pregnancy

Survival

The model used a lifetime horizon for those in the 2014 cohort. Life expectancy estimates were calculated for each outcome.

The model calculated both discounted life years gained and discounted quality-adjusted life years (QALY) gained (discounted life years multiplied by utility values).

Life expectancy

Both TOP and stillbirth resulted in zero life expectancy (although the family composition was not altered by TOP). For the NTD types that were alive at birth (NND and NNS), the 28-day survival estimates were identified for encephalocoele (0.777) and spina bifida (0.943).[65] These estimates were multiplied with the maximum life expectancy in years of NND 0.08 (28/365).

Anencephaly is fatal, and it was assumed that life expectancy is 0 years for NND and NNS.

Previous literature has reported shorter life expectancy rates compared to the analysis in this Report. Rabovskaja et al.[45] used a lifetime horizon, with a base case life expectancy of spina bifida patients at 43 years (transformed from the median of 35 years.[66] Given the potential for improvements in life expectancy since 1987-2002, a sensitivity analysis was performed to 84 years (normal life expectancy).[45] Access Economics estimated life expectancy of patients with spina bifida of 68.1 years for males and 73.8 years for females.[67]

The 20-year survival probability is 0.673 for encephalocoele,[68] 0.852 for spina bifida[69] and 0.99 for non-NTD affected births (sex weighted mortality rate in 2014 at age 20). The complement of these is the probability of survival (1-D=S). The relative risk of death for encephalocoele was 48.08 and for spina bifida was 21.73, compared with non-NTD affected births. This calculated relative risk was applied to the mortality rate (q) for both males and females, and the expected life expectancy was calculated (e). This resulted in life expectancies for encephalocoele of 64.55 years and spina bifida of 74.91 years (sex weighted). It was assumed that the sex ratio of births in 2014 was the same as NTD survivors.

Table 25: Life expectancy of outcomes (undiscounted)

Outcome	Life expectancy, years	Source
Termination of pregnancy	0	Access Economics. 2006
Stillbirth	0	Assumption
Anencephaly (NND)	0	Access Economics, 2006[70]
Anencephaly (NNS)	0	Access Economics. 2006[70]
Encephalocoele (NND)	0.0596	Wang et al. [65]
Encephalocoele (NNS)	64.55	Siffel et al.[68]; ABS 3302.0.55.001, 2012-2014; ABS, 3301.0, 2014 [48]
Spina Bifida (NND)	0.0723	Wang et al.[65]
Spina Bifida (NNS)	74.91	Shin et al.[69] ABS 3302.0.55.001, 2012-2014; ABS, 3301.0, 2014[48]
Non-NTD affected birth	82.30	ABS 3302.0.55.001, 2012-2014; ABS, 3301.0, 2014[48]

NND: 28-day survival estimate multiplied by 28 days in years
NNS: use 20-year survival probability to determine the relative risk of death for encephalocoele and spina bifida compared to non-NTD (Australian life tables)
Abbreviations: NND, neonatal death; NNS, neonatal survival

3.6.9 Costs

Initial hospitalisation

The model included the health care costs of NTD-affected pregnancies, including non-NTD affected delivery costs, termination of pregnancy, stillbirth, anencephaly, encephalocoele and spina bifida. The cost of a termination of pregnancy also included the cost of a non-NTD affected pregnancy discounted for 2 years as it was assumed that a termination would not alter the eventual family size. The analysis used procedure costs by AR-DRG in admitted public hospital patients (Table 26).

Table 26: AR-DRG procedure codes and costs

Outcome	AR-DRG code	Cost ($AUD)
Delivery cost for non-NTD pregnancy	O60A Vaginal Delivery W Catastrophic or Severe CC	7 590
Delivery cost for non-NTD pregnancy	O60B Vaginal Delivery W/O Catastrophic or Severe CC	4 826
Delivery cost for non-NTD pregnancy	O60C Vaginal Delivery Single Uncomplicated W/O Other Condition	3 588
Delivery cost for non-NTD pregnancy	Weighted average of O60A, O60B and O60C	4 899.83
Termination of pregnancy	O05Z Abortion W OR Procedure	2 257
Termination of pregnancy	O63Z Abortion W/O OR Procedure	1 175
Termination of pregnancy	Weighted average of O05Z and O63Z	2 075.75
Stillbirth	P60A Neonate, Died or Transferred <5 Days of Adm, W/O Significant OR Proc, Newborn	2 307
Anencephaly	P60B Neonate, Died or Transf <5 Days of Adm, W/O Significant OR Proc, Not Newborn	3 782
Encephalocoele	Z65Z Congenital Anomalies and Problems Arising from Neonatal Period	4 984
Spina bifida	Z65Z Congenital Anomalies and Problems Arising from Neonatal Period	4 984

Notes: costs in $AUD (2012)
Abbreviations: Adm; admission; AR-DRG, Australian refined diagnostic related groups; OR, Operating Room; Transf, Transferred; W, with; WO, without;
Source: National Hospital Cost Data Collection Cost Weights for AR-DRG Version 6.0x, Round 16 (2011-12) Public Hospital 2014[71]

For neonates with spina bifida, surgery is required to close the newborn's spinal opening. This surgery is performed within 24 hours after birth to minimise the risk of infection and to preserve existing function in the spinal cord. Neonates with encephalocoele require surgery to repair the hydrocephalus.

The survival rates of patients who survive infancy and childhood, and enter adulthood are similar to those without NTDs. Patients with NTDs regularly have problems related to hydrocephalus, neurogenic bladder, kidney involvement, orthopaedic complications, and psychosocial consequences.[72] These complications can cause severe disability, which adds a significant burden to the health system and to patients with NTDs.

Treatment for spina bifida includes surgery, medication, and physiotherapy. However, regular monitoring, ongoing therapy, and medical and/or surgical treatments are often necessary to prevent and manage complications throughout the individual's life.

The CBA performed by Access Economics for FSANZ in 2006 used unpublished data from the AIHW which had costs attached to ICD-10 codes[2,70] Access Economics used a top-down approach to determine the health care utilisation costs for spina bifida with respect to admitted hospital patients. This hospital cost was combined with a bottom-up costing approach for the average person with spina bifida, including the number of visits to specialists and allied health carers, pathology and imaging.

Based on this analysis, it estimated that the health system expenditure for spina bifida related causes per year per person was $AUD (2005) 13 535 for those aged 0 to 4 years.[67] This cost reduced to $AUD (2005) 4 354 for persons aged 5 to 14 years.

Similarly, Rabovskaja et al.[45] costed neonatal death at $AUD (2005) 12 616 which was the estimated health expenditure cost for anencephaly and encephalocoele related causes per person aged 0 to 4 years.[45] The cost of spina bifida was calculated as $AUD (2005) 13 535 for the first four years and $AUD (2005) 4 354 for every year after up to the age of 43 or 84 years. This cost was discounted by 5% to the net present value, a cost of $AUD (2005) 114 398 and $AUD (2005) 124 099 respectively.[45]

Health care resource use

The additional health care costs associated with NTDs compared to the general population were calculated. This was assessed on the basis of the international literature. This model assumed translatability between the relative health care resource uses in NTD-affected individuals in international populations to the Australian population.

A review by Yi et al.[72] found that of the 14 cost of illness studies included, seven of those included only medical costs, other studies included development and special education, caregiver time costs and indirect costs.[72]

International cost of illness studies[73-78] demonstrate that the cost of NTDs is driven by higher rates of hospitalisations and outpatient admissions. These are due to complications including decubitus ulcer, complications of hydrocephalus (including shunt complications), urinary tract infections, complications from devices/grafts/implants and wounds.[73,74] Compared to age-matched peers without NTDs, the differences in health care resource use diminish as the patient gets older.[75,76] Within the population with NTDs, spina bifida led to greater health care costs than encephalocoele, followed by anencephaly.[77]

3.6.10 Comparison with non-NTD patients

The literature reports higher health care utilisation in patients with spina bifida than their age-matched counterparts without spina bifida. Therefore, the incremental costs are estimated in this model.

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[2] "Expenditure related to spina bifida only, including hospital, general practice, specialists, pharmaceutical, pathology and imaging and allied health care". This includes ICD 10 codes for spina bifida (Q05, Q07.01, Q07.03 and Q76) and a proportion of maternal care for a (suspected) central nervous system malformation in the fetus (O35).

No differential resource use was identified for encephalocoele in the literature. Given that persons with encephalocoele had lower utility and survival compared to spina bifida patients, it was assumed that the cost of treating encephalocoele was higher. In the base case a multiplication factor was applied (1.2 times). In the sensitivity analysis, it was assumed that the cost of treating encephalocoele was the same as treating a patient with spina bifida (multiplication factor = 1).

It was assumed that no ongoing health care resource use costs were associated with the termination of pregnancy, stillbirth and anencephaly.

Infants and youth

In a review of the health care utilisation of Canadian youths (aged 13-17 years, n=164) with spina bifida by Young et al.,[79] the authors found that rates of hospital admissions were 19.4 times higher than for the general population.[79] Similarly, the rate of outpatient physician visits was 2.9 times higher than that of the general population.[79]

Ouyang et al.[80] performed a review of health care utilisation for people covered by employer-sponsored health insurance in the United States between 2001-2003.[80] The small sample size for patients age 0 (n=14) made it difficult to make comparisons between persons with and without spina bifida.[80] For children aged 1-17 years (n=510), there was a statistically significant difference in inpatient admissions (33.5 times) and outpatient visits (10.5) compared to age-matched peers without spina bifida.[80]

The difference in prescription drug use was not statistically significant at age 0, although for those aged 1-17 years, the difference in prescription drug use was 3.1 times more for those with spina bifida (p=0.0001).[80] However, as no information was provided on the types of drugs available, this information was not incorporated into the model as it was not expected to be a large driver of health care costs.

In the model, it was assumed that the additional inpatient and outpatient visits were distributed evenly within each of the age categories, for instance, 33.5 times inpatient admissions over the 17 years. This assumes the use of health services is uniform over time for each age category. This assumption will underestimate the cost (after discounting) if more services are used earlier than later for people with spina bifida. It will overestimate the cost (after discounting) if services are used later in each age category.

Adults

In the US study by Ouyang et al.,[80] for patients with spina bifida aged 18-44 years and 45-64 years, the rates of inpatient admissions were 12.1 and 4.1 times higher, respectively, than for persons without spina bifida. Outpatients visits were 4.7 and 2.6 times higher for patients aged 18-44 years and 45-64 years, respectively, than for persons without spina bifida.[80]

In a review of health care utilisation of Canadian adults (aged 23-32 years, n=120) with spina bifida by Young et al., [79] the authors found that the rates of hospital admissions were 12.4 times higher, and those for outpatient physician visits were 2.2 times higher than for the general population. This may be because young people who survive to adulthood are less likely to represent the most severe cases. Similarly, earlier intervention may help to avoid complications from spina bifida in the future, and therefore differences in resource use (and cost) between adults with and without spina bifida may be smaller.

3.6.11 Unit costs

Inpatient visits

The costs of hospital admissions were based on the NSW Cost of Care Standards for acute admitted care, excluding emergency department and intensive care cost groups ($AUD 3 840).[81]

Outpatient visits

The model assumed that outpatient visits consisted of the following Medicare Benefits Schedule (MBS) items:

- weighted average general practitioner (GP) visits (Weighted average GP visit (MBS item 3, 23, 36, 44);
- initial specialist visit initial (MBS 104); and
- subsequent specialist visit (MBS 105).

The assumed proportion of GP visits is 50% (compared to specialist visits). This Report assumed one initial specialist visit and classed the remaining visits as subsequent visits. This was a conservative assumption.

Table 27: Resource use for spina bifida patients

Category of health care use	Age in years	Years in period	Additional resource use for period[a] (unit)	Cost per unit ($AUD)[c]	Total cost ($AUD) for period	Average cost ($AUD) per year
Inpatient admission (hospital)	Age 1-17 years	17	33.5	3 840[81]	128 640	7 567
Inpatient admission (hospital)	Age 18-44 years	27	12.1	3 840[81]	46 464	1 721
Inpatient admission (hospital)	Age 45-64 years	20	4.1	3 840[81]	15 744	787
Outpatient visits (GP and specialist consultations)	Age 1-17 years	17	10.5	42 (GP); 89 (specialist initial); 43 (specialist subsequent)[b]	492	29
Outpatient visits (GP and specialist consultations)	Age 18-44 years	27	4.7	42 (GP); 89 (specialist initial); 43 (specialist subsequent)[b]	245	9
Outpatient visits (GP and specialist	Age 45-64 years	20	2.6	42 (GP); 89 (specialist initial);	156	8

Category of health care use	Age in years	Years in period	Additional resource use for period[a] (unit)	Cost per unit ($AUD)[c]	Total cost ($AUD) for period	Average cost ($AUD) per year
consultations)				43 (specialist subsequent)[b]		

a. Assumed resource use is distributed evenly across the age groups
b. Assumed proportion of GP visits is 50% (compared to specialist visit). Total cost is calculated = [resource use (no.) * proportion GP visits (%) * GP cost ($)] + [initial specialist visit (no. = 1) * initial specialist cost ($)] + [(resource use (no.) * proportion GP visits (%) - initial specialist visit (no. =1)) * subsequent specialist cost ($)]
c Cost per unit ($AUD) is for all age groups combined.
Abbreviations: $AUD, Australian dollar; GP, general practitioner
Source: Ouyang et al. 2007[80], New South Wales Government Health, 2011[81]; MBS. Medicare benefits schedule book: Operating from 01 November 2014. Australian Government Department of Health: 2014[82]

The modelling in this Report assumed that there was no differential health care resource use in spina bifida (or encephalocoele) patients compared with non-NTD persons from the age of 65 years onward.

Assistive technology

Assistive technology (AT) improves the ability to achieve independence for individuals with spina bifida. It includes the following: manual wheelchairs, (2) powered wheelchairs, (3) wheelchair cushions and seats, (4) wheelchair accessories and repairs, (5) wheelchair rental, (6) ambulatory aids, (7) orthotic and prosthetic devices, (8) positioning aids, (9) bathroom equipment, (10) beds and bed accessories, and (11) communication and hearing aids.[83]

The average annual Medicaid cost of AT was $USD 494 per enrollee per year (out of 848 enrollees), and AT accounted for 3.3% ($USD 434 172 paid) of all Medicaid costs for these individuals. AT related costs were highest for those aged 0-15 years and lowest for those aged 16-25 years.[83]

These yearly costs were converted into $AUD and inflated to 2014 costs using the Australian Health Price Index ($AUD 807.62). The costs were applied from ages 1 to 65 years for encephalocoele and spina bifida neonatal survivors.

3.6.12 Costs for industry and government

The costs for mandatory folic acid fortification include those incurred by industry and government. In 2006, Access Economics projected these costs for P295 (Consideration of mandatory fortification with folic acid) from both the government and industry perspective.[67]

Industry

The Australian Government Department of Health commissioned a review of compliance with, and enforcement impacts of, the mandatory fortification of bread with folic acid, the Catalyst report.[6] (See Section 8.2.2: Catalyst report).

The costs reported by industry members are presented in Table 28. The reported costs incurred by industry are lower than those projected in 2006. The 2014 costs reported in the Catalyst report[6] were used in the model. Upfront costs for bakers included the packaging write-off costs totalling $AUD 3 075 000. It was assumed in the model that 100% of these costs were due to the introduction of mandatory folic acid fortification. This assumption was made because all the costs are incurred no matter how many nutrient changes are mandated. In the future, it should not be assumed that multiple changes would be made at the same time.

In the First Review Report of P295 by FSANZ, amended equipment costs increased the 2007 projected industry costs to $AUD 7 886 000.[5] The reported industry costs in the Catalyst report[6] were lower than the projected industry costs.

Table 28: Cost to industry for mandatory folic acid fortification over three years

Cost attribution	Timing	2006 projected ($AUD)	Note	2014 reported ($AUD)	Note
Millers	Upfront	2 750 400[a]	Equipment and labeling	1 056 000	Engineering design; capital equipment and installation; information technology; analysis and verification testing; quality assurance systems, training and documentation; packaging redesign and wastage.
Millers	Ongoing	1 058 592 per year	Folic acid, analytical, premix, administration, clean out mill	456 600 per year	Ingredients; testing and verification; and quality assurance resources.
Bakers	Upfront	4 000 000	Packaging write-off	3 075 000	Packaging write-off, assume 100% of $AUD 3 075 000 due to mandatory folic acid fortification initiative
Bakers	Ongoing	Not specified	NA	0	Most of the companies identified no ongoing cost. A plausible alternative base case was $AUD 82 500[b].
Total	**Upfront (100%)**	**6 750 400**	**-**	**4 131 000**	**-**
Total	**Upfront (50%)**	**6 750 400**	**-**	**2 593 500**	**If two initiatives were introduced, then 50% of the upfront costs may be attributed to the mandatory folic acid fortification initiative**
Total	**Ongoing**	**1 058 592**	**-**	**456 600**	**-**

[a] 2007 projected costs are $AUD 3 886 000 due to amended equipment costs; labeling costs remain the same. FSANZ. Proposal P295 consideration of mandatory fortification with folic acid: First review report Food Standards Australia and New Zealand 2007

[b] One respondent reported annual cost of testing finished products, although this is not mandatory

Note: presented in $AUD (2006) costs as reported, not inflated for CPI

Source: Catalyst report 2015[6]; Proposal P295 consideration of mandatory fortification with folic acid first review report Food Standards Australia and New Zealand 2007[5]

Government

The First Review Report of P295 by FSANZ provided updated projected government costs. These were $AUD 27 169 for upfront enforcement costs and $AUD 121 336 for ongoing costs.[5]

Rabovskaja et al.[45] used the government ongoing cost estimate of $AUD 150 809. This included training and awareness raising, auditing content, administration and complaints handling. This excluded auditing of labels[9,45] The inclusion of auditing of labels increased the projected government costs to $AUD 567 945.[67]

The Catalyst report[6] suggested that the resources for monitoring and enforcement were managed within existing resources.

Cost of fortifying bread by industry and government, per capita

The per capita costs were calculated by dividing the total costs by the estimated resident population in 2014 which was 23 610 906 persons[47]

Table 29: Industry and Government costs for mandatory folic acid fortification

Industry or Government	Cost	Total ($AUD)	Per capita ($AUD)
Industry	Upfront (50%)	2 593 500	0.110
Industry	Upfront (100%)	4 131 000	0.175
Industry	Ongoing	456 600	0.019 per year
Government	Upfront	33 067	0.001
Government	Ongoing	147 677	0.006 per year
Total	**Total upfront (50% write-off)**	**-**	**0.111**
Total	**Total upfront (100% write-off)**	**-**	**0.176**
Total	**Total ongoing**	**-**	**0.026 per year**

Note: population is based on Australian Estimated Resident Population in 2014 ABS, 3101.0 - Australian Demographic Statistics, Jun 2015[47]
Source: Catalyst Report 2015[6], FSANZ. Proposal P295 consideration of mandatory fortification with folic acid first review report Food Standards Australia and New Zealand 2007.[5]

In Rabovskaja et al.[45] the per capita costs were calculated using the projected 2006 industry costs and the Australia population as at June 2009. The upfront and ongoing costs of the fortification initiative were calculated as $AUD 0.113 per capita (millers only) and $AUD 0.055 (millers and government) per capita per year, respectively.[45] Using the updated costs, the upfront cost per capita using actual industry costs from millers and bakers was $AUD 0.110 per capita ((1 056 000 plus 1 537 500) divided by 23 610 906 persons).[45] The ongoing cost for millers per capita per year was $AUD 0.020 (456 600 divided by 23 610 906 persons) as no ongoing costs were calculated for bakers.[45]

In the base case, only ongoing costs were included as the base year is 2014 (The industry and government upfront costs would have been incurred when industry commenced adding folic acid in 2009-2010).

Productivity losses

An extremely conservative approach was taken in relation to productivity within the model. Only the productivity difference for those with NTDs who are assumed to have survived in both alternatives was included. This approach results in the productivity changes associated with terminations and stillbirths not being included.

Productivity losses by carers

In addition to direct health care system costs associated with NTDs, carers of children with NTDs may incur additional time costs associated with caring over and above those required by a child without an NTD.[84] Carers could alternatively spend additional time with children (leisure) or as part of the workforce.

The amount of care provided by carers is dependent on the severity of spina bifida. This is determined by the lesion location; the higher the lesion, the greater the severity. For instance, Tilford et al.[85] found that in a sample of 98 American families caring for children (aged 0 to 17 years) with spina bifida in 2002, the mean reduction in work hours per week was 9.2 hours. For patients with a sacral lesion, this was 7.5 hours per week, and for upper lumbar/thoracic lesion, this increased to a mean reduction of 11.3 hours per week.[85]

Genereaux et al.[86] used an online retrospective survey to identify the parental and societal costs to families of children with an intellectual developmental disorder (n=80). This paper distinguished between income loss and caregiving time cost. This was reported as median annual cost. However, hours were not reported. The cost is increased with the severity of intellectual disability.[86] These findings are supported by Lipscomb et al.[87] who found that there were average reductions of 14 hours per week in paid work time for mothers and 5 hours per week for fathers in 104 families in North Carolina.

Table 30: Lost carer time

Parents of children with spina bifida by group	Mean work hours per week[a]	Source
Overall	-9.2	Tilford et al. (2005)[64]
Sacral lesion	-7.5	Tilford et al. (2005)[64]
Lower lumbar lesion	-9.8	Tilford et al. (2005)[64]
Upper lumbar/thoracic lesion	-11.3	Tilford et al. (2005)[64]
Apply proportions of lesions in Australia	-	-
Total for all spina bifida patients	-8.28	AIHW National Hospital Morbidity Database, Separation statistics by principal diagnosis (ICD−10−AM 8th edition), Australia, 2013−14[88]
Sacral lesion (and unspecified)	-5.22	AIHW National Hospital Morbidity Database, Separation statistics by principal diagnosis (ICD−10−AM 8th edition), Australia, 2013−14[88]
Lumbar lesion	-2.47	AIHW National Hospital Morbidity Database, Separation statistics by principal diagnosis (ICD−10−AM 8th edition), Australia, 2013−14[88]
Thoracic lesion	-0.59	AIHW National Hospital Morbidity

Parents of children with spina bifida by group	Mean work hours per week[a]	Source
		Database, Separation statistics by principal diagnosis (ICD−10−AM 8th edition), Australia, 2013−14[88]

a Values presented represent the mean reduction in work hours per week.

By using the market replacement method, the number of reduced hours at work was multiplied by an hourly wage. In Australia, the average hourly total cash earnings ($AUD [2014]), Employee Earnings and Hours, Australia, May 2014 was $AUD 35.30 for non-managerial employees. This wage was applied to the number of fewer hours worked. These costs were applied to the first 17 years of life for the neonate survivors (those that survived the first 28 days).

The AIHW Report[7] did not distinguish spina bifida affected neonates by lesion location. This information was collected from AIHW procedure codes.[88] The resulting reduction hours per week is 8.28, which resulted in 15 193.90 per year (292.19 per week multiplied by 52 weeks). Sensitivity analysis was performed using the distribution of disease severity (by lesion location) as seen in Tilford et al.[64]

No carer costs were identified for patients with encephalocoele. Therefore, it was assumed that these patients had the same carer costs as spina bifida patients.

Productivity losses by persons with NTDs

A study of persons with spina bifida in Germany illustrated that 53% of working age persons (aged 16 years and older) were employed (30 full-time and 17 part-time).[89] Of those employed, full-time employees lost 10.4 days per year due to spina bifida and part-time employees lost 24.4 days.[89]

Proportion of employed persons between those with no disability compared to those with ‘physical restriction’

On average, 35% (78% - 43%) more persons with no disability were employed (either full-time or part-time) compared to persons with physical restrictions.[90]

Table 31: Labour force status by disability status and disability group

Disability status	FT Employed	PT Employed	Total Employed	Unemployed	Total in labour force	Not in the labour force	Total
Physical restriction ('000)	383.7	265.3	646.8	58.1	705.9	781.8	1 488.3
No disability ('000)	7 246.3	3 048.5	10 296.5	527.6	10 824.4	2 294.2	13 117.9
Physical restriction (%)	26%	18%	43%	4%	47%	53%	100%
No disability (%)	55%	23%	78%	4%	83%	17%	100%

Includes all persons aged 15 to 64 years living in households
a Total in labour force is the sum of employed and unemployed persons.
Abbreviations: FT, full-time; PT, part-time
Source: calculated using ABS, Table 8, 4433.0.55.006 Disability and Labour Force Participation 2012[90]

The weekly wage for all non-managerial employees in May 2014 (i.e. part-time and full-time) was $AUD 1 161.60.[91] This was multiplied by 52 to estimate an annual salary of $AUD (2014) 60 403.20. The yearly earnings per person employed were estimated for those with physical restrictions compared to no disability. This difference was $AUD 21 141.12 in foregone salary.

Employed persons with physical restrictions work fewer hours than persons with no disabilities

For persons who are employed, those with a 'physical restriction' were likely to work fewer hours than persons with no disability. A higher proportion of employed persons with a physical disability worked between 1 to 34 hours per week, while a higher proportion with no disability worked 35+ hours per week.

Table 32: Hours worked by disability status and disability group

Disability status/sub-group	1 - 15 hours	16 - 24 hours	25 - 34 hours	35 - 39 hours	40 hours +	Total
Physical disability ('000), n (%)	111.6 (17)	74.0 (11)	80.7 (12)	122.6	261.2	646.8
No disability ('000)	1 089.5 (11)	914.8 (9)	1 044.6 (10)	2 102.9	5 143.1	10 296.5
Physical disability (%)	17%	11%	12%	19%	40%	100%
No disability (%)	11%	9%	10%	20%	50%	100%

Note: All employed persons aged 15 to 64 years living in households
Source: calculated using ABS, Table 11, 4433.0.55.006 Disability and Labour Force Participation 2012[90]

Using the midpoint hours (e.g., 7 hours, 20 hours, 29.5 hours etc.), the average hours worked per week for persons with physical disabilities and no disabilities was calculated. This led to an estimation of 2.96 fewer hours worked by those with 'physical restrictions' (29.96 hours per week) compared to 'no disabilities' (32.92 hours per week).[90] In Australia, the average hourly total cash earnings ($AUD [2014]), Employee Earnings and Hours, Australia, May 2014 was $AUD 35.30 for non-managerial employees. The yearly earnings per person employed were estimated for those with physical restrictions compared to no disability. This difference was $AUD 104.49 per year of additional salary for those with no disability.

In the model, these productivity costs ($AUD 21 141.12 + $AUD 104.49 = $AUD 21 245.61) were applied to neonatal survivors of encephalocoele and spina bifida between the ages of 18-54 years.

Adverse effect costs

Neurological adverse effects (exacerbating B_{12} deficiency)

There is some uncertainty about the costs associated with the potential increase in B_{12} neuropathy. B_{12} neuropathy can be a medically significant event with sub-acute combined degeneration of the spinal cord leading to considerable disability. However, subtle forms of B_{12} neuropathy can occur.

It was assumed that the neurological dysfunction that would be associated with mandatory folic acid fortification was the subtle form of B_{12} neuropathy, which would incur costs related to investigations and management.

Patients would require two GP visits (MBS 23*2), serum B_{12} test and blood tests (MBS 66838, 66840, 65070) and B_{12} injections (pharmaceutical benefits schedule [PBS] 2162T). This totals $AUD 150.50 per patient.

More severe cases of neuropathy would require an inpatient admission. This cost was assumed to be the weighted average of B71A and B71B (cranial and peripheral nerve disorders with and without complications) of $AUD 2 531.06 per patient.

These assumptions were challenged in the sensitivity analysis.

3.6.13 Parameters

Table 33: Parameters used in the model

Parameter	**Value**	**Lower**	**Upper**
Discount rate	0.05	0.03	0.07
Conditional probabilities	**Value**	**Lower**	**Upper**
persons at risk of AE	0.04	0.00	0.11
persons at risk of AE with neurological damage	0.33	0.26	0.40
anencephaly	0.43	0.3919	0.4594
encephalocoele	0.09	0.0712	0.1101
spina bifida	0.48	0.4508	0.5190
termination of pregnancy	0.446	0.4153	0.4769
Stillbirth: anencephaly	0.68	0.5956	0.7589
Stillbirth: encephalocoele	0.38	0.2710	0.4961
Stillbirth: spina bifida	0.46	0.4120	0.5111
neonatal survivors, out of live birth: anencephaly	0.00	-	-
neonatal survivors, out of live birth: encephalocoele	0.82	0.6914	0.9170
neonatal survivors, out of live birth: spina bifida	0.79	0.7369	0.8463
women of childbearing age (16-44 years) in Australia	0.20	0.2005	0.2009
pregnant women in women of childbearing age	0.06	0.0621	0.0639
male in population excluding women of childbearing age	0.62	0.6220	0.6225
male in population excluding women of childbearing age, < 55 years	0.75	0.7469	0.7474
female in population excluding women of childbearing age, < 55 years	0.32	0.3228	0.3235
Women aged < 20 years	0.0297	-	-
Woman aged 20-24 years	0.13	-	-
Woman aged 25-29 years	0.28	-	-
Woman aged 30-34 years	0.34	-	-
Woman aged 35+ years	0.22	-	-
NTD prior to mandatory fortification (pre) by age of mother: < 20 years	0.001260	0.001190	0.001333
NTD prior to mandatory fortification (pre) by age of mother: 20-24 years	0.000973	0.000911	0.001037
NTD prior to mandatory fortification (pre) by age of mother: 25-29 years	0.000804	0.000747	0.000862
NTD prior to mandatory fortification (pre) by age of mother: 30-34 years	0.000736	0.000682	0.000792
NTD prior to mandatory fortification (pre) by age of mother: 35+ years	0.000643	0.000593	0.000695
NTD post mandatory fortification (post) by age of mother: < 20 years	0.000549	0.000220	0.001365
NTD post mandatory fortification (post) by age of mother: 20-24 years	0.000672	0.000274	0.001645
NTD post mandatory fortification (post) by age of mother: 25-29 years	0.000647	0.000252	0.001662
NTD post mandatory fortification (post) by age of mother: 30-34 years	0.000664	0.000255	0.001727
NTD post mandatory fortification (post) by age of mother: 35+ years	0.000738	0.000281	0.001936

Parameter	Value	Lower	Upper
annual background reduction in NTD rate	-0.00005942	-0.0001085	-0.0000103
Utilities	**Value**	**Lower**	**Upper**
non-NTD affected pregnancy	0.87	0.86	0.87
termination of pregnancy	0	-	-
termination of pregnancy, no change in family size	0.87	-	-
Stillbirth	0	-	-
Anencephaly	0	-	-
Encephalocoele	0.45	0.09	1.00
spina bifida	0.55	0.09	1.00
decrement for adverse effect	0.00	0.00	0.00
termination of pregnancy for mothers	0.00	-0.22	0.00
stillbirth of pregnancy for mothers	0.00	-0.22	0.00
Survival, life years	**Value**	**Lower**	**Upper**
non-NTD affected pregnancy, discounted	78.38	-	-
termination of pregnancy	0	-	-
termination of pregnancy, no change in family size, discounted	18.73	-	-
stillbirth	0	-	-
neonatal deaths: anencephaly	0	-	-
neonatal deaths: encephalocoele	0.05961	0.05738	0.06152
neonatal deaths: spina bifida	0.07234	0.07173	0.07288
neonatal survivors (discounted): anencephaly	0	-	-
neonatal survivors (discounted): encephalocoele	20.16	19.82	20.37
neonatal survivors (discounted): spina bifida	20.48	20.16	20.63
Costs ($AUD [2014])	**Value**	**Lower**	**Upper**
non-NTD affected pregnancy, discounted	5 130.54	2 565.27	10 261.07
termination of pregnancy, discounted	2 173.49	1 086.74	4 346.97
termination of pregnancy, no change in family size, discounted	4 653.55	-	-
spina bifida, discounted	2 415.62	1 207.81	4 831.25
anencephaly, discounted	3 960.07	1 980.04	7 920.15
spina bifida, NND, discounted	5 218.67	2 609.33	10 437.34
anencephaly, NND, discounted	5 218.67	2 609.33	10 437.34
encephalocoele, health care, discounted	141 432.26	70 716.13	282 864.52
spina bifida, health care, discounted	120 104.56	60 052.28	240 209.13
fortification (industry and government), pre	0.00	-	-
fortification (industry and government), post	0.0256	0.01	0.05
Carer	192 804.27	96 402.14	385 608.55
adverse effect B_{12} masking	0.00	0.00	0.00
assistive technology	16 248.66	8 124.33	32 497.32
productivity loss for persons with NTD	154 903.41	77 451.71	309 806.83

Abbreviations: AE, adverse effect, NTD, neural tube defect;

3.6.14 Cost-effectiveness and Cost-utility analysis results

There are two sets of results in the base case model:

- the incremental effectiveness of mandatory folic acid fortification compared to that of no mandatory folic acid fortification; and

- the incremental cost of mandatory folic acid fortification compared that of no mandatory folic acid fortification.

The incremental effectiveness of mandatory folic acid fortification compared to no mandatory folic acid fortification was measured as health impacts: initially, the reduction in NTDs, then the improvement in life years and finally the change in QALYs. For all these measures, the modelling in this Report found there was a gain in health associated with mandatory folic acid fortification compared to the no mandatory folic acid fortification alternative. The results are presented in Table 34.

Another set of results is the incremental cost of mandatory fortification. This was calculated as the sum of the differences in health care costs, costs of mandatory fortification (industry and government) and changes in productivity. The costs attributed to implementing folic acid fortification were higher than the alternative of the status quo. However, these increased costs were outweighed by a decrease in health care costs and an increase in productivity associated with mandatory folic acid fortification. The results are presented in Table 35.

These two sets of results were combined in the cost-utility analysis. In this circumstance, mandatory folic acid fortification dominated the no mandatory folic acid fortification alternative, the pre-mandatory fortification suite of policies. This means that mandatory folic acid fortification was both more effective and less expensive than the no mandatory folic acid fortification alternative.

Effectiveness

Table 34: Results of effectiveness

Measure of effectiveness	No mandatory folic acid fortification initiative	Mandatory folic acid fortification initiative	Increment
NTD	215.2	200.9	-14.28
LY	-	-	134.58
QALY	-	-	131.00

Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis; Increment is 'Mandatory fortification' minus 'no mandatory fortification'
Abbreviations: NTD, neural tube defect; LY, life years, QALY, quality-adjusted life years

Mandatory folic acid fortification was found to be more effective that the no mandatory folic acid fortification. The mandatory folic acid fortification alternative resulted in approximately 14 fewer NTD-affected pregnancies. This translated into gains of 135 life years and 130 QALYs.

Cost

Table 35: Results of costs

Costs	No mandatory folic acid fortification initiative ($AUD)	Mandatory folic acid fortification initiative($AUD)	Increment ($AUD)
Total costs	1 472 061 245	1 471 717 219	-341 777[a]
Total incremental health costs associated with NTD	1 462 075 505	1 462 394 797	319 292
Total productivity loss associated with NTD	9 985 739	9 976 745	8 994[b]

Note: all cost groups include the cost of ongoing fortification by industry and government Increment is 'Mandatory fortification' minus 'no mandatory fortification'
a The mandatory fortification initiative costs less.
b The mandatory fortification initiative results in less productivity loss.
Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis
Abbreviation: NTD, neural tube defect

The incremental costs are presented in Table 35. In each case, the costs of mandatory fortification were included. In total, mandatory folic acid fortification produced $AUD 350 000 per year more value in terms of a combination of increased productivity and reduced health costs than the alternative of no mandatory fortification.

Cost-effectiveness

Mandatory folic acid fortification was found to be cost saving in the base case, compared to no mandatory folic acid fortification. The initiative was found to be more effective and resulted in greater QALYs gained, life years gained and neural tube defects avoided.

3.6.15 Sensitivity analysis

The assumptions made in the modelling process may not be completely accurate.[92] These assumptions may introduce uncertainty and bias into the model. Sensitivity analysis is used to analyse the uncertainty in the model.[93]

Sensitivity analysis can be undertaken by;

- varying the value of the parameters in the model one at a time to determine the importance of the parameter for the results (One-way sensitivity analysis)
- varying multiple parameters at a time over a distribution (Probabilistic sensitivity analysis) which determines the portion of the time one alternative is cost-effective relative to the other.
- scenario analysis, where additional parameters (such as adverse effects or one-off costs) are added to the model or parameters are set at an extreme value (Scenario analysis) This gives information about the appropriateness of the model structure.

One-way sensitivity analysis

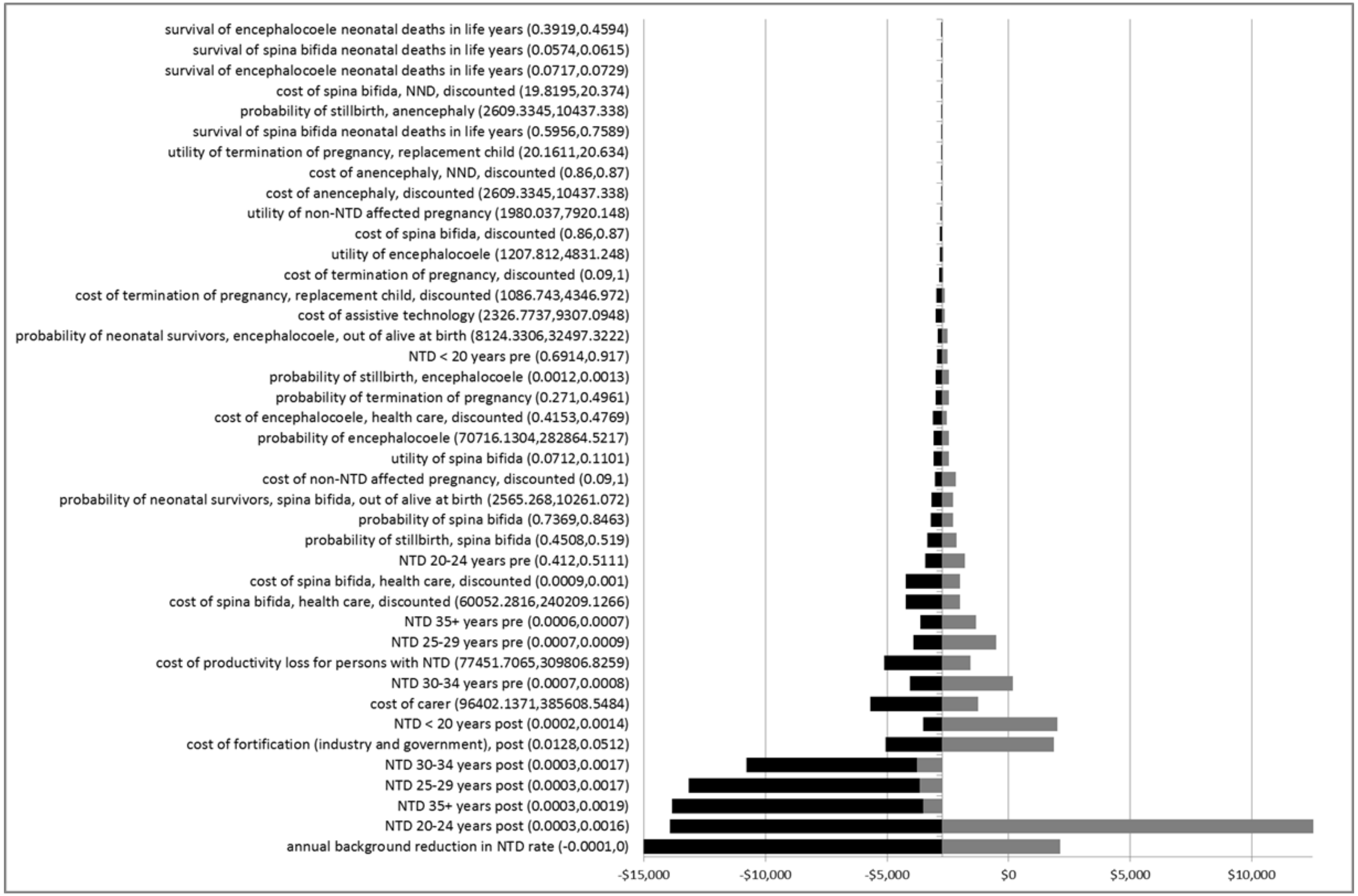
Figure 3 is a tornado diagram illustrating the results of varying the parameters of the model. The model was relatively insensitive to a number of parameters. Each line in the diagram represents the varying of a single parameter. The range that the parameter is varied over is presented in the brackets. The horizontal axis shows the cost per QALY. Because mandatory folic acid fortification is cost saving the cost per QALY is negative in the base case.

The parameters that most impacted on the results was the estimation of the post- fortification rate of NTDs and the estimation of the background rate of NTD decrease.

The 95% confidence intervals for these parameters were quite wide and therefore the model was sensitive to using the upper limits of the rate (which is very close to no difference between the pre-mandatory fortification and post-mandatory fortification prevalence of NTD). A similar situation existed with the background rate of NTD prevalence decrease. If the background rate decrease is higher than estimated in the model, it results in a decrease in the estimated effectiveness of mandatory folic acid fortification.

A longer period of follow-up or larger sample size would clarify the effectiveness of the mandatory folic acid fortification and decrease this source of uncertainty in the model.

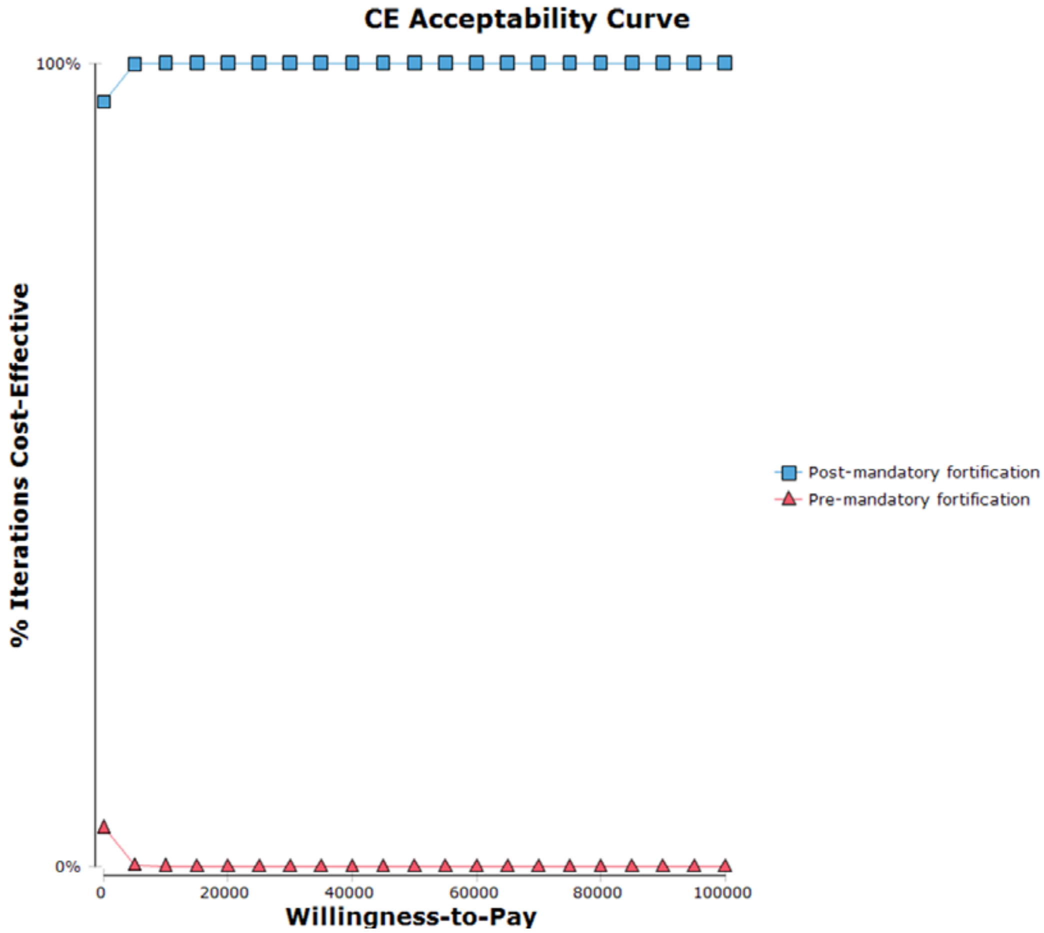
Figure 3: Tornado diagram for folic acid fortification economic evaluation base case



Probabilistic sensitivity analysis

The probabilistic sensitivity analysis was performed with 10 000 iterations. At a willingness to pay of $AUD 50 000 per QALY gained, post-mandatory folic acid fortification had a 99.01% probability of being more cost-effective than no mandatory fortification.

Figure 4: Cost-effectiveness acceptability curve for folic acid alternatives



Scenario analysis

A number of scenario analyses were conducted to assess the impact of certain assumptions. These included:

- the removal of the background rate of decrease in NTDs;
- the exclusion of the NSW data;
- the inclusion of adverse effects, specifically exacerbation of B_{12} deficiency leading to neurological damage (either costed as an outpatient visit or inpatient visit);
- the inclusion of utility decrement experienced by mothers for termination of pregnancy and stillbirth pregnancy outcomes;
- the cost of fortification:

- upfront (sunk costs) included in the alternative with the mandatory fortification initiative with no fortification cost in the pre-mandatory period to represent the situation in 2009;

- upfront (sunk costs) included in pre-mandatory fortification with no ongoing fortification costs in the post-mandatory period to represent a scenario of introducing voluntary fortification again;

- the removal of discounting; and

- the removal of the multiplication factor for encephalocoele.

For each scenario, the incremental benefit of adopting mandatory folic acid fortification was compared to the alternative of no mandatory folic acid fortification (the pre-mandatory fortification suite of policies). A positive number indicates that mandatory folic acid fortification initiative was superior for that index (so the cost has been changed to savings). The results are presented for the outcomes of NTDs reduced, the increased QALYs and the savings (reduced costs and increased productivity) with mandatory folic acid fortification.

In all scenarios, there were fewer NTDs with mandatory folic acid fortification. In the majority of scenarios, an increased number of QALYs was also associated with this initiative. The removal of the background rate had a dramatic impact on the effectiveness of mandatory folic acid fortification and increased the effectiveness. Similarly, the exclusion of the NSW data increased the number of NTDs avoided and increased the modelled benefit. This was because without the low NSW NTD rate, the estimated rate of NTDs increased and the potential benefit similarly increased. These results demonstrate that the approach taken in this evaluation is conservative, with regard to the calculated reduction in NTDs.

A particularly extreme scenario analysis involving adverse effects reduced the total number of discounted QALYs and resulted in a net health loss. This is partly due to discounting, where the temporally distant survival advantages were valued less highly than the more immediate adverse effects.

The consideration of start-up costs was interesting. The majority of these costs were incurred in moving from one type of fortification to another, for example from mandatory fortification to voluntary fortification (or the reverse). As such, they resulted in bias in favour of the status quo (whatever that may be). In the first year of moving to mandatory folic acid fortification, the start-up costs were large enough to reverse the discounted savings. On the other hand, the change back from mandatory fortification to the pre-mandatory fortification suite of policies would cost approximately $AUD (2014) 4.5 million in the first year.

Table 36: Outcome of scenario analysis

Scenario	Incremental Savings (Cost) $AUD[a]	Incremental QALY	Incremental reduction in NTD
Base	358 885	131.00	14.28
No background rate	1 548 875	293.68	32.01
NTD rate excluding NSW data	887 770	202.88	22.12
AE with outpatient cost	200 693	-237.35	14.28

Scenario	Incremental Savings (Cost) $AUD[a]	Incremental QALY	Incremental reduction in NTD
AE with hospital cost	-2 247 758	-237.35	14.28
Utility loss TOP/SB	356 525	134.10	14.28
Cost of fortification – Post-mandatory upfront	-3 204 000	131.00	14.28
Cost of fortification – Pre-mandatory upfront	4 521 488	131.00	14.28
No discounting	2 099 010	498.84	14.28
Cost of encephalocoele health care treatment same as spina bifida	349 441	131.00	14.28

a Positive indicates mandatory fortification is the superior alternative. Incremental is 'Mandatory fortification' minus 'no mandatory fortification')
Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis
Abbreviation: AE, adverse effect; NTD, neural tube defect; SB, stillbirth; TOP, termination of pregnancy

3.6.16 Model validation

The mandatory folic acid fortification initiative was expected to prevent between 14 and 49 NTDs against the background of 300 to 350 NTD affected pregnancies in Australia per year,[9] an anticipated reduction in NTD rates of 4% to 16%.[12] In Hilder,[12] NTD pregnancies by state and year of birth were expected to be 180 for NSW, Queensland, Western Australia, South Australia and the Northern Territory in 2011. In 2007 and 2008 the combined number of NTD pregnancies was 387 for NSW, Queensland (noting incomplete data prior to July 2007), Western Australia, South Australia and the Northern Territory.[12]

The model used the rates for isolated cases only and adjusted for the declining background rate in NTDs.

Table 37: Model validation for NTD cases in 2011

State	Population (N)	NTD cases with no mandatory folic acid fortification initiative	NTD cases with the mandatory folic acid fortification initiative	Incremental impact of mandatory folic acid fortification
Total Australian population	22 485 340	204.94	191.34	-13.60
New South Wales	7 247 669	66.06	61.68	-4.38
Victoria	5 574 455	50.81	47.44	-3.37
Queensland	4 513 009	41.13	38.40	-2.73
South Australia	1 645 040	14.99	14.00	-0.99

State	Population (N)	NTD cases with no mandatory folic acid fortification initiative	NTD cases with the mandatory folic acid fortification initiative	Incremental impact of mandatory folic acid fortification
Western Australia	2 387 232	21.76	20.31	-1.44
Tasmania	511 718	4.66	4.35	-0.31
Northern Territory	232 365	2.12	1.98	-0.14
Australian Capital Territory	370 729	3.38	3.15	-0.22

Note: Incremental ('Mandatory fortification' minus 'no mandatory fortification')
Source: ABS, 3101.0 Australian Demographic Statistics – December 2014[47]

3.6.17 Cost-benefit analysis results

For the CBA, the benefits were monetarised by assigning a monetary value to the QALYs.

The appropriate monetary value for a life year has been debated. The Office of Best Practice Regulation suggested that an amount of $AUD (2014) 182 000 per life year saved, provided an appropriate discount rate is used (5% in this model).[94] However, different amounts can be inferred using the revealed preferences of the Australian government for the purchase of health benefits through pharmaceuticals. Therefore, $AUD (2014) 15 000 and 75 000 per QALY are also used as alternatives.[95]

The base case assumptions are used for the CBA, that is, not including start-up costs for either alternative. The results are presented for a single year in Table 38. Unsurprisingly, the total benefit is dependent on the assessment of the value of health. If higher values are assigned to the benefits of health, mandatory folic acid fortification becomes increasingly positive. At the highest assessment of the value of health, mandatory folic acid fortification generated over $AUD (2014) 24 million of benefit. Over 90% of the value of the benefit was the health benefits attributable to mandatory fortification compared to its cost savings.

Table 38: Results of incremental cost-benefit analysis for folic acid

Outcome	$AUD 0 (zero) per QALY	$AUD 15 000 per QALY	$AUD 75 000 per QALY	$AUD 182 000 per QALY
Incremental QALYs	131	131	131	131
Benefit assigned to each QALY	0	1 965 041	9 825 206	23 842 501
Monetarised benefit	358 886	2 323 927	10 184 092	24 201 386

Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis
Value is in $AUD (2014)
Abbreviation: QALY, quality-adjusted life year

Threshold analysis for loss of consumer surplus

There is concern that mandatory fortification reduces choice. This reduced choice results in a lower satisfaction for the population called a loss of consumer surplus. This is not accounted for in the analysis. There is limited evidence that this reduction in consumer surplus is greater than zero and has been assumed to be zero through this evaluation of value for money.

The loss of consumer choice associated with mandatory fortification is a theoretical cost to consumers that could be included in economic evaluations.

Mandatory health programs restrict personal choice and deny consumers the ability to substitute particular goods or services.[21] For example, some people may value the loss of the availability of a good (such as folic acid-free bread) or incur the cost of buying a more expensive alternative (such as organic bread). Other examples are the preference to not be vaccinated on the basis of religious, medical or social reasons, having a high-risk aversion to adverse effects (about which, from a population perspective, the government is risk neutral), or preferring to exercise free choice in deciding what to consume. The 'restriction' on choice represents a loss in consumer welfare or more specifically a reduction in consumer surplus – a measure of the net benefit of consumption.[21]

While previous economic evaluations of fortification have recognised that the loss of consumer choice is potentially important, there has been a limited effort to quantify it.[21] The Access Economics CBA (2006) commented on the loss of consumer choice but did not quantify it. They commented that "mandatory fortification prevents consumers from avoiding fortified products unless they make considerable changes in their dietary habits".[70] Before mandatory folic acid fortification in Australia, Dalziel et al[96] undertook a cost-effectiveness analysis of mandatory folic acid fortification. In this analysis, the authors assumed a $AUD 1 cost per person per year for the loss of consumer choice.[96]

Parkinson et al.[97] conducted a proof of concept study to explore whether the utility impact of a loss of consumer choice from implementing mandatory health programs could be measured using stated preference methods. For folic acid fortification programs, the compensating variation was positive ($AUD 18) indicating that some level of compensation is required when introducing the program on a mandatory rather than voluntary basis. However, the 95% confidence intervals suggest that this estimate was not statistically significant. A small proportion of respondents always choose a voluntary program (9%) or no policy (6%). The mandatory program was not preferred, in general, to the voluntary program.

In 2003, Dixon and Shackley[98] published the results of interviews with 76 people in the United Kingdom (UK), in which 20% were opposed to fortification while 67% were in favor. A willingness to pay analysis was undertaken, and there was a net benefit associated with fortification.[98] The reasons for paying centered on the health benefits associated with the program. This analysis included valuation of the benefits as well as costs.

The potential loss of consumer choice has neither been quantified nor monetarised in the economic evaluation conducted for this Report. It was assumed that the loss of consumer choice had no cost. The likely bias of this decision will be in the direction of underestimating the costs associated with mandatory fortification. The size of the bias is unknown and could be negligible or zero. This assumption is tested using a threshold analysis.

The analysis of the impact of the loss of consumer surplus was conducted on the base case and used the results of the CBA presented in Table 38. The results are for one year and do not include any start-up costs for either alternative.

Table 39 demonstrates the loss of consumer surplus that would be required to reverse the decision to choose mandatory fortification as a dominant strategy. The amount required is related to the value assumed with regard to a QALY gain. If a value of $AUD 182 000 per QALY gained is chosen, then a loss of consumer surplus of $AUD 1 per person per year in Australia would be required to reverse the decision to introduce mandatory fortification. If the lower value of $AUD 15 000 is chosen, then a loss of $AUD 0.10 would be required to reverse the result of dominance for mandatory fortification. If the health gains were not valued, then only a small amount of consumer surplus loss would be required to reverse the decision ($AUD 0.01).

Table 39: Calculation of threshold for loss of consumer surplus to negate benefit

Outcome	$AUD 0 (zero) per QALY	$AUD 15 000 per QALY	$AUD 75 000 per QALY	$AUD 182 000 per QALY
Total value of benefit of mandatory fortification	358 886	2 323 927	10 184 092	24 201 386
Consumer surplus per capita required	0.01	0.10	0.43	1.03

Value is in $AUD (2014)
Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis

3.6.18 Limitations of value for money evaluation

Several data sources were obtained from non-Australian populations, including the cost of assistive technology, the incremental health services use with NTDs and the lost work for carers. The applicability to the Australian population is not known, but none of these was important in the one-way sensitivity analysis.

This evaluation did not directly assess changes in folic acid status in the population. The model did not consider any other health impacts that may be associated with sufficient folic acid status in the population.

Productivity impacts have been conservatively estimated. The productivity gains associated with decreased termination of pregnancy were not estimated for either the parents or the child. This potentially biases against mandatory fortification.

NTD rates have been conservatively estimated, the use of the full dataset rather than excluding NSW results in a reduced estimate of effectiveness. The NSW data is incomplete without all NTDs being included.[6,12]

It is difficult to determine attribution in a public health initiative. The value for money evaluation in this Report did not assume that changes in the NTD-affected pregnancy rate before and after mandatory folic acid fortification were solely due to this initiative. Information on changes in folic acid supplementation was not available, together with other initiatives including education.

The model attempted to address this uncertainty by adjusting for the declining annual background NTD rate. There are limitations to the use of a linear method of estimating the decreasing background NTD rate, i.e. the closer it gets to zero the more inappropriate the method is. Such a method should not be used to predict the counterfactual NTD rate several years into the future.

Interrupted time series would be a superior method of assessing the effectiveness of mandatory folic acid fortification.[40] But at the time that the review was conducted there were less than two years of data post-mandatory fortification, and three data points are usually required before and after the intervention for the conducting of an interrupted time series analysis.[40]

3.6.19 Summary of the economic evaluation

The value for money evaluation found that mandatory folic acid fortification was cost saving and health generating, compared to the alternative of no mandatory folic acid fortification. Therefore, it has satisfied the criterion for value for money.

The modelled reduction in NTDs was approximately 14 per year (for the 2014 Australian population), after adjusting for the declining background rate. This is consistent with the lower end of the pre-mandatory fortification estimates. Each year of mandatory fortification resulted in $AUD 350 000 in health system savings and increased productivity.

The base case for this evaluation was built using the information contained in previous reports (Catalyst report[6] and AIHW report.[7]). Extensions of the base case were developed to deal with the limitations of the information provided. The results were robust to most, but not all, of the assumptions made about the missing information. If the introduction of mandatory folic acid fortification results in a widespread testing of B_{12} and folate levels in the over 55 age group, this has the potential to limit the savings achieved and reverse the gains in health. There is no evidence to support widespread adverse effects associated with mandatory folic acid fortification.

The results were insensitive to most, but not all, of the parameters included in the model. As discussed in Hilder[12] and the AIHW report[7] there were limitations in the change in the NTD rate being based on a sub-national dataset and a short follow-up time. This resulted in a relatively wide confidence interval for the size of the reduction in the NTD rate. The results were sensitive to the number of NTDs prevented. These sensitivities were demonstrated in the probabilistic sensitivity analysis. At a threshold cost of $AUD 50 000 per QALY, mandatory folic acid fortification is 99% likely to be the superior alternative.

3.7 Conclusions

Against all three evaluations (implementation, overall policy objectives and value for money), mandatory folic acid fortification achieved most of its objectives. It was effective, equitable and efficient in comparison to the alternative of no mandatory folic acid fortification (the pre-mandatory fortification suite of policies). These conclusions are limited by the available data and the structure of the analysis.

3.7.1 Evaluation of implementation

The implementation of mandatory folic acid fortification was mostly, but not completely, demonstrated through assessing indicators outlined in the monitoring framework. A lack of comparable nationally representative data in the pre-mandatory fortification and post-mandatory fortification periods limited the demonstration of successful implementation.

Publications of research on smaller subgroups comparing nutrient intakes and/or nutrient status pre-mandatory folic acid fortification and post-mandatory folic fortification were consistent with successful implementation.

3.7.2 Evaluation of policy objective (NTD reduction)

The mandatory folic acid fortification initiative achieved its policy objective in Australia as assessed by the reduction in NTDs reported. It was assessed as being relatively effective but not absolutely effective. Supplementation of women intending to become pregnant and in early pregnancy as a policy is required to continue.

Mandatory folic acid fortification has improved equity in outcomes (reducing the disparity that existed in rates of NTDs) for young mothers and Indigenous mothers. It was not able to be demonstrated that social disadvantage inequities were reduced.

It was deemed to be cost-effective and efficient compared to the alternative of no mandatory fortification in 2014. The exact magnitude of the improvement in effectiveness requires a longer follow-up and additional statistical analysis.

Its sustainability has not been demonstrated. If the NTD rate without mandatory folic acid fortification continued to fall, then the value of mandatory folic acid fortification would also decrease.

In general, because the majority of the evaluation was conducted within (a pre-post comparison) it has low internal validity. The lack of comparable groups in the periods lowers the internal validity further. A base case population (Australia in 2014) was used to control for demographic changes and increase the comparability of the estimates of the pre-mandatory fortification and post-mandatory fortification periods. Further modelling was undertaken to control for the continuing reduction in NTDs, but other confounders could not be controlled for.

Comparable and nationally representative information in the pre-mandatory fortification and post-mandatory fortification periods would have improved the evaluation of mandatory folic acid fortification. This evaluation should be repeated when there is data over a longer period post-mandatory fortification to allow for more sophisticated analysis of the effectiveness of mandatory folic acid fortification.

3.7.3 Evaluation of value for money

The mandatory folic acid fortification initiative was assessed as being value for money. There are caveats on this assessment. The modelling of mandatory folic acid fortification found it to be health generating and cost saving, compared to the alternative of the no mandatory folic acid fortification (including advice on supplementation for pregnant women and those planning pregnancy) that existed prior to its introduction.

The modelled reduction in NTDs is approximately 14 per year (for the 2014 Australian population), after adjusting for the declining background rate of NTDs. This was consistent with the pre-mandatory fortification estimates. Each year of mandatory fortification results in $AUD 350 000 in health system savings and increased productivity. These are conservative estimates, and the use of the dataset excluding NSW increased the modelled reduction to 22 NTDs.

The base case was built upon on the information contained in the previous reports (Catalyst report[6] and Hilder.[12]). Modelling was undertaken to deal with the limitations of the information provided and the pre-post structure of the comparative analysis.

The results were robust to most, but not all, of the assumptions made about the missing information. The results were insensitive to most, but not all, of the parameters included in the model. There were limitations in the change in the NTD rate being based on a sub-national dataset and a short follow-up time.

The results were sensitive to the number of NTDs prevented. At a threshold cost of $AUD 50 000 per QALY, the mandatory folic acid fortification initiative is 99% likely to be the superior alternative in 2014.

Because the health costs, productivity gains, and health gains occur predominately in the future, discounting has a large impact on the measurement of cost and effectiveness. Without discounting, the savings were estimated at $AUD 2 million and the health outcomes at 500 QALYs for every year that mandatory folic acid fortification is in place.

4 Introduction to iodine

Mandatory iodine fortification was introduced in 2009 to address the re-emergence of iodine deficiency at a population level in Australia and New Zealand. The policy change required the mandatory replacement of non-iodised salt with iodised salt in bread the definition of bread and the exemptions (such as bread represented as organic) is reproduced in Section 8.1.3.

Iodine is an essential element for growth and development.[32] Iodine deficiency has been a problem for more than a century.[99] It is important in pregnancy for the neurodevelopment of the fetus. The use of iodine in the body occurs within the thyroid gland and the hormones it produces (including thyroxine). Iodine is essential for thyroid hormone production. Thyroid hormones regulate a wide variety of physiological processes.[100]

A deficiency of iodine can lead to a constellation of symptoms and diseases collectively referred to as Iodine Deficiency Disorders (IDDs). The consequence of iodine deficiency varies by age.[100] IDDs include enlargement of the thyroid (goitre), a decreased ability to produce thyroid hormone (hypothyroidism), and an autonomously functioning thyroid (multinodular goitre and hyperthyroidism) which have impacts during pregnancy.

Pregnancy increases the demand for iodine. A sufficient level of thyroid hormone is required for the development of the brain and nervous system of a fetus during pregnancy. At its extreme, severe iodine deficiency can result in cretinism and increased neonatal mortality. Cretinism results in a combination of mental retardation, sensory issues (e.g. deafness) and physical abnormalities (e.g. unusually short stature). However, even without cretinism, mild to moderate iodine deficiency during pregnancy may reduce cognitive performance.

IDDs are a global problem and considered the largest preventable cause of mental impairment.[2] A widespread public health intervention involving iodisation of salt has been in place since the 1920s. It has been suggested that the elimination of iodine deficiency by universal salt iodisation is one of the most cost-effective public health interventions.[2,99]

Different amounts of iodine are required at various stages of life. The measures of required intake are referred to as the nutrient reference values (NRV).

The most commonly used nutrient reference values in this Report are:

1. Estimated average requirement (EAR), a daily nutrient level estimated to meet the requirements of half the healthy individuals in a particular life stage and gender group;
2. Recommended daily intake (RDI), the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group; and
3. Upper level of intake (UL), the highest average daily nutrient intake level likely to pose no adverse health effect to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.[32]

The NRVs for iodine increases with age till adulthood and also at times of increased demand, such as during pregnancy and breastfeeding (Table 40). EAR can be used to examine the prevalence of inadequate intakes in the population.[32] Intake is considered adequate when 97-98% of the population is above the EAR.[100]

Iodine intake can be difficult to measure because the contribution of iodised table salt and salt used in cooking can be difficult to quantify.[100]

Table 40: Iodine requirements by age and life stage

Age/Sex and life stage	EAR	RDI	UL
1-3 years	65 µg/day	90 µg/day	200 µg/day
4-8 years	65 µg/day	90 µg/day	300 µg/day
9-13 years	75 µg/day	120 µg/day	600 µg/day
14-18 years	95 µg/day	150 µg/day	900 µg/day
>19	100 µg/day	150 µg/day	1 100 µg/day
Pregnant	160 µg/day	220 µg/day	1 100 µg/day[a]
Lactation	190 µg/day	220 µg/day	1 100 µg/day[a]

a UL is slightly lower for 14-18-year-olds who are pregnant or lactating
Abbreviations: EAR, estimated average requirement; RDI, Recommended daily intake; UL, Upper Level (of intake)
Source: NHMRC and NZ MoH 2006[32]

The upper level of intake is based on the impact of excess iodine. The first adverse effect seen is challenged thyroid function with an elevated thyroid stimulating hormone (TSH).[32] However, those individuals with thyroid disorders or who have been exposed to a long history of iodine deficiency may respond adversely at levels of iodine intake below the UL.[32]

The majority of iodine intake is excreted in the urine (greater than 90% for individuals with positive iodine balance) and therefore urinary iodine is an indicator of recent iodine intake.[100] The estimation can be performed using either a spot urine test or on a 24-hour collection. Spot urine collections are often used for convenience.[101]

While Urinary Iodine Concentration (UIC) may not be a good measure of an individual's iodine status because of day-to-day variation, it is used as an indicator of a population's iodine status because the day-to-day variation within an individual's results is evened out by a large number of individual samples.

The median urinary iodine concentration (MUIC) is a measure of a population's iodine status and iodine intake.[102] Initially, in 1990, an MUIC of 50 µg/L or less was proposed as identifying iodine deficiency. In 1992, this was increased to 100 µg/L or less.[102] In 2001, cut-offs were introduced for excessive intake.[102] These cut-off values were derived from school-age children.[102] Criteria for pregnant and lactating women were published in 2007[102] (Table 41). An additional criterion of less than 20% of the UIC results being under 50 µg/L is required to avoid being classified as having an insufficient intake.

Table 41: Iodine intake & status category based on median urinary iodine concentration

Status	Intake	Children and non-pregnant adults median urine iodine concentration (µg/L)	Pregnant women median urine iodine concentration (µg/L)
Severe iodine deficiency	Insufficient	<20	-
Moderate iodine deficiency	Insufficient	20-49	-
Mild iodine deficiency	Insufficient	50-99	<149[a]
Adequate iodine nutrition	Adequate	100-199	150-249
May pose a slight risk of more than adequate iodine intake in these populations	Above requirements	200-299	250-499
Risk of adverse health consequences	Excessive	≥300	≥500

a For pregnant women, the WHO does not define different cut-off values for different iodine-deficiency categories (severely deficient, moderately deficient and mildly deficient). Groups of pregnant women with median urinary iodine below 150 µg/L are considered to have "insufficient" iodine intake.
Source: World Health Organization 2013[102]

There are some concerns that the higher urinary volume of adults will reduce the concentration of iodine in the urine. This may result in urinary concentration estimates being lower than urinary excretion estimates. Validation of the association between UIC and iodine intake in adults is required.[100] The current practice is to express UIC as a concentration (µg/L).[100]

5 Mandatory iodine fortification in Australia

5.1 Introduction to the iodine status of the Australian population

Section 4 of this Report introduces iodine, including why it is necessary for fetal development, what the nutritional requirements are and how it is measured. This Section outlines Australia-specific information. It evaluates the implementation and impact of mandatory iodine fortification in Australia, to address the re-emergence of iodine deficiency on a population level.

Historically, Australia's population has been iodine deficient. Iodine deficiency was recognised in the late 19th and early 20th century. The iodisation of table salt was introduced in the 1920s. There was protection from iodine deficiency via the use of iodine-based sanitisers in the dairy industry which caused iodine contamination of milk.[103]

In addition to iodisation of salt, other programs were introduced to combat iodine deficiency. In 1947 an iodine tablet program was introduced to combat goitre. In 1953 bread was fortified in the ACT, and in 1966 Tasmania fortified bread with iodine. The fortification of bread ceased in Tasmania in 1976, in part, because of the rate of iodine-induced hyperthyroidism. The introduction of iodine based sanitisers was thought to have contributed to the development of iodine-induced hyperthyroidism.

Within Australia, iodine deficiency re-emerged on a population basis before mandatory iodine fortification. Studies in the early 1990s suggested Australia was iodine replete.[103] A series of studies across Australia in the late 1990s found there was the potential for mild iodine deficiency, especially in South-Eastern Australia. Tasmania adopted a state-based voluntary fortification process to counter this trend in 2001. This program improved the iodine status of the population of school children.[11] The success of the Tasmanian program demonstrated that the replacement of salt with iodised salt in bread could successfully address mild iodine deficiency.[10]

In 2004, the National Iodine Nutrition Survey (NINS) was conducted in New South Wales, Victoria, South Australia, Western Australia and Queensland in children. The results differed between states. While the unweighted sample suggested adequate iodine status, when reweighted it demonstrated a mild iodine deficiency in mainland Australia. Slightly different results were reported in different publications. The reweighted results from both Li et al.[104] and the Australian Population Health Development Principal Committee (APHDPC)[103] are reported below (Table 42). Multiple cross-sectional studies in children and pregnant women also demonstrated iodine intake as insufficient based on MUIC.[103]

Table 42:National Iodine Nutrition Survey results

State	Sample Size	MUIC (µg/L)	Population Iodine Intake Status
New South Wales	427	89	Mild deficiency
Victoria	348	73.5	Mild deficiency
South Australia	317	101	Adequate
Western Australia	323	142.5	Adequate
Queensland	294	136.5	Adequate
Total Sample (Unweighted)	1709	104	Adequate
Total Sample (Weighted) APHDPC	1709	98	Mild deficiency
Total Sample (Weighted) Li	1709	96	Mild deficiency

Abbreviations: MUIC, median urinary iodine concentration
Adapted from APHDPC 2007[26,103,104]

The reasons for the decline in iodine intake included decreased use of salt, a reduction in the use of iodine-containing sanitising agents in the dairy industry, and the use of non-iodised salt in processed food.[103]

Mandatory iodine fortification, replacing salt with iodised salt in bread, was implemented to address the re-emergence of iodine deficiency. It was implemented in October 2009.[7] The definition of bread, and the exemptions (such as bread represented as organic) is reproduced in Section 8.1.3

5.2 Monitoring framework for iodine

The monitoring framework developed by FRSC and the specific questions identified by the AIHW were used to assess the changes that occurred in food composition, nutrient intake, nutrient status (which was the health benefit) and adverse health effects from the pre-mandatory iodine fortification period to the post-mandatory iodine fortification period.[7] The monitoring framework is discussed in Section 2.2.

The monitoring framework was designed as an outcome hierarchy where each step represents an achievement required before the next step can be attained. For example, iodine had to be included in bread before increased intake of iodine occurs. The population of women of childbearing age (16-44 years) and children were the key subgroups of interest. The key monitoring questions for mandatory iodine fortification commenced with changes in the composition of food and concluded with addressing iodine deficiency on a population level (Table 43). The health benefit was also the policy objective.

Table 43: Iodine fortification monitoring questions

Framework Component	Monitoring question
Food composition and industry compliance	Has the level of iodine in our food supply increased? Is the food industry adequately complying with the mandatory fortification standards?
Nutrient intake	Have iodine intakes in the population increased?
Nutrient status	Has the iodine status of the population improved, in particular in women of childbearing age?
Health benefits	Has iodine deficiency been tackled?
Adverse health effects	Does mandatory iodine fortification result in adverse health effects for the population?

Source: AIHW Baseline report for monitoring 2011[26]

The AIHW report,[7] which used the monitoring framework, concluded that most of the desired outcomes had been achieved (Table 44). The assessment was conducted by answering the monitoring questions, mostly by comparing data for different indicators in pre-mandatory fortification and post-mandatory fortification periods. Overall, the AIHW assessed the objective of addressing the re-emergence of iodine deficiency at a population level was achieved.

One outcome was not demonstrated. The AIHW concluded that the increase in the proportion of the children aged 2-3 years that exceeded the UL of intake was not deemed to pose a health risk. This increase was therefore considered not applicable.[7] It was argued that this was because the thresholds in that age group were extrapolations from adults and the proportions exceeding the upper level fell with age.[7] Less than 1% of children aged over four years exceeded the upper level, so the impacts were transient.[7]

Table 44: Key mandatory iodine fortification outcomes in Australia

Key monitoring question and measurement	Pre-mandatory fortification	Post-mandatory fortification	Outcome
Has the level of iodine in our food supply increased? *Mean iodine level of bread*	<2 µg/100 g	53–70 µg/100 g	Desired Outcome Achieved
Are the food industries adequately complying with the mandatory fortification standards?	Not applicable	Salt manufacturers and bakers have systems in place to ensure compliance.	Desired Outcome Achieved
Have iodine intakes in the population increased, particularly in women of childbearing age and young children? *Mean iodine intakes*	Women aged 16–44 years: 98 µg/day Children aged 2–3 years: 127 µg/day	Women aged 16–44 years: 149 µg/day (51 µg/day increase; 52%) Children aged 2–3 years: 164 µg/day (37 µg/day increase; 29%)	Desired Outcome Achieved
Proportion of the population with iodine intakes below the EAR	Women aged 16–44 years (non-pregnant EAR): 60% Women aged 16–44 years (pregnancy EAR): 95% Women aged 16–44 years (lactating EAR): 100% Children aged 2–3 years: 9%	Women aged 16–44 years (non-pregnant EAR): 9% Women aged 16–44 years (pregnancy EAR): 65% Women aged 16–44 years (lactating EAR): 85% Children aged 2–3 years: <1%	Desired Outcome Achieved
Has the iodine status of the population improved, in particular in women of childbearing age and young children? *Median urinary iodine concentration (MUIC)*	Children aged 8–10 years: 96 µg/L	Children aged 5–8 years: 175 µg/L All women aged 16–44 years: 121 µg/L Pregnant women aged 16–44 years: 116 µg/L Breastfeeding women aged 16–44 years: 103 µg/L	Desired Outcome Achieved
Does mandatory iodine fortification result in adverse health effects for the population? *Proportion of the population with iodine intakes above the UL*	Women aged 16–44 years: 0% 19 years and over: 0% Children aged 4–8 years: 0% Children aged 2–3 years: 7%	Women aged 16–44 years: 0% 17 years and over: 0% Children aged 4–8 years: <1% Children aged 2–3 years: 20%	Not applicable

Abbreviations: MUIC, median urinary iodine concentration; UL, upper level (of intake)
Source: AIHW Report 2016[7]; Table O.2

The AIHW report[7] is critiqued in Section 8.2.4. Reliance on pre-mandatory fortification nutrition surveys, a lack of pre-mandatory fortification data and a lack of nationally representative datasets were among the limitations identified. Accurate measurement of iodine intake is difficult, because of the requirement to estimate the use of discretionary salt and the iodine content of that salt.[100]

5.3 Evaluation components

For this Report, the outcomes of mandatory iodine fortification were compared to those achieved using the pre-mandatory fortification suite of policies. These policies consisted of a combination of education, voluntary fortification, fortification of table salt, and supplementation. All these policies (except voluntary fortification in bread which was replaced by mandatory fortification) continued alongside mandatory iodine fortification, meaning that mandatory fortification did not replace these policies but rather complemented them.

The evaluations conducted in this Section relate to:

1. Implementation of mandatory iodine fortification;
2. The achievement of the policy objective (addressing the re-emergence of iodine deficiency); and
3. Value for money of mandatory iodine fortification.

For this Report, the implementation of mandatory iodine fortification was required to be assessed using the following outcomes as outlined in the monitoring framework (Section 5.4):

- changes in food composition;
- changes in nutrient intakes; and
- changes in nutrient status.

The evaluation criteria against which the overall policy objective (addressing the re-emergence of iodine deficiency) was required to be assessed were the effectiveness, equity, efficiency, certainty, feasibility and sustainability of iodine fortification in Australia (Section 5.5). This Reports assessment was both comparative (against the pre-mandatory fortification suite of policies) and absolute. The framework was extended beyond the policy objective to other aspects of the monitoring framework.

This Report also assessed the value for money of the mandatory iodine fortification initiative with an economic evaluation. The results of the CBA were not considered robust, and a cost-effectiveness analysis was conducted (Section 5.6).

5.4 Evaluation of implementation

5.4.1 Methodology

This Report evaluated the implementation of mandatory iodine fortification by assessing if the expected changes in food composition, changes in nutrient intakes and changes in biomedical measures had been achieved.

Success was achieved if the increase or change in magnitude estimated was at least as large as expected in the proposals for mandatory iodine fortification.

Each outcome was also required to be estimated using a comparison between two nationally representative datasets that allowed valid comparison. The complete success of the initiative's implementation required demonstration of successful implementation of all outcomes.

5.4.2 Results

This Report found that the implementation of mandatory iodine fortification in Australia was mostly, but not completely, demonstrated to be successful.

The level of iodine in the food supply (bread) increased, iodine intake increased and the iodine status of children increased. These results are discussed further below.

The iodine status of women of childbearing age was not estimated prior to mandatory fortification with a nationally representative survey, and therefore success was unable to be demonstrated for this population group.

Concerns exist about the lack of contemporary data underlying the estimation of nutrient intake and the nutrient status pre-mandatory fortification, especially for adults (Table 45).

Table 45: Assessment of implementation of mandatory iodine fortification in Australia

Implementation area	Measurement	Estimated difference expected in proposal	Actual estimated difference	Nationally representative data used in comparison	Assessment
Food composition	Mean iodine level of bread	46 µg/100 g bread	From <2 µg/100g to 53-70 µg/100g bread	Yes	Demonstrated to be successful
Nutrient intake	Iodine intake in women aged 16-44 years	46 µg/day increase	51 µg/day increase	Uncertain	Demonstrated (with caveats)
Nutrient intake	Iodine intake in children aged 2-3 years	38 µg/day increase	37 µg/day increase	Uncertain	Demonstrated (with caveats)
Nutrient status	MUIC in women aged 16-44 years	-	Not calculable	No	Not Demonstrated
Nutrient status	MUIC in children aged 8-10 years	-	From 96 µg/L to >150 µg/L	Yes	Demonstrated (with caveats)

Abbreviations: MUIC, median urinary iodine concentration
Source: AIHW Report 2016[7]

Iodine in the food supply

The implementation step of changing food composition of bread was successfully achieved as the fortified bread contained slightly higher than the expected level of iodine. The mean iodine level in the post-mandatory fortification bread samples exceeded the expected 46 µg per 100g of bread to 53-70 µg per 100g of bread.[7] This achievement was demonstrated on the basis of three analytical surveys using random bread selection. The surveys occurred in 2010, 2012 and 2013.[28] The third survey did not include Tasmania, South Australia or the Northern Territory in the random selection but the first two surveys did.[28]

Iodine intake

Iodine intake was estimated using the updated values of iodine in bread in FSANZ DIAMOND dietary monitoring program.[28] Except for the iodine content of bread, the data for the food consumption in the post-mandatory fortification period was not sourced from the post-mandatory fortification period.

For adults, FSANZ used the 1995 NNS food consumption data. For children, the 2007 ANCNPAS was used. It was argued that this was the best available data and that this was unlikely to make a major difference to the results when applied to the post-mandatory fortification period.[7,28]

However, the lack of use of contemporary food composition data from the 2011-2012 NNPAS is a limitation. A decrease was observed in the percentage of females aged 16-44 years who consumed bread from the 1995 NNS (74.6%) to the 2011-2012 NNPAS (58.2%).[28] Therefore, it is uncertain that the methodology employed was representative of the post-mandatory fortification population.

The pre-mandatory fortification estimate of children's iodine intake was originally derived from the 1995 NNS. The estimates calculated in the FSANZ Report used the 2007 ANCNPAS for assessing both the pre-mandatory fortification and post-mandatory fortification periods.[28] The pre-mandatory fortification estimates using the 2007 ANCNPAS re-calculated by FSANZ were the same order of magnitude as those of the 1995 NNS. This approach potentially improved comparability as the food usage was derived from a dataset which was more proximate to the introduction of mandatory iodine fortification.

The accurate measurement of dietary iodine is problematic because of variation in the use of iodised (and non-iodised) salt at the table and in cooking. The quantification of salt use may also be difficult. This would also affect estimations of iodine intake. FSANZ used two alternative methods: a market-weighted model and a consumer behaviour model.[28] The consumer behaviour model used two different assumptions: either no use of discretionary iodised salt or always using discretionary iodised salt. The market-weighted model used the portion of discretionary salt that is iodised.

These models produced three separate estimates of iodine intake. The three models are ordered from that which reports the least iodine use to the most: referred to as the consumer behaviour model (never choose iodised discretionary salt), the market-weighted model and the consumer behaviour model (always choose iodised discretionary salt). This approach (three separate estimates) was only applicable to the 1995 NNS. This was because the 2007 ANCNAPS identified the use of iodised discretionary salt.[28] The reported increase of 51 µg per day in the iodine intake of women aged 16-44 years is based on the market-weighted model.[28]

The use of supplements and complementary medicine use were not considered in the 1995 NNS. This was considered a weakness in assessing the difference in iodine intake over time that may not be derived from foodstuffs.[26] This may be especially important when considering the EAR for pregnant and lactating women. The number of modelled individuals below the EAR has decreased post-mandatory fortification (Table 46).

Table 46: Proportion of people with intake below EAR

Sex & Life stage	EAR (DFE) µg /day	Pre-mandatory fortification (%)	Post-mandatory fortification (%)	Difference
Children aged 2-3 years	65	9%	<1%	8%
Non-pregnant women	100	60%	9%	51%

Sex & Life stage	EAR (DFE) µg /day	Pre-mandatory fortification (%)	Post-mandatory fortification (%)	Difference
(16-44 years)				
Pregnant women	160	95%	65%	30%
Lactating women	190	100%	85%	15%
17 years and above	-	50%	6%	44%

Results use the market weighted model
Abbreviations: DFE, dietary folate equivalent; EAR, estimated average requirement
Source: AIHW Report 2016[7]; FSANZ 2016[28]; Table 6

The calculated increase in intake could be attributable to mandatory iodine fortification if all other variables have been held constant. Therefore, the modelling of iodine intake demonstrated the potential efficacy of mandatory iodine fortification.

Iodine intake status and health impact

The health impact of improvement in population iodine intake status and the nutrient status are measured with the same indicators, the MUIC, and the population iodine status.

Pre-mandatory fortification estimates were derived from the Australian NINS, a cross-sectional study of 1709 children aged 8-10 years living in New South Wales, Victoria, South Australia, Western Australia and Queensland conducted in 2003-2004.[105] Initially, the sample was reported as being an unbiased estimate of the population value,[105] but it was subsequently reweighted by population size.[104] This reweighting reduced the estimated MUIC from 104 µg/L to 96 µg/L (from adequate iodine nutrition to mild deficiency). This study was not nationally based as it did not involve Tasmania, ACT or Northern Territory (Table 42).

The post-mandatory fortification estimates were derived from a nationally representative study, the 2011-2012 NHMS. The pre and post-mandatory fortification comparison showed that the MUIC had increased in all states post-mandatory fortification to over 150 µg/L.[7]

In the AIHW Report[7] no pre-mandatory fortification estimate for women of childbearing age was reported, and no national data was available; the post-mandatory fortification level was derived from the NHMS. Therefore, the implementation of mandatory iodine fortification in women aged 16-44 years was considered not to have been demonstrated. The post-mandatory fortification MUIC for children was higher than the pre-mandatory fortification values reported in the NINS (Table 47).

Table 47: Australian MUIC and population iodine status

Sex & Life stage	Pre-mandatory fortification MUIC (NINS), µg/L	Post-mandatory fortification MUIC (NHMS), µg/L
Children aged 8-10 years (NSW)	89	177.0
Children aged 8-10 years (VIC)	73.5	162.6
Children aged 8-10 years (QLD)	136.5	165.9
Children aged 8-10 years (SA)	101	149.9
(WA)	142.5	261.3
Children aged 5-8 years	-	175
Women 16-44 years	-	121
Lactating Women	-	103
Pregnant Women	-	116
All People	-	131

Abbreviations: MUIC, median urinary iodine concentration; NHMS, National Health Measures Survey; NINS, (Australian) National Iodine Nutrition Survey
Source: AIHW Report 2016[7], ABS microdata, Li et al. 2008[104]

5.4.1 Review of other studies and discussion

Successful implementation was mostly but not completely demonstrated using the monitoring framework. The use of a pre-post structure has a low internal validity. The use of different population groups or surveys introduces more bias and lowers the internal validity of a comparison even further. For the purposes of comparison, to limit bias, the use of contemporary, nationally representative datasets was required in this Report's analysis to demonstrate success.

There are other studies, which, while not being nationally representative, have measured the impact of mandatory iodine fortification in specific subgroups using a comparison between the pre-mandatory fortification period and the post-mandatory fortification period. Some but not all of these studies have demonstrated an improvement in iodine status associated temporally with mandatory iodine fortification's introduction. These studies were conducted in pregnant women and in children and are detailed further below.

Comparative studies in pregnant women

Two of the three studies comparing pre and post-mandatory fortification periods in pregnant women found a statistical difference in the MUIC (Table 48).

Table 48: Comparative studies in pregnant women

Study	Recruitment & Area	Sample size	Pre-fortification MUIC (IQR), μg/L	Post-fortification MUIC (IQR), μg/L	Statistical estimation of difference
Rahman et al.[106]	Antenatal clinics in Gippsland, VIC	N = 86 • pre, n=26 • post, n=86	96.0 (45 - 153)	95.5 (60-156)	Yes (not significant)
Clifton et al.[107]	Lyell McEwin antenatal clinic, SA	Total women: N=196 • Pre: n=84 samples • Post: n=94 samples	68	84	Yes (p=0.01)
Charlton et al.[108]	Antenatal clinic, Illawarra, NSW	Total women: N=394 • Pre (2008): n=110 • 2011: n=106 • 2012: n=95	87.5 (62-123.5)	• 2011: 145.5 (91-252) • 2012: 166 (97-237)	Yes (p<0.05), between: • 2008 vs. 2012 and • 2008 vs. 2011

Abbreviations: IQR, interquartile range; MUIC, median urinary iodine concentration
Source: Charlton et al., 2013[108]; Clifton et al., 2013[107] Rahman et al., 2011[106]

Rahman et al.[106] was a cross-sectional observational study that reported the UIC from pregnant (later than 28 weeks) women from Gippsland, Victoria. The study recruitment crossed the start of mandatory iodine fortification in Australia (October 2009) and ran from January 2009 to February 2010. 86 women were recruited, 24 from the pre-mandatory period and 62 from the post-mandatory fortification period. There were no statistical differences between the MUIC of these two groups, measured at 96 μg/L pre-mandatory fortification and 95.5 μg/L post-mandatory fortification. The small sample size of this study and the relatively short post-mandatory fortification period limit the applicability of the results.

Clifton et al.[107] reported the UIC from pregnant women recruited from a South Australian antenatal clinic between January 2009 and July 2010. It was a prospective observational study. Multiple urine samples were collected, at 12, 18, 30 and 36 weeks from 196 women. For the subgroup of women not using iodine supplementation (potentially relying on fortification), the MUIC increased from 68 µg/L pre-mandatory fortification (84 samples) to 84 µg/L (94 samples) post-mandatory fortification. This difference was statistically significant. The unit of analysis was urine samples, not individuals.

Charlton et al.[108] reported the UIC of women recruited at a public antenatal clinic in NSW. Three convenience samples were recruited; one from 2008 (139 women), one from 2012 (146 women) and one from 2013 (109 women). The MUIC increased from 87.5 µg/L pre-mandatory fortification to 145.5 µg/L post-mandatory fortification in 2011 and 166 5 µg/L post-mandatory fortification in 2012. This difference was statistically significant for comparison between 2008 and 2011, and between 2008 and 2012. Post-mandatory fortification, the MUIC of women taking supplements exceeded 150 µg/L, but as a group, non-supplement users remained iodine deficient.

All of the studies in pregnant women suffer from a pre-post intervention structure with the inability to control for confounders. The reported use of iodine containing supplements doubled between 2008 and 2011.[108] The National Health and Research Medical Council advised all pregnant and breastfeeding women in Australia to take an iodine supplement in 2010.[24] Thus, education and advice changed after the introduction of mandatory iodine fortification.

Within each study, the recruitment strategy was the same in the pre and post-mandatory fortification periods but differed between the three studies. All the studies were institutionally based, and the recruitment strategy was one of convenience. The results demonstrated that mandatory iodine fortification, without supplementation, does not satisfy the iodine requirements for pregnant women. The larger studies had a statistically significant increase in the MUIC.

Comparative studies in children

DePaoli et al.[11] conducted a cross-sectional study of Tasmanian school children in 2011. The results were compared to previous studies of school-age students in Tasmania. The recruitment strategy was based on school classes: 52 were invited to participant, 42 from a previous study conducted during the time of voluntary fortification in Tasmania and an additional ten randomly selected classes. Thirty-seven of the 52 classes participated and 320 (36% of the students in the participating classes) students returned a urine sample. The MUIC was 129 µg/L, an increase from 111 µg/L reported in a 2007 survey conducted during the period of voluntary fortification in Tasmania. The differences between the surveys in the voluntary and mandatory fortification periods were statistically significant. However, both periods were characterised by satisfactory iodine population levels in children.

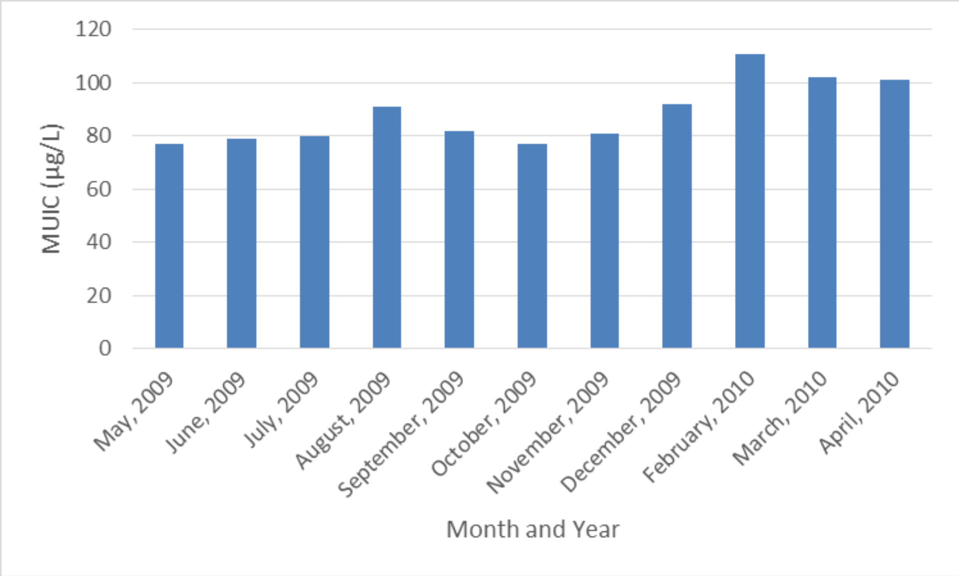
Samidurai, Ware and Davies[109] conducted a study using a convenience sample of 30 children aged 8-10 years and compared the results to the Queensland component of Australian National Iodine Study. The results indicated that the children had an average MUIC of 144 µg/L which was not statistically significantly different from the pre-mandatory fortification MUIC observed in Queensland.

Comparative studies in adults

The Victorian health monitor was conducted over 12 months between May 2009 and April 2010 (over the period of introduction of mandatory iodine fortification).[110] It was a statewide survey of 18-75 non-institutionalised Victorian. A stratified cluster design was employed with small clusters (clusters less than 100 households were excluded). The response rate for the biomedical component was 38%. The results were age-standardised to the 2006 population of Victoria. The

MUIC was 86 µg/L over the survey; the pre-mandatory fortification levels were estimated at 79 µg/L and the post-mandatory fortification at 90 µg/L (estimated from August 2009), and this difference was statistically significant. The last three months, from February 2010 all had an MUIC over 100 µg/L.

Figure 5: MUIC in Victoria Health Monitor data



Abbreviations: MUIC, median urinary iodine concentration
Source: Victoria Health Monitor, 2012[110]; Table 7.24

Overall, the successful implementation of mandatory iodine fortification was unable to be completely demonstrated in this Report. The limitations were due to a lack of contemporary information, a lack of pre-mandatory fortification data and a lack of nationally representative data.

However, the first step (food composition -increasing iodine availability in bread) and the last step (increased MUIC to iodine adequacy for children) were demonstrated. Other published research mostly but not completely demonstrated that implementation occurred with increases in MUIC in a variety of situations. The supporting research was mostly based on non-representative convenience samples. Two studies showed no increase in MUIC associated with mandatory iodine fortification, but both had a small sample size. Additionally, the Victorian Health Monitor data suggest the increase in MUIC does not occur exactly at the start date of mandatory iodine fortification, but that there may be some delay. The lack of an increase of MUIC observed by Rahman et al.[106] might also be due to such a delay.

The NHMS demonstrated that the population had iodine sufficiency and the relevant subgroups of children and women aged between 16-44 years had adequate iodine status. The results of the studies in pregnant women also confirmed that fortification without supplementation does not meet the iodine requirements of pregnant women.

5.5 Evaluation of policy objective (addressing iodine deficiency)

5.5.1 Background to policy objectives

The evaluation criteria were pre-specified in the 2005 expert public advice.[29] Box 2 from the expert public advice is replicated in this Report at Table 8: Evaluation criteria for mandatory fortification schemes (Section 3.5.1). The six criteria were effectiveness, equity, efficiency, certainty, feasibility and sustainability.

The 2005 expert report assessed the relative usefulness of each of the potential strategies for iodine fortification. These strategies included mandatory fortification, voluntary fortification, supplements, dietary education and the status quo. The strategy of mandatory iodine fortification was considered the most effective public health strategy (Table 49).

Table 49: Assessment of potential public health strategies to increase iodine intake

Criteria	Mandatory fortification	Voluntary fortification	Supplements	Dietary education	Maintaining status quo
Effectiveness	Yes	Yes	No[a]	No	No
Equity	Yes	No	No	No	NA
Efficiency	Yes	No[b]	Unsure	No	NA
Certainty	Yes	No	Yes[c]	No	NA
Feasibility	Yes	Yes	Yes	Yes	NA
Sustainability	Yes	No	No	No	NA

a Required early in pregnancy but large percentage unplanned.
b Ongoing implementation costs.
c Although supplements vary in dose.
Abbreviations: NA, not applicable
Source: Adapted from Box 4 of Expert Health Policy Advice 2005[29]

Mandatory iodine fortification was not expected to satisfy the requirements for iodine in pregnancy but, for completeness sake, this was included in the indicators of effectiveness. The key subgroups were women of childbearing age and children.

It should be appreciated that the majority of this Report's comparative evaluation was undertaken as part of a pre-post design. A pre-post design is weak in terms of internal validity. This limits the confidence that can be placed in the results of the assessment process. The assessment of the evaluation criteria was supplemented by the results of other research (which is not nationally representative).

5.5.1 Methodology

Indicators were developed for each of the criteria. Some indicators were absolute, that is, without a comparative element. Others were comparative against the pre-mandatory fortification suite of policies. The estimation of comparative differences required two results (one for pre-mandatory fortification and one for post-mandatory fortification) that are valid for comparison. This Report was required to assess the pre-determined criteria against the policy objective of addressing iodine deficiency on a population level. This Report also undertook additional evaluations of food composition and nutrient intake for completeness (Table 50).

Table 50: Evaluation criteria and indicators for mandatory iodine fortification

Criteria	Question/Indicator	Absolute or comparative	Threshold for success (data source) Table number in this Report (if appropriate)
Achievement of policy objective (also included in measures of effectiveness)	Was the population status with mandatory iodine fortification satisfactory	Absolute	Was the population iodine status adequate? (AIHW Report[7])
Effectiveness	Were nutrition needs satisfied by mandatory iodine fortification?	Absolute	Was the iodine intake of women of childbearing age sufficient? (AIHW Report[7]) Was the iodine intake of pregnant women sufficient? (AIHW Report[7]) Was the iodine intake of lactating women sufficient? (AIHW Report[7]) Was the iodine intake of children aged 2-3 years sufficient? (AIHW Report[7]) Was the iodine intake of all people satisfactory? (AIHW Report[7])
Effectiveness	Was the population status with mandatory iodine fortification satisfactory	Absolute	Was the population iodine status adequate? (AIHW Report[7]) Was the iodine status of the population of pregnant women adequate? (AIHW Report[7]) Was the iodine status of the population of women aged 16-44 years adequate? (AIHW Report[7]) Was the iodine status of the population of children aged 5-8 adequate? (AIHW Report[7])
Effectiveness	Was mandatory iodine fortification more effective at satisfying the nutrition needs than the alternative?	Comparative	Was there a reduction in the portion of the women of childbearing age with inadequate iodine intake from the pre-mandatory fortification period to the post-mandatory fortification period? (AIHW Report[7]) Was there a reduction in the portion of 2-3-year-old children with inadequate iodine intake from the pre-mandatory fortification period to the post-mandatory fortification period? (AIHW Report[7])
Effectiveness	Was mandatory iodine fortification effective at addressing population level iodine deficiency compared to the alternative?	Comparative	Was there a change in the iodine status of the population? (AIHW Report[7]) Was there a change in the iodine status of the subgroup of women of 16-44 years? (AIHW Report[7])

Criteria	Question/Indicator	Absolute or comparative	Threshold for success (data source) Table number in this Report (if appropriate)
			Was there been a change in the iodine status of the subgroup of children aged 8-10 years? (AIHW Report[7])
Equity	Did the population have access to foods fortified with iodine with mandatory iodine fortification?	Absolute	Was the iodine in the fortified food at the required level? (AIHW Report[7])
Equity	Was there equity in the distribution of iodine status between socio-economic groups?	Absolute	Was there no statistically significant difference between iodine status between SES? (AIHW Report[7])
Equity	Were there inequities in the distribution of iodine status between Indigenous and non-Indigenous populations?	Absolute	Was there no statistically significant difference between iodine status between Indigenous and non-Indigenous populations? (AIHW Report[7])
Equity	Has access to foods fortified with iodine improved?	Comparative	Has there been an increase in the level of iodine in bread? (AIHW Report[7])
Equity	Has the inequity between socio-economic status been reduced?	Comparative	Was a reduction in the difference in iodine status between socio-economic status demonstrated? (AIHW Report[7])
Equity	Has the inequity between Indigenous and non-Indigenous status been reduced?	Comparative	Was a reduction in the difference in iodine status between Indigenous and non-Indigenous populations demonstrated? (AIHW Report[7])
Efficiency	Has the strategy been implemented efficiently?	Absolute	Did the Catalyst report demonstrate any avoidable or excess costs? (Catalyst report[6])
Efficiency	Was the strategy the most efficient means of achieving adequate iodine status?	Comparative	Only estimated if efficiency is equal between options- Is the strategy the lowest cost alternative in the economic evaluation to achieve the outcome? (Section 5.6)
Feasibility	Was the strategy be successfully implemented	Absolute	Were all of the implementation outcomes demonstrated to be achieved as assessed in the implementation section?
Feasibility	Was the policy objective demonstrated to have been achieved?	Absolute	Was the population iodine status adequate? (AIHW Report[7])

Criteria	Question/Indicator	Absolute or comparative	Threshold for success (data source) Table number in this Report (if appropriate)
Feasibility	Was there sufficient quality assurance procedures in place?	Absolute	Were sufficient quality assurance procedures in place? (Catalyst report[6])
Certainty	Has the introduction of mandatory iodine fortification delivered iodine to those who need it most	Comparative	Assumed to have increased
Sustainability	N/A	Absolute	Assumed to have not been demonstrated because of the limited post-mandatory fortification period

5.5.2 Results

In this Report, the policy objective was achieved. The population iodine status was adequate post-mandatory iodine fortification in Australia.

The absolute effectiveness of mandatory iodine fortification was demonstrated for most but not all of the population (Table 51). As expected, mandatory iodine fortification did not meet the requirements of pregnant women.

The modelling of intake by FSANZ suggested children have enough iodine intake, but this was not true of adults with 6% of all adults estimated to have an intake below their EAR. Mandatory iodine fortification was associated with population sufficiency for the total population, and subgroups, with the exception of pregnant women. Caution should be used in interpreting the EAR for pregnant women as the estimates were based on the estimated intake for women aged 16-44 years; women who are pregnant may change their diet. Additionally, the estimates did not take into account the use of iodine supplements. The MUIC was in the adequate range for all but pregnant women.

Table 51: Absolute indicators for effectiveness of mandatory iodine fortification

Question	Indicator	Result	This Reports Conclusion
Was the iodine intake of women of childbearing age sufficient	Proportion of women aged 16-44 years with iodine intake below the EAR for non-pregnant women	9% (Table 46)	Not able to be demonstrated to be sufficient
Was the iodine intake of women of pregnant sufficient?	Proportion of women aged 16-44 years with iodine intake below the EAR for pregnant women	65% (Table 46)	Not able to be demonstrated
Was the iodine intake of lactating women sufficient?	Proportion of women aged 16-44 years with iodine intake below the EAR for lactating women	85% (Table 46)	Not able to be demonstrated
Was the iodine intake of 2-3-year-old children sufficient?	Proportion of children aged 2-3 years with iodine intake below the EAR for 2-3-year-old	<1% of children (Table 46)	Able to be demonstrated
Was the iodine intake of	Proportion of adults aged 17 and	6%	Not able to be

Question	Indicator	Result	This Reports Conclusion
people aged over 17 years sufficient?	over with iodine intake below the EAR	(Table 46)	demonstrated
Was the population iodine status adequate?	MUIC	131 µg/ L (Table 47)	The level was indicative of adequate iodine nutrition
Was the iodine status of the population of pregnant women adequate?	MUIC	116 µg/L (Table 47)	The level was indicative of iodine intake insufficiency
Was the iodine status of the population of women aged 16-44 years adequate?	MUIC	121 µg/L (Table 47)	The level was indicative of adequate iodine nutrition
Was the iodine status of the population of children aged 5-8 years adequate	MUIC	175 µg/L (Table 47)	The level was indicative of adequate iodine nutrition

Abbreviations: EAR, estimated average requirement; MUIC, median urinary iodine concentration
Source: AIHW report 2016[7]

Comparatively, against the pre-mandatory fortification suite of policies, mandatory iodine fortification was associated with an improvement in indicators of intake. Some indicators were not estimated because a nationally representative pre-mandatory fortification dataset for some populations was lacking. As mandatory fortification has demonstrated the improvement of the iodine status of the subgroup of children, it is relatively more effective than the pre-mandatory fortification suite of policies.

Table 52: Relative indicators for effectiveness for mandatory iodine fortification

Question	Indicator	Result	Conclusion
Was there a reduction in the portion of the women of childbearing age with inadequate iodine intake from the pre-mandatory fortification period to the post-mandatory fortification period?	Change in Proportion of women aged 16-44 years with iodine intake below the EAR for non-pregnant women	51% improvement (Table 46)	Demonstrated
Was there a reduction in the portion of 2-3-year-old children with inadequate iodine intake from the pre-mandatory fortification period to the post-mandatory fortification period	Change in the proportion of children aged 2-3 years with iodine intake below the EAR for 2-3-year-old	8% improvement (Table 46)	Demonstrated
Was there a change in the iodine status of the population?	Change in status of population	No nationally representative pre-mandatory fortification data was available for the population	Not able to be demonstrated
Was there a change in the iodine status of the subgroup of women of 16-44 years?	Change in status of population of women of 16-44 years	No nationally representative pre-mandatory fortification data was available for the population	Not able to be demonstrated
Was there a change in the iodine	Change in status of	From insufficient to	Demonstrated

Question	Indicator	Result	Conclusion
status of the subgroup of children aged 8-10 years?	population of children aged 8-10 years	adequate intake (Table 46)	with caveats

Abbreviations: EAR, estimated average requirement
Source: AIHW Report 2016,[7] FSANZ 2016[28]

The absolute indicators for equity were met. Although there were differences between the MUICs of different groups, the population status of each group indicated adequate iodine status. Thus mandatory iodine fortification is equitable as assessed by these indicators.

Table 53: Absolute indicators for equity of mandatory iodine fortification

Question	Indicator	Result	Conclusion
Does the population have access to foods fortified with iodine with mandatory iodine fortification?	Was the iodine in the fortified food at the required level in the AIHW report?	The iodine level of bread was at the required level (Table 45)	Absolute increase in access to iodine
Was there equity in the distribution of iodine status between socio-economic groups?	MUIC by SES	Those with a lower SES (more disadvantage) had a higher MUIC, 132 µg/L vs. 113 µg/L (AIHW Report[7]: Figure 3.16)	Socio-economic status revealed a difference in MUIC, but the population status was not different between SES
Were there inequities in the distribution of iodine status between Indigenous and non-Indigenous populations?	MUIC by Indigenous Status	Indigenous adults had a higher MUIC than the general population (AIHW Report[7]: Figure 3.18)	The population iodine status was not different between Indigenous adults and the general population

Abbreviations: MUIC Median Urinary Iodine Concentration; SES Socio-economic status
Source: AIHW Report 2016[7]; Figure 3.16; Figure 3.18

A lack of comparable data in the pre and post-mandatory fortification indicators made it difficult to determine if mandatory iodine fortification is more or less equitable than the pre-mandatory fortification suite of policies. The distribution of iodine status by socio-economic status was available post-mandatory fortification but not pre-mandatory fortification from a nationally representative sample.

Table 54: Relative indicators for equity of mandatory iodine fortification

Question	Indicator	Result	Conclusion
Has access to foods fortified with iodine improved?	Difference in iodine content of bread	The iodine level increased in bread (see Section 5.4)	Improvement in equity of access
Has the inequity between socio-economic status been reduced?	Difference in inequity prior to mandatory fortification and after in population status	No nationally representative dataset	Not demonstrated
Has the inequity between	Difference in inequity	Both Indigenous and	Not

Question	Indicator	Result	Conclusion
Indigenous and non-Indigenous status been reduced?	prior to mandatory fortification and after in population status	non-Indigenous had the same iodine population (to each other) status pre and post-mandatory fortification	demonstrated

Source: AIHW Report 2016[7]

In Australia, generally, the mandatory fortification program has proved to be efficient. The Catalyst report[6] did not demonstrate any unexpected costs. The cost-effectiveness analysis in this Report found that mandatory fortification was associated with an improvement in population iodine status at a small additional cost.

The Tasmanian experience suggests more public health resources would be required to increase the effectiveness of voluntary iodine fortification.[11] Ongoing promotion and encouragement are not required to the same extent under a mandatory scheme as an intensive voluntary scheme. The cost-effectiveness analysis in this Report suggested that mandatory fortification is more efficient than the Tasmanian voluntary fortification program (see Uncounted public health resources).

Alternatives to mandatory fortification, either cannot ensure an adequate population iodine status (the pre-mandatory fortification suite of policies) or are more expensive (the Tasmanian voluntary fortification program).

Feasibility was mostly demonstrated with implementation observed to have mostly but not completely occurred (see Section 5.4: Evaluation of implementation). A lack of a nationally representative pre-mandatory fortification data for adults was a key limitation in demonstrating implementation. The use of earlier nutrition surveys also limited the demonstration of feasibility. The feasibility of achieving the policy objective was achieved.

The Catalyst report[6] concluded that sufficient quality assurance procedures were being conducted (Section 8.2.2: Catalyst report)

Certainty was assumed to have improved because of the increase in the iodine content of bread.

Sustainability was assumed not to have been demonstrated due to the short period of time after mandatory fortification.

5.5.3 Discussion of whether policy objective (iodine sufficiency) achieved

Mandatory fortification addressed the re-emergence of iodine deficiency in a manner that the pre-mandatory fortification suite of policies did not. An increase occurred in the MUIC in all jurisdictions. The population subgroup of pregnant and breastfeeding women did not, as was expected, achieve iodine sufficiency as measured by MUIC.

Mandatory iodine fortification was effective in achieving most of the nutrient requirements and is associated with adequate iodine status at a population level. Comparatively, it improved the population level MUIC of children and the population is no longer classifiable as iodine-deficient by WHO criteria.[7] The extent of the improvement within different subgroups was unclear due to the lack of comparable information regarding pre-mandatory fortification status.

The results of comparative studies were inconsistent. Most, but not all, comparative studies showed an increase in MUIC as discussed in the evaluation of implementation (Section 5.4:

Evaluation of implementation) The comparative studies confirmed that, without supplementation, the MUIC for adequate iodine nutrition for pregnant women was not reached. The FSANZ work also confirmed that, based on the 1995 NNS, 65% of the key subgroup of 16-44 years-year-old women do not reach the EAR for pregnancy[28] However, Mackerras et al.[111] found, using the Australian Longitudinal Study of Women's Health data (which included dietary information from 2003) that the bread consumption of pregnant women was higher than their peers. Eleven per cent of pregnant women reported that they changed their diet to increase iodine in a cross-sectional survey pre-mandatory fortification[112] and 22% of pregnant women reported changing post-mandatory fortification.[113] Consequently, the use of all women in the 1995 NNS may overestimate the portion of pregnant women who had a dietary iodine intake less than the EAR even without considering the lack of supplementation data.

The results of repeated surveys in Tasmanian school children suggests that both the approach taken by Tasmania (its voluntary fortification scheme) and the Australia-wide policy of mandatory fortification combated the re-emergence of iodine deficiency[11]. There were differences in the results. Mandatory fortification resulted in a higher MUIC (129 µg/L as opposed to 108 µg/L) compared to the state-based scheme. Moreover, the proportion of the school-age population with an MUIC below 50 µg/L was lower with mandatory fortification. Both differences are statistically significant. However, both policy options resulted in a population with an adequate iodine status as measured by the WHO population criteria. Accordingly, from that perspective, they were equally effective.[11]

The pre-mandatory fortification status of the Indigenous populations was mildly deficient, as was estimated to be the case for the Australian population as a whole.[26,114]

The AIHW found that socio-economic status had an impact on iodine status, with lower socio-economic status associated with a higher MUIC. However, the iodine status of all socio-economic status groups was found to be adequate (i.e., over 100 µg/L).[7]

Geographical location also has an impact on iodine status. There were previously identified state-based differences between children sampled in the 2003-2004 NINS.[105] Children from Western Australia and Queensland had a higher MUIC. Children in NSW and Victoria as a population were, however, mildly iodine deficient. The AIHW report[7] cautioned against comparing between the NINS and the NHMS. It does appear, however, that the differences between the states have been reduced.

The lack of information on potentially high-risk populations remains an issue. There may be individuals with pre-existing thyroid disorders, co-morbidities or genetics who are predisposed to adverse effects below the upper levels of intake (as estimated in the AIHW report). These impacts have not been assessed as part of the evaluation in this Report. They may thus represent an inequity that has not been estimated.

Mandatory fortification has resulted in improved equity in relation to the access to fortified foods. Under voluntary fortification, product differentiation may result in fortified foods being more expensive than unfortified foods.

The modelling undertaken in Section 5.6 suggests that mandatory iodine fortification is efficient. Mandatory fortification is less expensive than scaling up the Tasmanian voluntary fortification program.

The demonstration of the feasibility of implementation was limited by available data. A lack of nationally representative pre-mandatory fortification data and a reliance on the 1995 NNS to determine intake were key limitations. The feasibility of achieving the policy objective was demonstrated.

The certainty of iodine fortification of bread was greater with mandatory fortification than with the pre-mandatory fortification suite of policies. As discussed in the Catalyst report,[6] the addition of iodised salt to bread was subject to significant quality assurance practice. The mean iodine levels in bread were consistent as measured in the FSANZ bread surveys.[7]

This Report did not conclude that sustainability of mandatory iodine fortification was established because of the short follow-up period. However, the higher level of MUIC in Tasmania with mandatory fortification compared to the state-based scheme suggested an increased level of sustainability.

The history of iodine deficiency re-emerging in developed countries such as Australia and New Zealand after previous successful efforts to address it suggests, however, that mandatory fortification's sustainability cannot be guaranteed.

The amount of salt used in bread manufacturing may reduce as a result of increased demand for low salt diets. If this occurs, the iodine level in salt may need to be re-considered and increased to ensure sufficient iodine intake. Alternatively, changes in the consumption of bread (either increases or decreases) may require consideration of additional vehicles for fortification.

Monitoring and periodic reconsideration of the level of fortification and the foodstuffs that are fortified is recommended. The identification and monitoring of high-risk subgroups is also likely to be required to ensure continued sustainability.

5.6 Evaluation of value for money

The purpose of a CBA was to ascertain if the community is better off with one scenario rather than an alternative scenario.[44] A CBA allowed consideration of all costs and benefits rather than for decision making based on selected outcomes.[44]

For this Report's purposes, a high-quality, robust CBA was unable to be conducted. A key reason for this was a lack of information about the differences able to be attributed to either mandatory iodine fortification and the alternative of no mandatory iodine fortification in terms of health-related quality of life, intelligence quotient (IQ), human capital and productivity. Information was also lacking about how these differences would be distributed across the population. These outcomes could neither be quantified nor monetarised.

A model was built that linked the distributions in the UIC to health related outcomes (Section 5.6.1). The evidence to support the link between UIC and the health outcomes was not, however, considered strong enough in the Australian setting to be the basis of modelling.

An indicative CBA was conducted which suggests that small changes in productivity as a result of the introduction of mandatory fortification would result in large benefits (Section 5.6.10 and Section 5.6.11). That is, if fortification results in an adequate iodine status which in turn results in an increased IQ and if an increased IQ results in increased productivity, then mandatory iodine fortification will produce more in productivity than it costs for the fortification initiative to continue.

Additional information on CBA can be found in Section 8.5.

Consequently, a cost-effectiveness analysis was conducted with the outcome being the cost per million people (or more correctly samples) moved from below the appropriate MUIC cut-off to above it (100 µg/L for the majority of the population and 150 µg/L for the subgroup of pregnant women).

5.6.1 Methods

The economic evaluation uses a decision analytic framework to assess the benefits and costs of mandatory iodine fortification compared to no mandatory iodine fortification, using a cohort approach.

A cost-effectiveness analysis is undertaken by comparing the costs and effectiveness of two alternatives:

- Australia with mandatory iodine fortification – mandatory fortification (including the pre-mandatory fortification suite of policies); and
- The counterfactual of Australia without mandatory iodine fortification – no mandatory fortification (retaining the pre-mandatory fortification suite of policies).

Population level estimates of the iodine distribution are derived using a model. A base-case is constructed based on the outcome of interest (population iodine sufficiency) with and without the inclusion of start-up or sunk costs.

A secondary comparison is made between mandatory fortification and the voluntary program undertaken in Tasmania (by the inclusion of public health resources).

The 2014 population statistics were used to estimate the changes in population level iodine sufficiency. The costs were sourced from the Catalyst report,[6] with limitations; it should be noted that information is limited regarding the public health resources that were deployed in the pre-mandatory fortification suite of policies. This limitation is explored in a scenario analysis.

An indicative CBA in undertaken by estimating and then monetarising the benefit associated with increased productivity able to be attributed to mandatory fortification.

Assumptions

Loss of choice

Because the CBA was not considered to be sufficiently robust to determine a monetary value for mandatory iodine fortification the value of the loss of choice was not assessed. The bias created by not including the loss of choice may result in an underestimation of the costs associated with mandatory iodine fortification.

Assumptions of pre-post structure

The economic evaluation of mandatory iodine fortification is based on a pre-post approach. That is, it is assumed that the pre-post approach produces the correct estimation of the incremental change associated with moving from the alternative of the status quo to the alternative of a policy of mandatory fortification. This assumption is incorrect if other policies and choices are changing over the same time, for example, dietary choices or supplementation. A pre-post structure has a low internal validity.[115]

Some confounders, such as demographic changes, can be controlled for by using a reference population. For this evaluation, a reference population of Australia in 2014 is used.

A potential issue that arises from the pre-post structure is that of start-up/one-off /sunk costs. Sunk costs such as the write-off in packaging were incurred in the change from the pre-mandatory fortification suite of policies to the introduction of mandatory fortification. While it may be appropriate to consider sunk costs when estimating the change from one set of programs to another, that is not the main evaluation that is being considered in this Report. This evaluation focuses on the world in 2014 with the mandatory fortification initiatives compared to the world in 2014 without the mandatory fortification initiatives. For transparency, the results are presented with and without sunk costs.

Health benefits and adverse effects

The AIHW report[7] did not identify any health benefits or patient relevant adverse effects associated with iodine fortification. The health benefit was defined as the population or subgroup with iodine sufficiency. There is evidence that mandatory iodine fortification can lead to transient adverse effects (8.8 Iodine fortification safety). These were not estimated within the monitoring framework.

The approach taken in the economic evaluation was to assume no adverse effects or health benefits. This is on the basis that there are no adverse effects identified within the monitoring framework. The economic model does allow for the inclusion of a variety of transitory and permanent adverse effects (and iodine deficiency disorders) in order to calculate their potential impact, e.g. based on future evidence.

5.6.2 Approach

Iodine status was modelled using gamma distributions to describe the data available on urinary iodine concentration of the different population groups before and after mandatory fortification. Distributions are fitted based on the MUIC (required), proportion of people with urinary iodine concentration <50 µg/L (optional), proportion of people with urinary iodine concentration <100 µg/L (optional), interquartile range (optional) and the restriction that the proportion of people with < 20 µg/L pre-mandatory fortification is equal to or higher than the proportion of people with < 20 µg/L post-mandatory fortification.

The proportion of the population with urinary iodine concentration ≥ 100 µg/L (for children and non-pregnant adults) and the proportion of the subgroup of pregnant women with urinary iodine concentration ≥ 150 µg/L was quantified using modelling.

It should be noted that individuals with iodine levels below 100 µg/L (for non-pregnant people) are not necessarily at risk of iodine deficiency disorders, nor do they necessarily benefit from iodine fortification. The MUIC distributions are a population measure of iodine sufficiency and have not been translated into individual effects.

In an iodine adequate population, the MUIC (*median* urinary iodine concentration) signals iodine sufficiency (i.e. an MUIC of ≥100 µg/L for non-pregnant people). However, in an iodine adequate population, up to 50% of the population will have urinary iodine concentrations below the MUIC (i.e. below 150 µg/L for pregnant women).

Costs for the health system, the population, government and manufacturers are valued in Australian dollars.

5.6.3 Population, modelled alternatives and outcomes of interest

The model initially includes the 2014 Australia population in 2014 and updates each year according to the population projections published by the Australian Bureau of Statistics. Subpopulations within the model are newborns, children <16, men aged 16-44 years, non-pregnant women aged 16-44 years, pregnant women and older adults aged ≥45.

The two alternatives considered in the economic evaluation are:

- Australia with mandatory iodine fortification – mandatory fortification (including the pre-mandatory suite of policies); and
- the counterfactual of Australia without mandatory iodine fortification – no mandatory iodine fortification (retaining the pre-mandatory fortification suite of policies).

The outcomes of interest that have been identified for the base case economic evaluations include changes in the modelled proportion of people with urinary iodine concentration ≥100 µg/L (for children and non-pregnant adults) and the modelled proportion of the pregnant women with urinary iodine concentration ≥150 µg/L. These thresholds are used as the measure of outcome in the base case because it is the outcome of interest in the evaluation of the success of the program. A societal perspective was used for the economic evaluation.

5.6.4 Linked cost-effectiveness extensions

In the extensions of the base-case, two different outcomes of interest are considered, in the first extension the outcome of interest is the incremental difference in the human capital that occurs between the alternative of mandatory fortification and the alternative of no mandatory fortification. Given the use of MUIC (a population measure) and the lack of evidence that exists about the treatment effect associated with a change in MUIC, this is subject to considerable uncertainty. The clinical evidence is discussed in Section 8.7.

In the second extension, the improvement in human capital is monetarised into a difference in productivity that could be attributed to an improvement in human capital. A literature review of the previous econometric methods of linking IQ changes to productivity is reported in Section 8.7. The monetarisation of human capital (including IQ changes) associated with small changes in human capital is subject to considerable uncertainty and limited by the external validity.

In these extensions, the portion of the population that experiences a human capital benefit and a productivity benefit is required to be calculated using the changes in MUIC. This **should not** be taken to imply the changes in MUIC only impact a portion of the population; this assumption is used to estimate the portion of the population that may experience a benefit for the purposes of modelling.

5.6.5 Decision analytic framework

The model structure is presented in Figure 6. Essentially the population is divided into six main groups: newborns, children <16, men age 16-44 years, non-pregnant women age 16-44 years, pregnant women and older adults age ≥45.

A Markov model with a cycle length of 1 year, 70-year time horizon and 5% discount rate for costs was constructed. The health states are “healthy”, “elevated autoantibodies”, “hypothyroidism (unmonitored)”, “hypothyroidism (monitored)”, “Hashimoto disease” and “cretinism”. For this Report only the health state “healthy” is included. Mortality is modelled implicitly by using population projections to derive the proportion of people per age group over time.

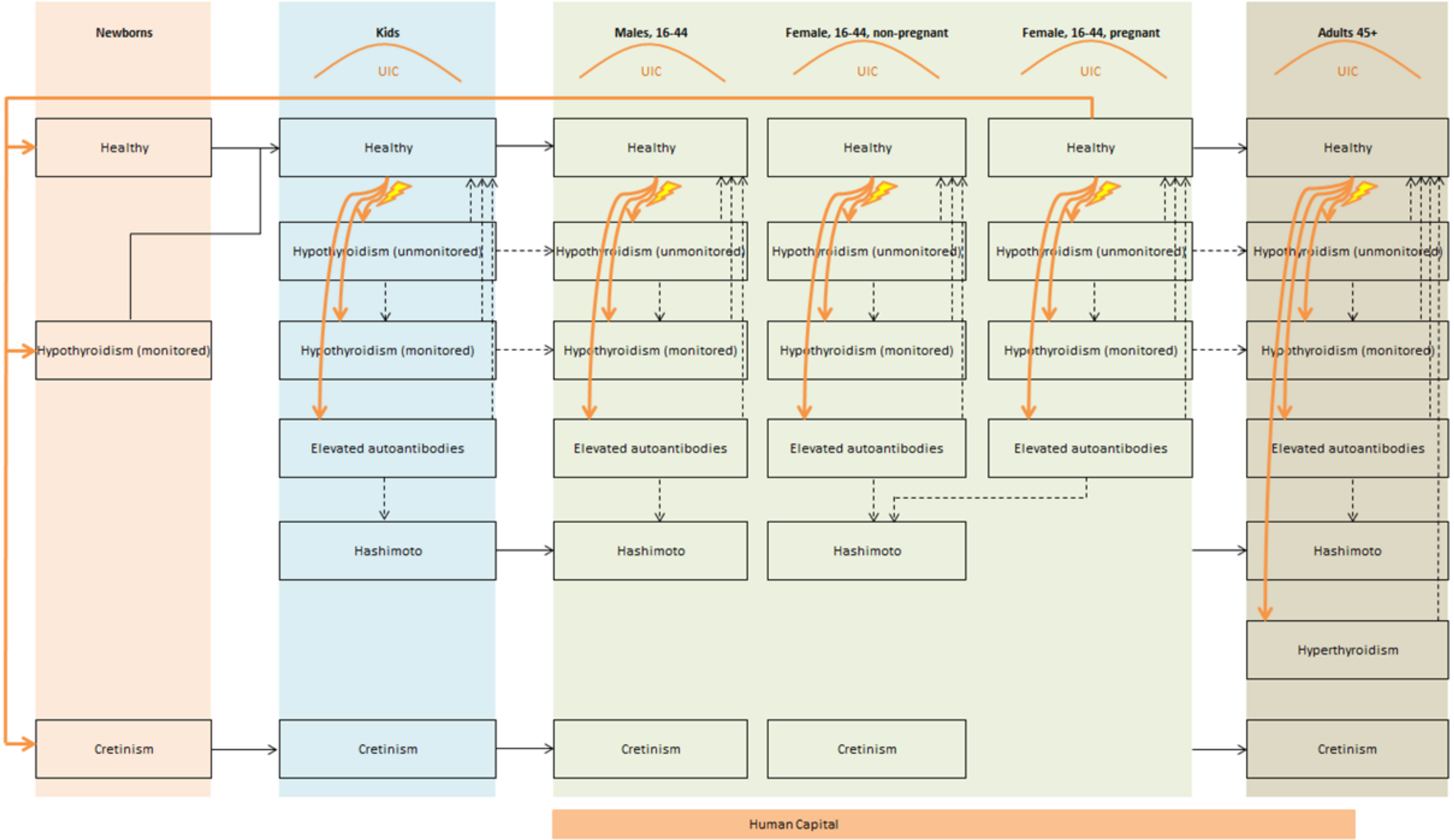
The model uses a 70-year time horizon in order to allow for maternal iodine status to impact the development of human capital in newborns and its financial impact during their adult working life. Given the lack of reliable data on this effect, it is not included in the base case.

Transition probabilities are based on urinary iodine status for children and adults, and maternal urinary iodine status for newborns. The probability of iodine-associated adverse effects is transitory, meaning it was assumed to have a temporary effect in the first year after mandatory fortification was introduced. Given the lack of reliable data on adverse effects and iodine deficiency disorders, adverse effects were excluded from the cost-effectiveness analysis (CEA) and CBA.

Urinary iodine status for the different population subgroups differed before and after the introduction of mandatory fortification.

The model was built in Microsoft Excel 2010.

Figure 6: Iodine fortification economic evaluation model structure



The orange arrows symbolise transition probabilities that are dependent on the UIC distributions per population group. The lightning bolts symbolise transitory effects, only in the first year after iodine fortification is introduced. Black, dotted arrows symbolise constant transition probabilities. Black solid arrows symbolise transitions with a probability of 1.
Abbreviations: UIC, urinary iodine concentration.

5.6.6 Model inputs

Health outcomes

Table 55, Table 56, Table 57, Table 58 and Table 59 provide the urinary iodine status and fitted gamma distributions for different population subgroups, before and after the introduction of mandatory iodine fortification.

Table 55: UIC distributions of children

UIC of children	Median UIC provided (μg/L)	Other UIC information provided (μg/L)	Median from gamma distribution (μg/L)	Mean from gamma distribution (μg/L)	SD
Australia pre-mandatory fortification[26]	96	IQR: 66-135	96	105	54
Australia post-mandatory fortification[7]	163	UIC <50 μg/L: 7% UIC <100 μg/L: 22%	163	185	111

Abbreviations: SD, standard deviation; IQR, interquartile range; UIC, urinary iodine concentration

Table 56: UIC distributions of men (aged 16-44 years)

UIC of men aged 16-44	Median UIC provided (μg/L)	Other UIC information provided (μg/L)	Median from gamma distribution (μg/L)	Mean from gamma distribution ((μg/L))	SD
Australia pre-mandatory fortification[25]	79	IQR: 57-103	79	87	45
Australia post-mandatory fortification[26]	138	UIC <50 μg/L: 13% UIC <100 μg/L: 38%	138	161	107

Abbreviations: SD, standard deviation; IQR, interquartile range; UIC, urinary iodine concentration

Table 57: UIC distributions of women (aged 16-44 years)

UIC of men aged 16-44	Median UIC provided (μg/L)	Other UIC information provided (μg/L)	Median from gamma distribution (μg/L)	Mean from gamma distribution ((μg/L))	SD
Australia pre-mandatory fortification[25]	79	IQR: 57-103	79	89	52
Australia post-mandatory fortification[7]	125	UIC <50 μg/L: 19% UIC <100 μg/L: 40%	125	150	108

Abbreviations: SD, standard deviation; IQR, interquartile range; UIC, urinary iodine concentration

Table 58: UIC distributions of pregnant women

UIC of pregnant women	Median UIC provided (µg/L)	Other UIC information provided (µg/L)	Median from gamma distribution (µg/L)	Mean from gamma distribution ((µg/L))	SD
Australia pre-mandatory fortification[108]	88	IQR: 62-124	88	96	48
Australia post-mandatory fortification[108]	166	IQR: 97-237	166	189	115

Abbreviations: SD, standard deviation; IQR, interquartile range; UIC, urinary iodine concentration

Table 59: UIC distributions of adults aged 45 years and over

UIC of aged 45 years and over	Median UIC provided (µg/L)	Other UIC information provided (µg/L)	Median from gamma distribution (µg/L)	Mean from gamma distribution ((µg/L))	SD
Australia pre-mandatory fortification[25]	79	IQR: 57-103	79	87	47
Australia post-mandatory fortification[7]	132	IQR: 16-39	132	155	105

Abbreviations: SD, standard deviation; IQR, interquartile range; UIC, urinary iodine concentration

5.6.7 Costs

Cost of fortification initiative

The costs for the mandatory iodine fortification initiative include those incurred by industry (salt manufacturers, bakers) and government.

Industry

The Catalyst report[6] reviewed the costs incurred by industry for iodine fortification in Australia and New Zealand. Table 60 presents the number and type of organisations interviewed.

Table 60: Organisations approached in iodine fortification review in Australia

Organisation	Number approached	Number participating
Enforcement agency[a]	8	8
Bakers	8	8
Salt manufacturers	2	2
Total	**18**	**18**

[a]. The nature of the enforcement agency differed in each of the state/territory jurisdictions in Australia. Seven state/territory departments of Health and one Food Authority were interviewed.
Source: Catalyst report 2015[6]; page 7

The projected costs and the actual costs reported by industry members are presented in Table 61.

Table 61: Anticipated and realised (undiscounted) cost impacts of iodine fortification

Sector/Organisation	Timing	Projected costs, $AUD (2007)	Realised costs, $AUD (2014)	Modelled costs, $AUD (2014)
Salt manufacturer	Up-front	161 000	666 000	545 566
Salt manufacturer	Ongoing[a]	314 000	Unable to determine at aggregated level	208 250
Baking	Up-front	6 950 000	25 000-2 700 000	681 250
Baking	Ongoing[a]	30 000	Minimal	217 250
Government	Up-front	31 000	NA	-
Government	Ongoing[a]	137 000	NA	-

a per annum.
Abbreviations: $AUD, Australian dollar; NA, not available

Up-front costs to salt manufacturers

In the review by Catalyst, up-front costs for salt manufacturers were estimated to be $AUD 666 000 in total. Since the model requires these costs to be divided between Australia and New Zealand, they were allocated based on population size. Given the population sizes in December 2014 and the purchasing power parities (PPPs) for Australia (1.47) and New Zealand (1.42), up-front costs for salt manufacturers were $AUD 545 566 in Australia.

Ongoing costs to salt manufacturers

Table 61 shows that the review by Catalyst was unable to determine the ongoing costs to salt manufacturers at aggregated level. The review provided three different estimates of the direct ongoing costs/tonne of salt: $AUD 4.00, $AUD 19.00 and $AUD 45.00. The review also estimated that ~8 500 tonnes of iodised salt were used in bread in Australia. Multiplied by the costs per tonne of salt, this results in $AUD 34 000 to $AUD 382 500 for iodised salt for the use in bread in Australia. The base case will assume the mean costs of $AUD 208 250.

Up-front baking costs

The review by Catalyst estimated the up-front baking costs to range between $AUD 25 000 and $AUD 2 700 000, covering changes for both the iodine and the folic acid fortification programs. Costs were assumed to be an average of $AUD 1 362 500 for Australia.

Ongoing baking costs

The review by Catalyst estimated the ongoing baking costs to be $AUD 0.19 to $AUD 0.60 (mean $AUD 0.395) per tonne of bread. Assuming 550 000 tonnes of bread were baked in Australia, results in a total of $AUD 217 250 in Australia.

Government

Government costs were assumed to be zero in the base case. These costs are varied in a scenario analysis.

There are two sources of potential government costs that could be included. The first is the costs associated with enforcement agencies. As discussed in the Catalyst report[6] these resources were not increased, and the enforcement agencies managed the additional workload within current resources. This does not identify the opportunity cost. However the enforcement of the mandatory fortification initiatives is taking place within a larger quality assurance framework, and the marginal cost of adding a single activity may be minimal.

One of the issues identified in the review of the Catalyst report[6] (Section 8.2) is the lack of identification of public health resources used in managing the issue of iodine deficiency and how it has been managed or re-deployed as a result of the change from the pre-mandatory fortification suite of policies to the post-mandatory fortification suite of policies.

Tasmania is an example of a jurisdiction that devoted resources to an intensive voluntary fortification program, and some of these resources may be able to have been redeployed following the adoption of mandatory fortification. The impact of additional public health resources being released is tested in the scenario analysis by way of a threshold analysis. The cost of a National Health and Medical Research Council (NHMRC) research officer ($AUD 76 789) is used as the cost of public health resources in Australia. The salaries are inflated by 25% for on-costs.

5.6.8 Model results

Table 62 provides the total costs and effects of iodine fortification for Australia over a 1-year, 10-year and 70-year horizon. These include the up-front costs required to implement the fortification program. Since these up-front costs cannot be regained (they are "sunk costs"), it is valuable to evaluate the ongoing costs and effects, i.e. the costs and effects of continuing with the current program. These are provided in Table 63.

Table 62: Iodine cost-effectiveness results, including sunk costs, Australia

Horizon	Measure	Pre	Post	Incremental difference
1-year horizon	Costs in $AUD	0	2 346 315	2 346 315
1-year horizon	Proportion of population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	0.36	0.67	0.30
1-year horizon	Incremental costs ($AUD) per percentage point increase in the proportion of the population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	-	-	77 112
10-year horizon	Costs in $AUD	0	5 370 693	5 370 693
10-year horizon	Proportion of population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	0.36	0.67	0.30
10-year horizon	Incremental costs ($AUD) per percentage point increase in the proportion of the population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	-	-	176 509
70-year horizon	Costs in $AUD	0	10 576 624	10 576 624
70-year horizon	Proportion of population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	0.36	0.67	0.30
70-year horizon	Incremental costs ($AUD) per percentage point increase in the proportion of the population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	-	-	347 604

Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis
Abbreviations: $AUD, Australian dollar

Table 63: Iodine cost-effectiveness results, excluding sunk costs, Australia

1-year horizon, Australia, measure	Pre	Post	Incremental difference
Costs in $AUD	0	425 500	425 500
Proportion of population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	0.36	0.67	0.32
Incremental costs ($AUD) per percentage point increase in the proportion of the population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	-	-	13 984
Population size, Australia (2014)	-	-	23 524 055
Incremental number of Australians with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	-	-	7 157 722
Yearly cost ($AUD) of improving iodine of 1 000 000 Australians from below to above the threshold of 100 µg/L (non-pregnant) or 150 µg/L (pregnant)	-	-	59 446

Abbreviations: $AUD, Australian dollar

5.6.9 Scenario Analyses

A number of scenario analyses/threshold analyses were conducted to assess the impact of certain assumptions. These included:

1. Uncounted public health resources
2. Costs of fortification
    a. upfront costs (sunk costs) included in the post-mandatory fortification with no fortification cost in the pre-mandatory period, representing the situation in 2009; and
    b. upfront costs (sunk costs) included in the pre-mandatory fortification with no fortification cost in the post-mandatory period, representing the situation if mandatory iodine fortification was ceased.

Uncounted public health resources

The redeployment of public health resources to a mandatory fortification program that could be deployed elsewhere is analysed using a threshold analysis. The number of public health officers that would need to be re-deployed is calculated to compensate for the increased cost associated with mandatory fortification. Two approaches were taken; first calculating the total number of public health officers that would be required for the mandatory program, and second, the number required per 1 000 000 of the population. The number of public health officers required to be re-deployed in Australia is 4.2, or 0.2 per million head of population (Table 64)

Table 64: Threshold analysis of uncounted public health resources

Measure	Count
Number of public health officers required to be redeployed	4.2
Number of public health officers required to be redeployed per million persons	0.2

In the 2006 CBA undertaken by Access Economics, the Tasmanian supplementation program was estimated to cost $AUD (2006) 140 000, which converts to approximately $AUD (2014) 175 000.[70] This implies the mandatory iodine fortification initiative is less expensive than scaling up the Tasmanian iodine fortification program to other states in Australia, assuming constant returns to scale.

Therefore, compared to the alternative of the Tasmanian iodine fortification scheme the mandatory iodine fortification scheme is as effective and less expensive.

Upfront costs of fortification

The impact of sunk costs is presented in Table 65. The impact is, as expected, to increase the cost of the alternative.

Table 65: Iodine cost-effectiveness scenario analyses, Australia

Yearly cost ($AUD) of improving iodine status of 1 000 000 moved from below to above ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	Australia ($AUD)
Sunk costs applied to the mandatory fortification alternative	327 802
Sunk costs apply to the no mandatory fortification alternative	Mandatory fortification is dominant

5.6.10 First linked extension: From iodine sufficiency to human capital

The first linked extension is from the iodine intake sufficiency (or insufficiency) to human capital (including intellectual performance).

Understanding the relationship between iodine sufficiency and intellectual performance is a requirement to convert the improvement in population iodine status into a dollar value. Iodine sufficiency (in addition to avoiding congenital cretinism) improves average neurocognitive functioning in neonates and children compared to iodine insufficiency. This improvement represents an increase in human capital. Thus, the total human capital of society is increased.

Human capital can be defined as “the knowledge, skills, competencies and attributes embodied in individuals that facilitate the creation of personal, social and economic well-being”.[116] Iodine deficiency can impact on competencies/skills (language and numeracy) and attributes (diminished IQ) depending on its severity. Likewise, reducing or relieving iodine deficiency can increase the human capital of a population.

The link between iodine sufficiency and measures of human capital is discussed in Section 8.7. In summary, while the relationship between iodine intake insufficiency and changes in IQ is well established in severe iodine deficiency, it is less well established in mild iodine deficiency.

There are two populations of interest in considering the relationship between iodine sufficiency and human capital. The populations studied are children (where UIC is studied in children) and pregnant women (where the UIC is studied in pregnant women). The outcomes are measured in children in both situations.

Modelling issues

There are two key issues for the modelling;

1. The number/portion of the population that benefits from an increase in the human capital due to an improvement in iodine status; and
2. The size of the improvement.

The portion that benefits from an increase in iodine intake

The smallest change required to move the MUIC to the threshold (100 µg/L) is estimated as the portion of the population that benefits with mandatory iodine fortification. The smallest number of test results that have to change is half the number of tests results that were below the threshold.

It is important to note that test results do not refer to the number of individuals whose iodine intake changes. The number of individuals may be much larger, but this is the smallest possible number of test results that are required to change and therefore the smallest number of possible beneficiaries.

The population is considered to be iodine sufficient (excluding pregnant women) if the MIUC is greater than 100 µg/L. The portion of the population that is modelled to benefit from mandatory iodine fortification is not the change in population with a UIC less than 100 µg/L; it is the change in the excess (over 50%) portion of the population under that threshold. This is consistent with research indicating that in populations with adequate iodine status there is no disadvantage associated with a low UIC.[117]

Therefore, using the proportion of children with a modelled UIC <100 µg/L before fortification, approximately 2% of Australian children would benefit from fortification (52% minus 50%). For Australian, non-pregnant women this is approximately 15% (65% minus 50%). For pregnant women, (using a UIC <150 µg/L) this was 37% (87% minus 50%). These figures may represent the absolute minimum benefit. A similar calculation could be undertaken with the changes in the EAR (Table 46). This would result in larger estimated changes, so the use of the modelled UIC is conservative.

The size of the improvement

The size of the human capital improvement is discussed in Section 8.7. The impact ranges from 0 to 2.5 IQ points (mean 1.2, median 1.15). A midrange of 1.2 IQ points is assumed (see Table 101).

5.6.11 Second linked extension: From human capital to productivity increase

The size of the productivity benefit

It is assumed that the increase in wages represents the increase in productivity that occurs.

The potential increase in an individual's annual wages is assumed to be 0.4% per IQ point increase (see Section 8.7.3, Table 105). A conservative value, approximately half of the 0.9% was used because of the substantial uncertainty. For Australia, in May 2014, the average annual weekly earnings were $AUD 1 122.50, resulting in an annual figure of $AUD 58 370.[118] This is adjusted by the participation rate in the Australian economy and discounted, assuming to start during pregnancy (one year prior to birth). The potential benefit is presented in Table 66. These numbers are highly speculative and should be treated with caution. However, even assuming only 2% of children benefit from fortification results in a benefit larger than the cost including the sunk costs ($AUD 32 versus $AUD 7).

Table 66: Benefit of human capital development for Australia

Measure	Result with minimum (0.02)	Result with median (0.15)	Source
IQ Change per benefited individual	1.2	1.2	Section 8.7
Percentage increase per IQ point	0.4%	0.4%	Section 8.7
Average Wage (annual)	$AUD 58 370	$AUD 58 370	ABS[118]
Total lifetime wage change adjusted for timing and participation	$AUD 1 597	$AUD 1 597	ABS[119]
Portion of children benefiting	0.02	0.15	Table 55
Average benefit per child	$AUD 32	**$AUD 239**	-
Average cost of fortification per new child (pregnancy) without sunk costs	$AUD 1	$AUD 1	Table 62
Average cost of fortification per new child (pregnancy) with sunk costs	$AUD 7	$AUD 7	Table 63

Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis
Abbreviations: $AUD, Australian dollar

5.6.12 Limitations of the economic evaluation

The economic evaluation assumed that all changes in urinary iodine concentration before and after the mandatory fortification initiative were due to this initiative. In reality, part of the improvements may have been due to other factors, for example, changes in the use of iodine supplementation or increased consumption of iodised salt.

The economic evaluation did not assess the effect of changes in iodine status on the incidence of iodine deficiency disorders (e.g. cretinism) and/or potential adverse effects (e.g. elevated autoantibodies, Hashimoto, hyperthyroidism). The monitoring framework did not include collecting data on health impacts. Some of these impacts may have been transient and therefore could be treated as sunk costs.

Available evidence on the impact of fortification on iodine deficiency disorders (for mildly deficient populations) and adverse effects was limited and ambiguous. Therefore, outcomes were presented in terms of (costs per) proportion of the population moving to iodine levels ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant), instead of (costs per) quality-adjusted life year gained.

Several of the data sources for the MUIC may not have been nationally representative and therefore the estimates of change are potentially uncertain. The estimation of the MUIC for pregnant women, both pre-mandatory fortification and post-mandatory fortification, are an example of this.

5.6.13 Summary of the economic evaluation

The incremental cost-effectiveness ratio per million people moved from a UIC of below 100 μg/L to over 100 μg/L is $AUD 59 446 per year.

The small additional costs associated with the mandatory program may be mitigated if there was a redeployment of public health resources from encouraging iodine intake in the non-pregnant population. The comparison against an expanded version of the Tasmanian voluntary fortification program demonstrates that mandatory fortification is a more efficient alternative in achieving adequate iodine status.

Two extensions were undertaken which linked the health outcome of interest (the change in population iodine sufficiency) to economic outcomes. The first link is from the health outcome to human capital. This link estimates the human capital benefit, as measured by IQ.

The second linked extension is to monetarise or value the change in human capital as an increase in the productivity of society. The results of these linked extensions suggested that the value of the additional productivity exceeded the cost of mandatory iodine fortification.

Both these links have significant limitations that result in the final estimation being unreliable for decision making. There is no high quality evidence regarding the relationship between an improvement in mild population level iodine deficiency and an increase in human capital. The external validity of the econometric studies to the Australian population is questionable (see Section 8.7). The assumption that individual wage changes are an appropriate measure of productivity increase is also not confirmed. Taken together these limitations mean the monetarisation of changes in population level iodine studies is likely not to be useful for decision making.

However, the cost of mandatory iodine fortification is small compared to the potential gains in productivity. If these gains occurred, then mandatory iodine fortification represent value for money. Likewise, if mandatory iodine fortification improved health-related quality of life, it would also represent value for money.

5.7 Conclusion

Against two evaluations (implementation and overall policy objectives) mandatory iodine fortification achieved most of its objectives. The iodine population status was regarded as adequate, as were the iodine status of the two key subgroups, women (aged 16-44 years) and children. The evaluation of value for money was not able to show the initiative had achieved its objectives, requiring additional assumptions or the objective of achieving adequate iodine status to be valued in its own right. There were limitations in the data available, notably health impacts and pre-mandatory fortification population status.

5.7.1 Evaluation of implementation

The implementation of mandatory iodine fortification was mostly, but not completely, demonstrated. The use of old information regarding food composition and a lack of nationally representative pre-mandatory fortification data limited the comparisons. Other studies that had been conducted mostly, but not completely, showed an increase in the MUIC of subgroups. The MUIC of children is regarded as an indicator of the population iodine status and using this measure the last step was successfully demonstrated.[101]

5.7.2 Evaluation of policy objective (adequate iodine status)

The mandatory iodine program in Australia achieved its policy objectives as assessed because it addressed the re-emergence of mild iodine deficiency.

The post-mandatory fortification data demonstrated that the population status of iodine was adequate. The quality of the information post-mandatory fortification was higher than that pre-mandatory fortification. This has an impact on the strength of the comparative assessment.

The absolute and relative efficiency was demonstrated, albeit in an analytic framework of low internal validity. As expected, mandatory iodine fortification did not meet the requirements of pregnant or breastfeeding women.

Equity was demonstrated as measured in the post-mandatory fortification period. Although there are differences between subgroups on the basis of the MUIC, the population iodine status was equal between these subgroups. The lack of inclusion of health outcomes (other than UIC) means that some key issues concerning equity, the distribution of health-related quality of life and productivity changes, were not able to be assessed, and this is a weakness in the claim of equity demonstration.

Certainty was assumed to have increased with the increase in the iodine content of bread. Feasibility was mostly, but not completely, demonstrated.

Sustainability has not been demonstrated due to the short period of time post-mandatory fortification. There is also the potential for changes in manufacturing practices and food consumption to occur in the future that may impact on iodine intake and therefore population iodine status.

5.7.3 Evaluation of value for money

The mandatory iodine fortification initiative did not have a comprehensive CBA conducted. The assumptions required and the data limitations meant that a robust CBA was not able to be conducted. The lack of health outcomes is a significant limitation with regard to the economic evaluation.

The incremental cost-effectiveness ratio per million people moved from a UIC of below 100 µg/L to over 100 µg/L is $AUD 59 446 per year. The value of these changes in biomedical measures was not able to be estimated.

These small increases in cost may be mitigated if there was a redeployment of public health resources for encouraging iodine intake in the non-pregnant population. It is likely that mandatory iodine fortification provides value for money compared to the intensive voluntary fortification undertaken in Tasmania.

Only small changes in productivity or health-related quality of life are required to have the benefits exceed the costs of mandatory iodine fortification.

The analysis was conducted in a pre-post framework. This limits both the internal validity and the external validity. The use of a reference population controls for demographic change. Other confounders were not controlled for. Pre-post evaluations may overestimate the benefit of interventions.[115] In some situations, a pre-post analysis of a subgroup could be conducted. These were limited to school children, either in Tasmania or the comparison between the NINS and the

NHMS. The iodine status of children has previously been used as a measure of population status.[101]

These three evaluations demonstrate that the iodine status (as measured by MUIC or population iodine status) had improved, and the population has an adequate iodine status. This result will require confirmation in the future.

The impacts of iodine fortification on susceptible individuals were not able to be assessed as part of the evaluation. The UL may not be an appropriate measure for these individuals, and no morbidity data were available. Additionally, the health improvements associated with the improvement in population iodine status were not able to be assessed.

6 Mandatory iodine fortification in New Zealand

6.1 Introduction to the iodine status of the New Zealand population

Section 4 of this Report introduced iodine, including why it is necessary for fetal development, nutritional requirements and measurement. This Section outlines New Zealand-specific information. It evaluates the implementation and impact of mandatory iodine fortification in New Zealand, especially in addressing the re-emergence of iodine deficiency on a population level.

There are naturally low levels of iodine in the soil in New Zealand. This means the major food source of iodine was of marine origin.[32] Early in the twentieth century, studies found a large proportion of school-age children had a goitre. Up to one-third of school children had significant thyroid enlargement.[120] Consequently, iodised salt was introduced in 1924. Iodine deficiency persisted, and the level of iodisation was increased in 1938. In the 1950s the prevalence of goitre diminished to approximately 1% of the population. Iodine based sanitisers were also introduced in the dairy industry in the 1960s, and the unintentional contamination of milk increased the iodine intake further.[10]

However, mild to moderate iodine deficiency has re-emerged.[10] In 1997 a survey of adult blood donors showed that those not taking supplements had an MUIC of 100 µg/L. This was closer to 50 µg/L for women.[120] Further studies showed that children (aged 8-10 years) had an MUIC of less than 100 µg/L.[120]

Four different mechanisms explained the decrease in iodine status, all related to a reduction in iodine intake.[120] These include:

- a reduction in the use of iodine based sanitisers in the dairy industry;
- a reduction in the use of salt in home cooking;
- increasing use of commercially prepared food which is manufactured with non-iodised salt; and
- the rise in popularity of non-iodised or rock salts.[31]

The presence of iodine deficiency at a population level was confirmed in children by the 2002 National Children's Nutrition Survey.[121] In adults, the 2008/2009 New Zealand Adult Nutrition Survey (ANS) confirmed insufficient intake and mild to moderate iodine deficiency[122] (Table 67).

Table 67: Adult iodine MUIC in New Zealand- 2008/2009

Age and Sex	MUIC (95% CI)	Percentage < 50 µg/L (95% CI)	Population Iodine Intake Status
Total	53 (50–56)	47% (44–50)	Mild deficiency
Males	55 (52–61)	44% (40–48)	Mild deficiency
Females	50 (47–55)	50% (46–54)	Mild deficiency
Females (16-44 years)	48	50% (46-58)	Moderate deficiency

Abbreviations: CI, confidence interval; MUIC, median urinary iodine concentration
Adapted from Ministry of Health 2011[122]; Table 8.9; MPI companion report 2016[8]; Table 3

From July 2010, the New Zealand Ministry of Health recommended pregnant and breastfeeding women take a 150 µg daily iodine tablet.[123] These tablets are subsidised when prescribed by a midwife or doctor.[124]

From September-October 2009, New Zealand required that salt be replaced with iodised salt in bread making. Organic and unleavened bread was exempt.[8] (Section 8.1.3 contains the definition of bread and the exceptions).

6.2 Monitoring framework for iodine

The monitoring framework developed by the FRSC and the specific questions identified by the AIHW were used in this Report to assess the changes that occurred in food composition, nutrient intake, nutrient status (which was the health benefit) and adverse health effects between the pre-mandatory and the post-mandatory iodine fortification period.[7] The monitoring framework is discussed in Section 2.2.

The monitoring framework was designed as an outcome hierarchy where each step represents an achievement required before the next step can be attained (Table 43). The last step of the monitoring framework was also the measure of the policy objective.

The AIHW report[7] used the monitoring framework, mostly assessed the key questions by conducting a comparison of data between pre-mandatory and post-mandatory fortification periods. The AIHW report[7] is critiqued in Section 8.2.4. A lack of post-mandatory fortification data, a lack of coverage of the population and non-representative samples were among the limitations identified. Information from the MPI companion report[8] and Jones et al.[31] was used to undertake the assessments in this Report.

Overall, the objective of addressing the re-emergence of mild iodine deficiency at a population level was achieved, subject to limitations in the data. Post-mandatory fortification, at a population level, the adult MUIC was 103 µg/L, and the child MUIC was 116 µg/L.

The key subgroup of women aged 16-44 years had an MUIC of 104 µg/L, which was above the threshold of 100 µg/L for adequate iodine nutrition. However, 21% of women in this subgroup had an MUIC of less than 50 µg/L, technically, the iodine intake of this population subgroup was marginally (1%) above the 20% cut-off for adequate iodine nutrition (see Section 4 for a discussion of the two criteria for adequate iodine nutrition).

The proportion of children aged 2-3 years that exceeded the UL of intake was considered not applicable.[7] The AIHW reported that iodine intake in women of 18-44 years of age had increased but not to the extent required; thus, this outcome was assessed as partially achieved (Table 68).[7]

Table 68: Key mandatory iodine fortification outcomes in New Zealand

Key monitoring question and measurement	Pre-mandatory fortification	Post-mandatory fortification	Outcome
Has the level of iodine in our food supply increased? *Mean iodine level of bread*	<2 µg/100 g (mean)	28–49 µg/100 g (median)	Desired outcome achieved
Are the food industries adequately complying with the mandatory fortification standards?	Not applicable	Salt manufacturers and bakers have systems in place to ensure compliance.	Desired outcome achieved

Key monitoring question and measurement	Pre-mandatory fortification	Post-mandatory fortification	Outcome
Have iodine intakes in the population increased, particularly in women of childbearing age and young children? *Mean iodine intakes*	Women aged 16–44 years: 99 µg/day Children aged 5–14 years: 45 µg/day	Women aged 18–44 years: 108 µg/day Children aged 5–14 years: 93 µg/day (48 µg/day increase)	Partial achievement
Proportion of the population with iodine intakes below the EAR	Women aged 16–44 years: 68%[a] Children aged 5–14 years: 95%[b]	Women aged 18–44 years: 39%[a] Children aged 5–14 years: 21%[b]	Partial achievement
Has the iodine status of the population improved, in particular in women of childbearing age and young children? *Median urinary iodine concentration (MUIC)*	Women aged 16–44 years: 48 µg/L Children aged 8–10 years: 68 µg/L	Women aged 16–44 years: 104 µg/L Children aged 8–10 years: 116 µg/L	Mostly achieved, 21% of women aged 16-44 years were below MUIC 0f 50 µg/L
Does mandatory iodine fortification result in adverse health effects for the population? *Proportion of the population with iodine intakes above the UL*	Adults: 0% Children aged 5–14 years: <1%	Adults: Not applicable Children aged 5–14 years: <1%	Not applicable

The MUIC for women of childbearing age, and children has been replaced, altering the results and the findings reported in the AIHW report, 2016
a Different methods and sub-groups were used in the pre-mandatory and post-mandatory fortification period to estimate the proportion of women with iodine intakes below the EAR
b The results reported in the AIHW report and replicated above for children do not include discretionary salt (see Table 71)
Abbreviations: MUIC, median urinary iodine concentration; UL, upper level (of intake)
Source: Adapted from AIHW report 2016[7]; Table O.3, Jones et al. 2016[31]; MPI companion report 2016[8]

6.3 Evaluation components

For this Report, the outcomes of mandatory iodine fortification were compared to those achieved using the pre-mandatory fortification suite of policies. These policies consisted of a combination of education, voluntary fortification, fortification of table salt, and supplementation. All these policies continued alongside mandatory iodine fortification (except voluntary fortification in bread which was replaced by mandatory fortification), meaning that mandatory fortification did not replace these policies but rather complemented them.

The evaluations conducted in this Section relate to:

1. Implementation of mandatory iodine fortification;
2. The achievement of the policy objective; and
3. Value for money of mandatory iodine fortification

Mandatory iodine fortification's implementation was assessed using the following outcomes as outlined in the monitoring framework (Section 6.4):

- changes in food composition;

- changes in nutrient intakes; and
- changes in nutrient status

The evaluation criteria against which the overall policy objective (addressing the re-emergence of iodine deficiency) was required to be assessed were the effectiveness, equity, efficiency, certainty, feasibility and sustainability of iodine fortification in New Zealand (Section 6.5). This assessment was both comparative (against the pre-mandatory fortification suite of policies) and absolute. This framework was extended beyond the policy objective to other aspects of the monitoring framework.

It was also planned to assess the mandatory iodine fortification initiative in terms of value for money using a CBA. However, the results of the CBA were not considered robust, and a cost-effectiveness analysis was conducted (Section 6.6).

6.4 Evaluation of implementation

6.4.1 Methodology

The implementation of mandatory iodine fortification was evaluated by assessing if the expected changes in food composition, changes in nutrient intakes and changes in biomedical measures had been achieved.

Success was achieved if the increase or change in magnitude estimated was at least as large as expected in the proposal for mandatory iodine fortification.

Each outcome was also required to be estimated using a comparison between two nationally representative datasets that allowed valid comparison. The complete success of the initiative's implementation required that the successful implementation of all outcomes be demonstrated.

6.4.2 Results

The results of the evaluation indicate that the implementation of mandatory iodine fortification in New Zealand was partly but not completely demonstrated to be successful. The level of iodine in the food supply (bread) increased but not always to the level predicted. The iodine status of women of childbearing age increased to be satisfactory (at a population level) as did the iodine status of children (albeit not using nationally representative data) (Table 69). Limitations were identified in the comparability of data for iodine intake (with different measures of iodine intake being used in adults pre and post-mandatory fortification) and the use of smaller sub-national surveys.

Table 69: Assessment of implementation of mandatory iodine fortification in New Zealand

Implementation area	Measurement	Estimated difference expected in proposal	Actual estimated difference	Nationally representative data used in comparison	Assessment
Food composition	Mean iodine level of bread	46 µg/100g bread (mean)	From <2 µg/100g to 28-49 µg/100g bread	Yes	Partially demonstrated to be successful

Implementation area	Measurement	Estimated difference expected in proposal	Actual estimated difference	Nationally representative data used in comparison	Assessment
			(median)		
Nutrient intake	Iodine intake in women aged 16-44 years	76 µg/day increase	Not able to be calculated	No	Not demonstrated
Nutrient intake	Iodine intake in children aged 2-3 years	45 µg /day increase	48 µg/day increase	Yes	Demonstrated (with caveats)
Nutrient status	MUIC in women aged 16-44 years	-	56 µg/L (48 to 104 µg/L)	Yes	Demonstrated
Nutrient status	MUIC in children aged 8-10 years	-	47 µg/L (from 69 to 116 µg/L)	No	Not Demonstrated

Abbreviations: MUIC, median urinary iodine concentration
Source: AIHW Report 2016[7]; MPI companion Report 2016[8]; Jones et al. 2016[31]

Iodine in the food supply

The level of iodine in bread was assessed using the results of two analytical surveys undertaken in 2010[125] and 2012.[126] A wider variety of breads was analysed in the 2012 survey. Iodine content of bread varied by bread type, with several types having a lower iodine content than predicted.[7] Fruit bread was consistently lower in iodine content than other bread types.

In 2010, 526 bread samples were analysed. In 2012, 428 samples were analysed. The data obtained in 2010 were skewed with a large range of mixed grain bread. In 2010, the various bread types that were required to contain iodine had median iodine levels between 32 and 53 µg/100g. For some bread categories, this was less than the 46 µg/100g predicted when developing the mandatory fortification framework.[7] (Table 70).

Some of the variation seen within a bread category was due to the uneven distribution of iodine within bags of salt, and some was due to the salt content of different types of bread.[125] Fruit bread contained less salt than other types of bread partly because of the addition of fruit.[125] Additionally, the Standard allows an iodine range in the salt required to be added to bread of 25-65 mg per kg and therefore variation could be expected. As the iodine content of servings of bread was lower than expected, implementation in terms of changes in food composition was assessed as having been partially demonstrated.

Table 70: Post-mandatory fortification analytical results of iodine content of bread

Bread category	Mean iodine content 2010 µg/100g	Median iodine content 2010 µg/100g	Range iodine content 2010 µg/100g	Median Iodine content 2012 µg/100g	Iodine per slice 2010	Iodine per slice 2012
Fibre white	52.6	48.5	31-109	49.3	15.8-23.7	14.8-22.2
Fruited	31.8	29	18.9-81	30.1	9.5-14.3	9-13.5
Mixed grain	44.4	41	2.9-380	40	13.3-20	12-18
Rye	41.6	42	24-72	32.9	12.5-18.7	9.9-14.8

Bread category	Mean iodine content 2010 µg/100g	Median iodine content 2010 µg/100g	Range iodine content 2010 µg/100g	Median Iodine content 2012 µg/100g	Iodine per slice 2010	Iodine per slice 2012
White	50.3	49	30-115	41.3	15.1-22.6	12.4-18.6
Wholemeal	47.2	44	29-95	38.8	14.2-21.3	11.7-17.5

Source: MAF 2012[125]; Table 5; MPI 2014[126]; Table 6.

Iodine intake

Iodine intake was estimated in several MPI publications. Different approaches were used for adults and children.

Iodine intake for adults

A sample of 301 adults (from an initial 1525 individuals randomly selected from the electoral roll, including 54 respondents recruited using a "snowball" technique-i.e., word of mouth, previous participants) were recruited from Dunedin and Auckland.[127] Iodine intake was estimated using 24-hour urinary iodine collections. The MUIC from these samples was 73 µg/L.[127] The iodine intakes estimated from 24-hour iodine excretion was compared to the EAR and the portion below the EAR calculated (32% of adults). The mean iodine excretion was over 100 µg/day, that is, estimated iodine intakes were on average, above the EAR for non-pregnant adults.

Compared to the New Zealand population, the study sample were urban dwellers, had a higher income and was more likely to be New Zealand Europeans or others; thus, the representativeness of this sample was questionable. Caution should be used in comparing pre and post-mandatory fortification intake derived from food composition and intake.[7] Due to the lack of a nationally representative dataset and a lack of comparability of the measures; implementation is assessed as not having been demonstrated.

Iodine intake for children

Iodine intake for children aged 5-14 years was estimated using the updated values of iodine in bread as assessed by the results of 2010 and 2012 analytical surveys[125,126] within the dietary monitoring program (Dietary Modelling of Nutritional Data (DIAMOND)).[7] Except for the iodine content of bread, the data used to assess food consumption in the post-mandatory fortification period was not sourced from the post-mandatory fortification period. Instead, the source of the dietary information, with the exception of bread, was the 2002 New Zealand Children's Nutrition Survey. This was conducted in 3 275 children aged 5-14 years and used the second day adjusted method.[7]

It was not possible to accurately determine the quantity of discretionary salt used, and the proportion of salt that was iodised was not able to be determined from the responses to the survey questions.[7] The 2014 MPI report (using the 2012 analytical bread survey) noted the results with and without 1 gram of iodised discretionary salt. There was a difference in the results with and without salt (which added 48 µg of iodine per child). This represents approximately half of the daily EAR and has an impact on the proportion of children calculated to be below the EAR. The results used in the AIHW report[7] and reported in Table 69 are the results without the addition of iodised discretionary salt.

The calculated increase in intake in iodine could be inferred to be attributable to mandatory iodine fortification as essentially all other variables have been held constant in the modelling. Therefore, it demonstrated the potential efficacy of mandatory iodine fortification in New Zealand for children.

Table 71: Proportion of people with iodine intake below EAR in New Zealand

Sex &Life stage	Assumption regarding salt	EAR µg/day	Pre-mandatory fortification (%)	Post-mandatory fortification (%)	Difference
Children 5-14 years	With discretionary iodised salt	-	7%	<1%	6%
Children 5-14 years	Without discretionary salt	-	95%	21%	74%
Children 5-8 years	With discretionary iodised salt	65	0%	0%	0%
Children 5-8 years	Without discretionary salt	65	95%	14%	81%
Children 14 years	With discretionary iodised salt	95	48%	<1%	47%
Children 14 years	Without discretionary salt	95	95%	49%	46%
Non-pregnant women[b]	Market weighted model/urinary iodine excretion	100	68%[a]	39%	29%[a]
Adults 18-44 years	Market weighted model/urinary iodine excretion	100	>50%[a]	32%	>18%[a]

Calculations for children include the results for food with and without discretionary salt, for adults the market weighted model is presented. For adults, the post-mandatory fortification results are obtained from urinary iodine excretion.
a pre-mandatory fortification estimates from 1997 and calculated from food survey so not comparable to post-mandatory fortification
b The age of non-pregnant women is 18-44 years in the post-fortification analysis and 16-44 years in the pre-fortification period
Abbreviations: EAR, estimated average requirement
Source: MPI 2014[126]; Table 9, MPI 2013[127]; Table 4; FSANZ 2008[10]; Table 4, Table 6

Iodine status and health impact

The health impacts of improvement in population iodine status and the nutrient status are measured in the same manner, using the MUIC. For children, the additional biomarker of thyroglobulin was also reported (see Section 8.1.5).[31]

Adults

Pre-mandatory fortification estimates were derived from the 2008/2009 New Zealand ANS. A total of 4 721 individuals aged 15 years and above were recruited. The weighted response rate to the survey was 61%, and the response rate for urine was 44%.[122]

Post-mandatory fortification estimates were derived from the 2014/2015 New Zealand Health Survey (as reported in the MPI companion report[8]). Spot urine was collected from 4 997 individuals; the results were re-weighted to the most recent census.

The population, as a whole, had mild iodine deficiency pre-mandatory fortification and adequate iodine nutrition post-mandatory fortification (Table 72).

Some subgroups had mild iodine deficiency post-mandatory fortification (for example Women aged over 70 years). Women aged 16-44 years just exceeded the 20% cut-off for the proportion of the subgroup with an MUIC of less than 50 µg/L with 21% having an MUIC of less than 50 µg/L (see Section 4 for a discussion of the two criteria for adequate iodine nutrition).

Table 72: New Zealand MUIC and population iodine status

Sex/Group (age)	Pre-mandatory fortification MUIC (ANS) µg/L	Pre-mandatory fortification % < 50 µg/L	Post-mandatory fortification MUIC (NZHS) µg/L	Pre-mandatory fortification % < 50 µg/L
All (15+ years)	53	47	103	20
Male (15+ years)	55	44	110	14
Female (15+ years)	50	50	91	26
Women (16-44 years)	48	52	104	21
Men (71+ years)	66	38	105	12
Female (71+ years)	56	45	80	28
NZEO Women (16-44 years)	47	53	96	24
Pacific Women (16-44 years)	71	30	117	6
Maori Women (16-44 years)	52	48	114	16
NZDep1 Females	51	49	93	25
NZDep5 Females	56	42	105	19

Abbreviations: ANS, (New Zealand) Adult Nutrition Survey; MUIC, median urinary iodine concentration; NZDep, New Zealand index of deprivation (1 is least deprived) NZEO, New Zealand European Other; NZHS, New Zealand Health Survey
Source: MPI companion report 2016[8]; Table 3

Children

Pre-mandatory fortification results came from the 2002 New Zealand Children's Nutrition Survey which found an MUIC of 66 µg/L in children aged 5-14 years.[128]

Post-mandatory fortification, the median was 116 µg/L. The post-mandatory fortification results were obtained from samples collected by Jones et al.[31] In this study, 415 children (aged 8-10 years) were recruited from Auckland and Christchurch. Single sex schools and schools of less than 100 children were excluded. All schools in Christchurch (38) and the majority of schools in the Auckland region (60 of 69) were invited to participate and between 60 and 100 information packs were distributed by the school to classes in the target age. Eleven Auckland schools and seven Christchurch schools participated. The majority of children attended schools located in high socio-economic areas. Serum thyroglobulin collected with a fingerprick sample had a median result of 8.7 µg/L and confirmed adequate iodine status.[129]

The assessment of the implementation of mandatory iodine in New Zealand was limited by several factors. These included variations in the iodine content of bread, different approaches to the assessment of intake in adults, and a potentially non-representative sample for children post-mandatory fortification. Taken together this limited the demonstration of implementation.

6.4.3 Review of other studies

Brough et al.[130] compared two cross-sectional studies conducted in Palmerston North. Lactating and pregnant (in the third trimester) women were recruited, via advertising either in the maternity provider or in the community (newspaper or website). Recruitment was undertaken in 2009 and 2011; there was a statistically significant increase in the MUIC but not to the level required for adequate iodine nutrition. Iodine supplement use was also higher in the post-mandatory fortification period (Table 73).

Table 73: Pre and post-mandatory fortification MUIC for pregnant and breastfeeding women

Recruitment	Status	Number	MUIC µg/L	Below EAR (%)	Using iodine supplement (%)
2009 (Pre-mandatory fortification)	Pregnant	25	47	80%	16%
2009 (Pre-mandatory fortification)	Lactating	32	34		19%
2010 (Post-mandatory fortification)	Pregnant	34	85	26%	70%
2010 (Post-mandatory fortification)	Lactating	36	74		36%

Abbreviations: EAR, estimated average requirement; MUIC, median urinary iodine concentration
Source: Brough 2015[130]; Table 2, Table 3

6.5 Evaluation of policy objective (addressing iodine deficiency)

The evaluation criteria were specified in the 2005 expert public health advice, and Box 2 from the expert public health advice is replicated in Table 8 (in Section 3.5.1). The criteria were effectiveness, equity, efficiency, certainty, feasibility and sustainability.

The 2005 expert public health advice assessed the relative usefulness of each of the potential strategies for iodine fortification. These strategies included mandatory fortification, voluntary fortification, supplements, dietary education and the status quo. The strategy of mandatory iodine fortification was considered the most effective public health strategy (see Table 49).

Mandatory iodine fortification was not expected to satisfy the requirements for iodine in pregnancy but, because the assessment was intended to reflect the nutrition needs of the population, the measure was included in the indicators of effectiveness. While women of childbearing age and children are the subgroup of interest for mandatory iodine fortification, pregnant women also have iodine requirements.

Some indicators were absolute, that is, without a comparative element. Others were designed to be compared to the pre-mandatory fortification suite of policies. The estimation of comparative differences requires two results (one for pre-mandatory fortification and one for post-mandatory fortification) that are valid for comparative purposes. For the purposes of this Report, the pre-determined indicators were assessed against the policy objective of addressing iodine deficiency at a population level.

For completeness, additional evaluations were conducted regarding food composition and nutrient intake.

6.5.1 Methodology

The same indicators were used for the New Zealand mandatory iodine fortification initiative as for the Australian initiative, but the data sources were altered to the appropriate New Zealand data (Table 74).

Table 74: Evaluation criteria and indicators for mandatory iodine fortification

Criteria	Question/indicator	Absolute or comparative	Threshold for success (and data source) Table number in this Report
Achievement of policy objective (also included in measures of effectiveness)	Was the population status with mandatory iodine fortification satisfactory	Absolute	Was the population iodine status adequate? (MPI companion report[8]) (Table 72)
Effectiveness	Were nutrition needs satisfied by mandatory iodine fortification?	Absolute	Was the iodine intake of women of childbearing age satisfactory? (2013 MPI report?[127]) (Table 71) Was the iodine intake of pregnant women sufficient? (2013 MPI report[127]) (Table 71) Was the iodine intake of lactating women sufficient? (2013 MPI report[127]) (Table 71) Was the iodine intake of children aged 5-14 years sufficient? (2014 MPI report[126]) (Table 71) Was the iodine intake of all people sufficient? (AIHW report[7]) (Table 71)
Effectiveness	Was the population status with mandatory iodine fortification satisfactory	Absolute	Was the population iodine status adequate? (MPI companion report[8]) (Table 72) Was the iodine status of the population of pregnant women adequate? (MPI companion report[8]) (Table 72) Was the iodine status of the population of women aged 16-44 years adequate? (MPI companion report[8]) (Table 72) Was the iodine status of the population of children aged 8-10 years adequate? (MPI companion report[8]) (Table 72)
Effectiveness	Was mandatory iodine fortification more effective at satisfying the nutrition needs than	Comparative	Was there a reduction in the portion of the women of childbearing age with inadequate iodine intake from the pre-mandatory fortification period to the post-mandatory

Criteria	Question/indicator	Absolute or comparative	Threshold for success (and data source) Table number in this Report
	the alternative?		fortification period? (2013 MPI report[127]) (Table 71) Was there a reduction in the portion of 5-14-year-old children with inadequate iodine intake from the pre-mandatory fortification period to the post-mandatory fortification period? (2014 MPI report[126]) (Table 71)
Effectiveness	Was mandatory iodine fortification effective at addressing population level iodine deficiency compared to the alternative?	Comparative	Was there a change in the iodine status of the population? (MPI companion report[8]) (Table 72) Was there a change in the iodine status of the subgroup of women of 16-44 years? (MPI companion report[8]) (Table 72) Was there a change in the iodine status of the subgroup of children aged 5-14? (MPI companion report[8]) (Table 72)
Equity	Does the population have access to foods fortified with iodine with mandatory iodine fortification?	Absolute	Was the iodine in the fortified food at the required level? (AIHW report[7]) (Table 69)
Equity	Is there equity in the distribution of iodine status between socio-economic groups?	Absolute	Was there no statistically significant difference between iodine status between socio-economic status (MPI companion report[8]) (Table 72)
Equity	Were there inequities in the distribution of iodine status between ethnicities?	Absolute	Was there no statistically significant difference between iodine status between ethnicity? (MPI companion report[8]) (Table 72)
Equity	Has access to foods fortified with iodine improved?	Comparative	Has there been an increase in the level of iodine in bread? (AIHW report[7]) (Table 69)
Equity	Has the inequity between socio-economic status been reduced?	Comparative	Was there a reduction in the difference in iodine status between socio-economic status (MPI companion report[8]) (Table 72)
Equity	Has the inequity between ethnicities been reduced?	Comparative	Was there a reduction in the difference in iodine status? (MPI companion report[8]) (Table 72)
Efficiency	Has the strategy been implemented efficiently?	Absolute	Did the Catalyst report demonstrate any avoidable or excess costs? (Catalyst report[6])
Efficiency	Was the strategy the most efficient means of achieving adequate iodine status?	Comparative	Only estimated if efficiency is equal between options- Is the strategy the lowest cost alternative in the economic evaluation to achieve the outcome? (see Section 6.6)
Feasibility	Was the strategy be successfully implemented	Absolute	Were all of the implementation outcomes demonstrated to be achieved as assessed in the implementation section? (see Section 6.4)

Criteria	Question/indicator	Absolute or comparative	Threshold for success (and data source) Table number in this Report
Feasibility	Was the policy objective demonstrated to have been achieved?	Absolute	Was the population iodine status adequate? (MPI companion report[8]) (Table 72)
Feasibility	Was there sufficient quality assurance procedures in place?	Absolute	Were sufficient quality assurance procedures in place as reported in the Catalyst report? (Catalyst report[6])
Certainty	Has the introduction of mandatory iodine fortification delivered iodine to those who need it most	Comparative	Assumed to have increased.
Sustainability	N/A	Absolute	Assumed to have not been demonstrated because of the limited post-mandatory fortification period

6.5.2 Results

In this Report, the policy objective was achieved. The population iodine status was adequate post-mandatory iodine fortification for adults in New Zealand.

The absolute effectiveness of mandatory iodine fortification was demonstrated for some indicators but not others, and also not for all of the population (Table 75). As expected, mandatory iodine fortification did not meet the requirements of pregnant women.

Almost one-third of adults were estimated as having iodine intakes that were below the EAR. This result should be treated with caution because of the method of estimation. The modelling of intake suggested that children have adequate iodine intake.

Mandatory iodine fortification resulted in an adequate iodine status for the total population. However, some subgroups still have mild iodine deficiency. Slightly more than 20% of women of childbearing age (16-44 years) have an iodine level less than 50 µg/L. Therefore, technically, this population subgroup is not iodine sufficient.

Table 75: Absolute indicators for effectiveness of mandatory iodine fortification

Question	Indicator	Result	Conclusion
Was the iodine intake of women of childbearing age sufficient?	Proportion of women aged 18-44 with iodine intake below the EAR for non-pregnant women	39% below EAR (Table 71)	Not demonstrated
Was the iodine intake of women of pregnant sufficient?	Proportion of women aged 18-44 with iodine intake below the EAR for pregnant women	Not assessed	Not calculated but given EAR not achieved for non-pregnant women unlikely to be achieved
Was the iodine intake of lactating women satisfactory?	Proportion of women aged 18-44 with iodine intake below the EAR for lactating women	Not assessed	Not calculated but given EAR not achieved for non-pregnant women unlikely to be achieved
Was the iodine intake of 5-14-year-old children satisfactory?	Proportion of children aged 5-14 with iodine	<1% of children below EAR (Table	Able to be demonstrated (with caveats)

Question	Indicator	Result	Conclusion
	intake below the EAR for 5-14-year-old	71)	
Was the iodine intake of people aged over 15+ satisfactory?	Proportion of adults aged 15+ and over with iodine intake below the EAR	32% below EAR (Table 71)	Not able to be demonstrated
Was the population iodine status adequate?	MUIC	103 µg/ L & 20% cut-off achieved (Table 72)	The level was indicative of adequate iodine nutrition
Was the iodine status of the population of pregnant women adequate?	MUIC	Not reported,	Not able to be demonstrated
Was the iodine status of the population of women aged 16-44 years adequate?	MUIC	104 µg/L & 21% below the cut-off (Table 72)	The level was indicative of iodine intake insufficiency (the cut-off was above 20%)
Was the iodine status of the population of children aged 8-10 years adequate?	MUIC	116 µg/L & 20% cut-off achieved	The level was indicative of adequate iodine nutrition- but not national

Abbreviations: EAR, estimated average requirement; MUIC, median urinary iodine concentration
Source: AIHW report 2016[7], MPI companion report 2016[8]

Compared to the pre-mandatory fortification suite of policies, mandatory iodine fortification was associated with an improvement in indicators of intake for children. Some indicators were not able to be estimated because the pre-mandatory fortification and post-mandatory fortification indicators for adults were conducted using different measures. As mandatory fortification has been demonstrated to improve the iodine status of the population of both adults and children, it is judged to be relatively more effective than the pre-mandatory fortification suite of policies. However, it is not possible to be as certain regarding the results for children due to the lack of a nationally representative sample post-mandatory fortification.

Table 76: Relative indicators for effectiveness for mandatory iodine fortification

Question	Indicator	Result	Conclusion
Was there a reduction in the portion of the women of childbearing age with inadequate iodine intake from the pre-mandatory fortification period to the post-mandatory fortification period?	Change in Proportion of women aged 16-44 years with iodine intake below the EAR for non-pregnant women	Not able to be assessed as the methods were different	Comparison of pre-mandatory fortification and post-mandatory fortification not possible given different measurement of intake
Was there a reduction in the portion of 5-14-year-old children with inadequate iodine intake from the pre-mandatory fortification period to the post-mandatory fortification period	Change in the proportion of children aged 5-14 with iodine intake below the EAR for 5-14-year-old	8% decrease (Table 71)	Able to be demonstrated
Was there a change in the iodine status of the population?	Change in status of population	The population moved from mild iodine deficiency to	Able to be demonstrated in adults

Question	Indicator	Result	Conclusion
		adequate status (Table 72)	
Was there a change in the iodine status of the subgroup of women of 16-44 years?	Change in status of population of women of 16-44 years	The population moved from moderate iodine deficiency to insufficient (Table 72)	Able to be demonstrated
Was there a change in the iodine status of the subgroup of children aged 8-10 years?	Change in status of population of children aged 8-10 years	From mildly deficient to adequate	Demonstrated with caveats

Abbreviations: EAR, estimated average requirement
Source: AIHW Report 2016[7], FSANZ 2016[28]; MPI companion report 2016[8]

The absolute indicators for equity were not met as the results show differences in the MUICs of specific groups. Women in lower New Zealand deprivation index (NZDep) (higher socio-economic status) and New Zealand women of European origin/others were mildly iodine deficient.

Table 77: Absolute indicators for equity

Question	Indicator	Result	Conclusion
Does the population have access to foods fortified with iodine with mandatory iodine fortification?	Was the iodine in the fortified food at the required level?	The iodine level of bread was almost at the required level (Table 69)	Not demonstrated
Was there equity in the distribution of iodine status between socio-economic groups?	MUIC by SES	Those with a lower SES (More disadvantage) had a higher MUIC, for women the higher SES was associated with an MUIC of less than 100 µg/L (Table 72)	Socio-economic status revealed a difference in MUIC and the population status was different for women in different SES
Were there inequities in the distribution of iodine status Ethnicities?	MUIC by Ethnicity?	Maori and Pacific adults had a higher MUIC than the NZEO; NZEO women had an MUIC of less than 100 µg/L (Table 72)	The population iodine status was not the same between Ethnicities

Abbreviations: MUIC Median Urinary Iodine Concentration; SES Socio-economic status
Source: AIHW Report 2016[7]; MPI companion Report 2016[8]

However, some subgroups improved their status from mildly deficient to adequate. Thus, the differences between subgroups have actually increased with mandatory iodine fortification. The results were similar by status between ethnicities and across socio-economic status as measured by the NZ2006 quintiles in the 2008/2009 ANS.[122] The MPI companion report[8] also describes differences in iodine status between groups. However, the gradients across socio-economic status and ethnicity as estimated by MUIC were similar between the two national surveys.

Table 78: Relative indicators for equity of mandatory iodine acid fortification

Question	Indicator	Result	Conclusion
Has access to foods fortified with iodine improved?	Difference in iodine content of bread	The iodine level increased in bread (see Section 6.4)	Improvement in equity of access
Has the inequity between socio-economic status been reduced?	Difference in inequity prior to mandatory fortification and after in population status	Differences in SES population status increased between 2008/2009 ANS and MPI companion report (Table 72)	Not demonstrated- There was no difference in iodine status in the 2008/2009 ANS
Has the inequity between ethnicities been reduced?	Difference in inequity pre and post-mandatory fortification and after in population status	Differences in population status of ethnicities increased between the 2008/2009 and MPI companion report (Table 72)	Not demonstrated

Abbreviations: MUIC Median Urinary Iodine Concentration; SES Socio-economic status
Source: AIHW Report 2016[7]

In New Zealand, generally, the mandatory fortification program is efficient. The Catalyst report[6] did not demonstrate any unexpected costs. The results of the cost-effectiveness analysis model demonstrate that mandatory fortification is associated with an improvement in population iodine status at a small additional cost.

Feasibility of implementation was partly demonstrated (see Section 6.4). The most significant constraint to feasibility was in relation to the demonstration of improvement in the iodine content of bread and of iodine intake in adults. The achievement of the policy objective was demonstrated to be feasible. The Catalyst report[6] concluded that sufficient quality assurance procedures were being conducted (see Section 8.2.2)

Certainty was assumed to have increased because of the increase in the iodine content of bread. However, the increase was not as much as expected.

Sustainability was assumed not to have been demonstrated due to the short period of time post-mandatory fortification.

6.5.3 Discussion of whether policy objective (iodine sufficiency) achieved

Mandatory fortification addressed the re-emergence of iodine deficiency in a manner that the previous pre-mandatory fortification suite of policies. The population subgroup of pregnant and breastfeeding women has not achieved iodine sufficiency as measured by MUIC, as was expected. However, the population subgroup of women aged 16-44 years also did not achieve iodine sufficiency.

Mandatory iodine fortification was effective in producing adequate iodine status at a population level. Comparatively, it improved both the population level MUIC of children which means that the population is no longer classifiable as iodine-deficient by WHO criteria.

Mandatory fortification did not appear to be effective in completely satisfying nutrient requirements, as measured by EAR, for either adults or children. However, comparatively, mandatory fortification is superior to the pre-mandatory fortification suite of policies. The MUIC of all subgroups has increased.

Assessing the impact of mandatory fortification on equity is complicated. In New Zealand, mandatory fortification has resulted in some subgroups with an adequate iodine status at a population level while others have remained mildly deficient.

A comparison of the results of the 2008/2009 and 2014/2015 surveys showed that all age and sex groups had an increased MUIC. However, the increase was not distributed equally over the population, being less in older women.

The lack of information on potentially high-risk populations is an issue. There may be individuals with pre-existing thyroid disorders, co-morbidities or genetic pre-dispositions to adverse effects who have iodine intake below the recommended UL and suffer adverse effects. However, it was not possible to assess the impact of mandatory fortification on these subgroups due to data limitations. Thus, this may represent an inequity that has not been estimated.

Mandatory fortification has resulted in improved equity in relation to the access to fortified foods. Under voluntary fortification, product differentiation may result in fortified foods being more expensive than unfortified foods.

The modelling undertaken in Section 6.5 suggests that mandatory iodine fortification is efficient.

The Catalyst report[6] and AIHW report[7] demonstrated that the mandatory iodine fortification in New Zealand is potentially feasible. However, the availability of information confirming the nutrient intake of adults would be useful in addressing some of the concerns with regard to implementation. Additionally, clarity around the variation observed in the iodine levels of bread would help confirm the feasibility of mandatory iodine fortification in New Zealand.

Mandatory iodine fortification was found to be more sustainable in addressing the re-emergence of iodine deficiency on a population basis than the pre-mandatory fortification suite of policies.

The sustainability of the mandatory fortification initiative in addressing the re-emergence of iodine deficiency on a population basis is superior to the pre-mandatory fortification suite of policies.

However, the history of iodine deficiency re-emerging in developed countries such as Australia and New Zealand after previous successful efforts to address it suggests the sustainability of mandatory initiatives cannot be guaranteed.

The adequacy, on a population level, of the iodine status of adults is borderline. The 20% threshold is almost exceeded, and the MUIC of the population is 103 µg/L. A minimal change in intake would result in the adult population becoming, once again, mildly iodine deficient

The amount of salt used in bread manufacturing may reduce as a result of increased demand for low salt diets. This may already be occurring in New Zealand. If this occurs, the mandated iodine level in salt may need to be reconsidered and increased to ensure sufficient iodine intake. Alternatively, changes in the consumption of bread (either increases or decreases) may require consideration of additional vehicles for fortification.

Monitoring and periodic reconsideration of the level of fortification and the foodstuffs that are fortified is required. The identification and monitoring of high-risk subgroups is also likely to be required to ensure continued sustainability.

6.6 Evaluation of value for money

The purpose of a CBA is to ascertain if the community is better off with one scenario rather than an alternative scenario.[44]

A high-quality CBA was unable to be conducted for reasons outlined in Section 5.6. Consequently, a cost-effectiveness analysis was conducted. The outcome measured was the cost per million people (or more correctly samples) moved from below the appropriate MUIC cut-off to above it (100 µg/L for the majority of the population and 150 µg/L for pregnant women).

An indicative CBA was conducted; the results suggest that small changes in productivity as a result of the introduction of mandatory fortification would result in large benefits (see Section 6.6.10 and Section 6.6.11). That is if fortification results in an adequate iodine status which, in turn, results in an increased IQ and if that increased IQ results in increased productivity, then mandatory iodine fortification would produce more in productivity than it costs to continue the program.

6.6.1 Methods

The methods used to conduct the cost-effectiveness analysis are described in Section 5.6.1 (Methods). A secondary comparative analysis against the Tasmanian voluntary program was not conducted for the New Zealand mandatory iodine fortification initiative.

6.6.2 Assumptions

See Section 5.6.1 for a discussion of the assumptions used in the model. Briefly, the assumptions included no health impacts and no loss of consumer choice.

6.6.3 Population, modelled alternatives and outcomes of interest

The model initially included the population of New Zealand in 2014 and was updated each year according to the population projections published by Statistics New Zealand. Sub-populations within the model are newborns, children <16 years, men aged 16-44 years, non-pregnant women aged 16-44 years, pregnant women and older adults aged ≥45 years.

The two alternatives considered in the economic evaluation are:

- New Zealand with mandatory iodine fortification – mandatory fortification (including the pre-mandatory fortification suite of policies); and
- the counterfactual of New Zealand without mandatory iodine fortification – no mandatory fortification (retaining the pre-mandatory fortification suite of policies).

The outcomes of interest identified for the base case economic evaluations included changes in the proportion of people with urinary iodine concentration ≥100 µg/L (for children and non-pregnant adults) and the proportion of pregnant women with urinary iodine concentration ≥150 µg/L. These thresholds were used as the measure of outcome in the base case because they were the outcomes of interest in evaluation the initiative's success. A societal perspective was used for the economic evaluation.

6.6.4 Linked cost-effectiveness extensions

Two extensions to the cost-effectiveness analysis were undertaken. In the first extension, the outcome of interest measured was the incremental difference in the human capital attributable to mandatory fortification compared to the pre-mandatory fortification suite of policies. Given the use of MUIC (a population measure) and the lack of evidence about the treatment effects associated with a change in MUIC, the results obtained using outcome are subject to considerable uncertainty. The clinical evidence is discussed in Section 8.7.

In the second extension, the improvement in human capital was monetarised into a difference in productivity that could be attributable to an improvement in human capital. A literature review of previous studies which used econometric methods to investigate a link between changes in IQ and productivity was undertaken and is reported in Section 8.7. The monetarisation of human capital (including IQ changes) associated with small changes in human capital is subject to considerable uncertainty and limited external validity.

6.6.5 Decision analytic framework

The model structure is presented in Figure 6. Essentially the population is divided into six main groups as outlined in Section 6.6.3. Source information about iodine status was not broken down by the same age categories as required in the model. In these cases, a weighted average of the iodine status of available age categories was calculated based on the number of people per age category as reported by Statistics New Zealand.

A Markov model was constructed with a cycle length of 1 year, 70-year time horizon and 5% discount rate for costs. The health states are "healthy", "elevated autoantibodies", "hypothyroidism (unmonitored)", "hypothyroidism (monitored)", "Hashimoto disease" and "cretinism". For the base case only the health state "healthy" was included. Mortality is modelled implicitly by using population projections to derive the proportion of people per age group over time.

The model uses a 70-year time horizon to allow for maternal iodine status to impact the development of human capital in newborns and its financial impact during their adult working life. Given the lack of reliable data on this effect, this was not included in the base case.

Transition probabilities are based on urinary iodine status for children and adults, and maternal urinary iodine status for newborns. The probability of iodine-associated adverse effects is assumed to be transitory, meaning it was assumed to have a temporary effect in the first year after mandatory fortification was introduced. Given the lack of reliable data on adverse effects and iodine deficiency disorders, these were excluded.

Urinary iodine status for the different population subgroups differed before and after the introduction of mandatory fortification.

6.6.6 Model inputs

Health outcomes

Table 79 provides the urinary iodine status and fitted gamma distributions for children before and after the introduction of mandatory iodine fortification.

Table 79: UIC distributions of children

UIC of children	Median UIC provided (µg/L)	Other UIC information provided (µg/L)	Median from gamma distribution (µg/L)	Mean from gamma distribution ((µg/L))	SD
New Zealand pre-mandatory fortification[31]	68	UIC <50 µg/L: 29% UIC <100 µg/L: 82%	68	73	35
New Zealand post-mandatory fortification[31]	116	UIC <50 µg/L: 5% UIC <100 µg/L: 38%	116	124	54

Given that the MPI companion report broke iodine status down by different age groups (15-18, 19-30, 31-50 years), a weighted average of the iodine status of these age groups was taken to inform the model based on population size data from Statistics New Zealand.
Note: the UIC for pregnant women in post-mandatory fortification period was from the 2014/2015 NZHS but was not reported in the MPI Companion report
Abbreviations: IQR, interquartile range; UIC, urinary iodine concentration

Table 80: UIC distributions of men (aged 16-44 years)

UIC of men aged 16-44	Median UIC provided (µg/L)	Other UIC information provided (µg/L)	Median from gamma distribution (µg/L)	Mean from gamma distribution ((µg/L))	SD
New Zealand pre-mandatory fortification[8]	54	UIC <50 µg/L: 44% UIC <100 µg/L: 80%	54	64	45
New Zealand post-mandatory fortification[8]	111	UIC <50 µg/L: 14% UIC <100 µg/L: 43%	111	126	77

Given that the MPI companion report broke iodine status down by different age groups (15-18, 19-30, 31-50 years), a weighted average of the iodine status of these age groups was taken to inform the model based on population size data from Statistics New Zealand.
Note: the UIC for pregnant women in post-mandatory fortification period was from the 2014/2015 NZHS but was not reported in the MPI Companion report
Abbreviations: IQR, interquartile range; UIC, urinary iodine concentration

Table 81: UIC distributions of women (aged 16-44 years)

UIC of men aged 16-44	Median UIC provided (µg/L)	Other UIC information provided (µg/L)	Median from gamma distribution (µg/L)	Mean from gamma distribution ((µg/L))	SD
New Zealand pre-mandatory fortification[8]	48	UIC <50 µg/L: 52% UIC <100 µg/L: 81%	48	61	50
New Zealand post-mandatory fortification[8]	104	UIC <50 µg/L: 21% UIC <100 µg/L: 48%	104	126	94

Given that the MPI companion report broke iodine status down by different age groups (15-18, 19-30, 31-50 years), a weighted average of the iodine status of these age groups was taken to inform the model based on population size data from Statistics New Zealand.
Note: the UIC for pregnant women in post-mandatory fortification period was from the 2014/2015 NZHS but was not reported in the MPI Companion report
Abbreviations: IQR, interquartile range; UIC, urinary iodine concentration

Table 82: UIC distributions of pregnant women

UIC of pregnant women	Median UIC provided (µg/L)	Other UIC information provided (µg/L)	Median from gamma distribution (µg/L)	Mean from gamma distribution ((µg/L))	SD
New Zealand pre-mandatory fortification[131]	38	IQR: 24-56	38	43	25
New Zealand post-mandatory fortification[8]	114	UIC <50 µg/L: 21% UIC <100 µg/L: 45%	114	148	126

Given that the MPI companion report broke iodine status down by different age groups (15-18, 19-30, 31-50 years), a weighted average of the iodine status of these age groups was taken to inform the model based on population size data from Statistics New Zealand.
Note: the UIC for pregnant women in post-mandatory fortification period was from the 2014/2015 NZHS but was not reported in the MPI Companion report
Abbreviations: IQR, interquartile range; UIC, urinary iodine concentration

Table 83: UIC distributions of adults aged 45 years and over

UIC of aged 45 years and over	Median UIC provided (µg/L)	Other UIC information provided (µg/L)	Median from gamma distribution (µg/L)	Mean from gamma distribution (µg/L)	SD
New Zealand pre-mandatory fortification[8]	58	UIC <50 µg/L: 44% UIC <100 µg/L: 75%	58	72	57
New Zealand post-mandatory fortification[8]	95	UIC <50 µg/L: 22% UIC <100 µg/L: 51%	95	116	87

Given that the MPI companion report broke iodine status down by different age groups (15-18, 19-30, 31-50 years), a weighted average of the iodine status of these age groups was taken to inform the model based on population size data from Statistics New Zealand.
Note: the UIC for pregnant women in post-mandatory fortification period was from the 2014/2015 NZHS but was not reported in the MPI Companion report
Abbreviations: IQR, interquartile range; UIC, urinary iodine concentration

6.6.7 Costs

Cost of fortification initiative

The costs for the mandatory iodine fortification initiative include those incurred by industry (salt manufacturers, bakers) and government.

Industry

The Catalyst report[6] reviewed the costs incurred by industry for iodine fortification in Australia and New Zealand. Table 84 presents the number and type of organisations interviewed.

Table 84: Organisations approached in iodine fortification review in New Zealand

Organisation in New Zealand	Number approached	Number participating
Enforcement agency[a]	1	1
Bakers	10	7
Salt manufacturers	1	1
Total	**12**	**9**

Source: Catalyst Report 2015[6]; page 7

The projected costs and realised costs reported by industry members are presented in Table 87.

Table 85: Anticipated and realised (undiscounted) cost impacts of iodine fortification

Entity	Timing	Projected costs, $NZD (2007)	Realised costs, $NZD (2014)	Modelled costs, $NZD (2014)
Salt manufacturer	Up-front	303 000	666 000	104 022
Salt manufacturer	Ongoing[a]	20 000	NA[b]	40 166
Baking	Up-front	1 500 000	300 000	300 000
Baking	Ongoing[a]	30 000	Minimal	110 100
Government	Up-front	8 000	NA	NA
Government	Ongoing[a]	89 000	NA	NA

a per annum. b Unable to determine at aggregated level; Abbreviations: NA, not available; $NZD, New Zealand dollars

Up-front costs to salt manufacturers

In the review by Catalyst, up-front costs for salt manufacturers were estimated to be $AUD 666 000 in total. Since the model requires these costs to be divided between Australia and New Zealand, they were allocated based on population size. Given the population sizes in December 2014 and the purchasing power parities (PPPs) for Australia (1.47) and New Zealand (1.42), up-front costs for salt manufacturers were $NZD 104 022 in New Zealand.

Ongoing costs to salt manufacturers

Table 61 shows that the review by Catalyst was unable to determine the ongoing costs to salt manufacturers at aggregated level. The review provided three different estimates of the direct ongoing costs/tonne of salt: $AUD 4.00, $AUD 19.00 and $AUD 45.00. The review also estimated that ~8 500 tonnes of iodised salt were used in bread in Australia. Multiplied by the cost per tonne of salt, this results in $AUD 34 000 to $AUD 382 500 for iodised salt for the use in bread in Australia. The base case will assume the mean costs of $AUD 208 250. Since information about the quantity of salt being used in bread in New Zealand is unknown, it was assumed proportional to the quantity of salt being used in bread in Australia. Given the difference in population size and PPPs (see the previous paragraph), the ongoing costs for salt manufacturers were assumed to be $NZD 40 166 in New Zealand.

Up-front baking costs

The review by Catalyst estimated the up-front baking costs to range between $AUD 25 000 and $AUD 2 700 000, covering changes for both the iodine and the folic acid fortification programs. Costs were assumed to be an average $NZD 300 000 for New Zealand.

Ongoing baking costs

The review by Catalyst estimated the ongoing baking costs to be $AUD 0.19 to $AUD 0.60 (mean $AUD 0.395) per tonne of bread. Assuming 288 549 tonnes of bread in New Zealand results in a total of $NZD 110 100 in New Zealand.

Government

Government costs, the costs associated with the enforcement agencies, were assumed to be zero. As discussed in the Catalyst report[6] these resources were not increased, and the enforcement agencies managed the additional workload within current resources. This assumption does not identify the opportunity cost. However, the enforcement of the mandatory fortification initiatives is taking place within a larger quality assurance framework, and the marginal cost of adding a single activity may be minimal.

6.6.8 Model results

Table 86 provides the total costs and effects of iodine fortification for New Zealand over a 1-year, 10-year and 70-year horizon. These include the up-front costs needed to implement the fortification program. Since these up-front costs cannot be regained (they are "sunk costs"), it is also valuable to evaluate the ongoing costs and effects, i.e. the costs and effects of continuing with the current program. These are provided in Table 87.

Table 86: Iodine cost-effectiveness results including sunk costs, New Zealand

Horizon	Measure	Pre	Post	Incremental
1-year horizon	Costs in $NZD	0	554 288	554 288
1-year horizon	Proportion of population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	0.21	0.54	0.32
1-year horizon	Incremental costs ($NZD) per percentage point increase in the proportion of the population with UIC ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	-	-	17 183
10-year horizon	Costs in $NZD	0	1 622 354	1 622 354
10-year horizon	Proportion of population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	0.21	0.54	0.32
10-year horizon	Incremental costs ($NZD) per percentage point increase in the proportion of the population with UIC ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	-	-	50 293
70-year horizon	Costs in $NZD	0	3 460 840	3 460 840
70-year horizon	Proportion of population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	0.21	0.54	0.32
70-year horizon	Incremental costs ($NZD) per percentage point increase in the proportion of the population with UIC ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	-	-	347 604

Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis
Abbreviations: $NZD, New Zealand dollars

Table 87: Iodine cost-effectiveness results, excluding sunk costs, New Zealand

1-year horizon, New Zealand	Pre	Post	Incremental
Costs in $NZD	0	150 266	150 266
Proportion of population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	0.21	0.54	0.32
Incremental costs ($NZD) per percentage point increase in the proportion of the population with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)			4 658
Population size, New Zealand (2014)			4 509 680
Incremental number of New Zealanders with urinary iodine concentration ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)			1 454 742

1-year horizon, New Zealand	Pre	Post	Incremental
Yearly cost ($NZD) of improving iodine status of 1 000 000 New Zealanders from below to above ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)			103 294

Abbreviations: $NZD, New Zealand dollars

6.6.9 Scenario Analyses

Two scenario analyses to assess the impact of assuming no upfront costs. These were:

1. upfront costs (sunk costs) included in the post-mandatory fortification with no fortification cost in the pre-mandatory period, representing the situation in 2009; and

2. upfront costs (sunk costs) included in the pre-mandatory fortification with no fortification cost in the post-mandatory period, representing the situation if mandatory iodine fortification was terminated.

Upfront costs of fortification

The impact of sunk costs is presented in Table 88. As expected, the impact was to increase the cost of the alternative to which with the sunk cost is attributed.

Table 88: Iodine cost-effectiveness scenario analyses, New Zealand

Yearly cost ($NZD) of improving iodine status of 1 000 000 moved from below to above ≥100 µg/L (non-pregnant) or ≥150 µg/L (pregnant)	New Zealand ($NZD)
Sunk costs applied to the mandatory iodine fortification alternative	381 022
Sunk costs apply to the no mandatory fortification alternative	Mandatory fortification is dominant

Abbreviations: $NZD, New Zealand dollars

6.6.10 First linked extension: From iodine sufficiency to human capital

The link between iodine sufficiency and measures of human capital is discussed in Section 8.7. In summary, the relationship between iodine insufficiency and changes in IQ is well established in severe iodine deficiency. This relationship, however, is less well established in mild iodine deficiency.

There are two populations of interest in considering the relationship between iodine sufficiency and human capital. The populations studied are children and pregnant women (where the UIC is studied in both subgroups). The outcomes are measured in children in both situations.

Modelling issues

The key modelling issues are discussed in Section 5.6.10. The differences between the New Zealand and Australian iodine models are the parameters.

The portion that benefits from an increase in iodine intake

Using the proportion of children with a modelled UIC <100 µg/L before fortification approximately 32% of New Zealand children would benefit from fortification (82% minus 50%). For non-pregnant women, this is approximately 31% (81% minus 50%). For pregnant women (UIC <150 µg/L), it is approximately 25%.

The size of the improvement

The size of the human capital improvement is presented in Section 8.7. The impact ranges from 0 to 2.5 IQ points (mean 1.2, median 1.15). A midrange of 1.2 IQ points is assumed (see Table 101).

6.6.11 Second linked extension: From human capital to productivity increase

For the purposes of this Report, it was assumed that an increase in wages represents an increase in productivity.

The potential increase in an individual's annual wages is assumed to be 0.4% per IQ point increase (see Section 8.7.3, Table 105). A conservative value, approximately half of the 0.9% was used because of the substantial uncertainty. In New Zealand, in June 2014, the average weekly earnings from wages and salary is NZD 991,[132] which corresponds to an annual figure of $NZD 51 532. The participation rate was age-adjusted by Statistics NZ data for ages 15-65 years.[133] The largest potential benefit is presented in Table 89 below adjusting for fortification starting with pregnancy (one year before birth). These benefits are compared to the total costs of fortification per child born. These numbers are highly speculative and should be treated with caution. However, the benefits, as calculated are much larger, than the costs.

Table 89: Benefit of human capital development for New Zealand

Measure	Result	Source
IQ Change per benefited individual	1.2	Section 8.7
Percentage increase per IQ point	0.4%	Section 8.7
Average Wage (annual)	$NZD 51 532	Statistics New Zealand[132]
Total lifetime wage change adjusted for timing and age-adjusted participation	$NZD 1 596	Statistics New Zealand[133]
Portion of children benefiting	0.25	Table 79
Average benefit per child	**$NZD 399**	-
Average cost of fortification per new child (pregnancy) without sunk costs	$NZD 3	Table 86
Average cost of fortification per new child (pregnancy) with sunk costs	$NZD 9	Table 87

Discounting is performed to reduce the value of costs and events that occur in the future, 5% per annum is used in this analysis
Abbreviations: $NZD, New Zealand dollars

6.6.12 Limitations of the economic evaluation

The economic evaluation assumed that all changes in urinary iodine concentration before and after mandatory fortification were due to this initiative. In reality, part of the improvements may have been due to other factors, for example, changes in the use of iodine supplementation or changing dietary habits. The introduction of subsidised iodine tablets in 2010 may have been responsible for some of the increase in the MUIC of pregnant women.[130]

The economic evaluation did not include the effect of changes in iodine status on the incidence of iodine deficiency disorders (e.g. cretinism) and/or potential adverse effects (e.g. elevated autoantibodies, Hashimoto's, hyperthyroidism). Some of these impacts may have been transient and therefore could be treated as sunk costs.

The monitoring framework did not include collecting data on health impacts. Available evidence on the impact of fortification on iodine deficiency disorders (for mildly deficient populations) and adverse effects was limited and ambiguous. Therefore, outcomes were presented in terms of (costs per) proportion of the population moving to iodine levels ≥100 μg/L (non-pregnant) or ≥150 μg/L (pregnant), instead of (costs per) quality-adjusted life year gained.

The results of the study by Jones et al.[31] conducted in 8-10-year-old New Zealand children was used to inform the modelling for all children. These results may not be representative of children of other ages as the MUIC of children decreased with age in the Australian data.[7] A similar distribution of results might occur in the New Zealand children.

6.6.13 Summary of the economic evaluation

The incremental cost-effectiveness ratio per million people moved from a UIC of below 100 μg/L to over 100 μg/L is $NZD 103 294 per year.

The two extensions of the base case linked the health outcome of interest (the change in the population's iodine sufficiency) to economic outcomes. The first link was from the health outcome to human capital. This link estimated the human capital benefit, as measured by IQ.

The second link was to monetarise or value the change in human capital as an increase in society's productivity. The results of these linked extensions suggest that the value of additional productivity produced by mandatory fortification of iodine exceeded the cost of the initiative.

Both links have significant limitations that result in the final estimation being unreliable for decision making. There are no high quality studies which measure the expected increase in human capital due to the improvement in mild population level iodine deficiency. The external validity of the econometric studies to the New Zealand population is questionable. The assumption that individual wage changes are an appropriate measure of productivity increases is also not confirmed. Taken together these limitations mean that the monetarisation of changes in population level iodine studies is likely not to be useful for decision making.

However, the cost of mandatory iodine fortification is small compared to the potential gains in productivity. If these gains occurred, then mandatory iodine fortification would represent value for money. Likewise, if mandatory iodine fortification improved health-related quality of life, it would also represent value for money.

6.7 Conclusion

6.7.1 Evaluation of implementation

The implementation of mandatory iodine fortification was partly but not completely demonstrated. Different approaches were used to assess intake in the pre and post-mandatory fortification periods, and there was variation in the iodine content of bread. The use of non-nationally representative surveys in children was a limitation.

6.7.2 Evaluation of policy objective (iodine sufficiency)

Mandatory iodine fortification in New Zealand achieved its policy objective of addressing the re-emergence of mild iodine deficiency.

The post-mandatory fortification data demonstrated that the population's iodine status was adequate. This was on the basis of a comparison of the results of two large national surveys. The relative efficiency of mandatory iodine fortification was demonstrated albeit within an analytic framework of low internal validity. As expected, mandatory iodine fortification did not meet the requirements of pregnant or breastfeeding women. It was also not demonstrated that the iodine status of women aged 16-44 years was adequate or that intake was sufficient. However, comparatively, mandatory fortification was superior to the pre-mandatory fortification suite of policies.

The equity of mandatory iodine fortification was not well demonstrated. Although there were improvements in MUIC post-mandatory fortification, not all subgroups had an adequate iodine status post-mandatory fortification.

The lower than expected iodine content of bread in some of the surveys means that the criterion of certainty is subject to limitations.

Sustainability has not been demonstrated due to the short period of time post-mandatory fortification. There is also the potential for changes in manufacturing practices and food consumption to occur in the future that may impact on iodine intake and therefore population iodine status. The lower than expected level of iodine in bread also has implications for sustainability.

6.7.3 Evaluation of value for money

The assumptions required and the data limitations meant that a robust CBA was not able to be conducted. The lack of health-related outcomes is a significant limitation with regard to the economic evaluation.

The incremental cost-effectiveness ratio per million people moved from a UIC of below 100 µg/L to over 100 µg/L is $NZD 103 294 per year. The value of these changes in biomedical measures was not able to be estimated.

Only small changes in productivity or health-related quality of life are required before the benefits exceed the costs of mandatory iodine fortification.

These results should be interpreted cautiously, all three evaluations (implementation, policy objective and value for money) were conducted in a pre-post framework. The use of a reference population controls for demographic change. But other confounders were not controlled for. In New Zealand, other policies with regard to iodine supplementation were changing at the same time.[8] This will impact on the modelling of the effectiveness of mandatory fortification in pregnant women. The impacts of iodine fortification on susceptible individuals were not able to be assessed as part of the evaluation due to a lack of morbidity data. Additionally, the health improvements associated with the improvement in population iodine status were not able to be assessed in this Report.

7 Monitoring framework and recommendations

7.1 Monitoring framework adequacy

AHMAC approved a five-step framework to monitor the outcomes of mandatory fortification (for folic acid and iodine). The five key monitoring areas were:

1. Food composition and food industry compliance
2. Nutrient intake
3. Nutrient Status
4. Health Benefits
5. Adverse health effects

This Report assessed the framework as being a logical and consistent means of monitoring implementation, flowing from food composition to the health benefits. The first four key monitoring areas proved compatible with a stepwise approach to evaluating implementation.

While the framework was logical and consistent, the application of the framework, and in particular data limitations, impacted on the resulting evaluation of the mandatory folic acid and iodine fortification initiatives. These limitations included both a lack of data and the validity, representativeness and capacity for comparison of the available data.

The earlier decision not to collect data to enable monitoring of potential adverse health effects proved to be the most challenging issue to address in terms of the independent evaluation required for the purposes of this Report. While no conclusive evidence was identified of any adverse effects or safety issues associated with mandatory folic acid fortification, the same cannot be said for mild thyroid abnormalities associated with mandatory iodine fortification. These potential adverse health effects were identified as an issue prior to the introduction of mandatory iodine fortification.[10] Their omission from the monitoring framework was a weakness that flowed from the AIHW report[7] and therefore could not be remedied in this Report.

The majority of the results reported involved a comparative exercise. That is, the impact of mandatory fortification was compared to the alternative of no mandatory fortification. The lack of comparability in the available data was another weakness in applying the framework, as identified in Sections 3, 5 and 6. Limitations with validity and representativeness are outlined in Sections 3, 5 and 6 of this Report. The lack of complete national information about the identified health impacts of mandatory folic acid fortification, that is, the decrease in NTDs, remains a concern.

A requirement for this Report was the identification and review of any unexpected outcomes of mandatory fortification. However, the limited data collected under the monitoring framework constrained the capacity to describe any unexpected health outcomes. Pre-specification of the adverse effects as the meta-analysis of cancer risk in folic acid supplementation trials limited the ability to assess unexpected outcomes. Except for NTDs and MUIC levels, there was no collection of data about health outcomes in Australia or New Zealand.

However, none of the literature searches regarding the safety of mandatory fortification has identified any adverse health effects in Australia or New Zealand. Other articles reviewed which outlined the introduction of mandatory iodine fortification in New Zealand and mandatory folic acid and iodine fortification in Australia did not discuss any unexpected effects or health impacts. However, it is not possible to be certain that no unexpected impacts on health occurred.

The monitoring framework was less adequate in informing the evaluation of the performance of the mandatory fortification initiatives against the six pre-determined policy criteria and the initiatives value for money. The health outcome of reducing NTDs was easily identifiable, measurable and quantifiable. The exact portion of the decrease in NTDs attributable to mandatory folic acid fortification initiative, as opposed to the trend, is uncertain, due to the presence of confounders, which were not measured as part of the monitoring framework.

The health outcome of addressing the re-emergence of iodine deficiency was identifiable and potentially measurable (on a binary basis). It was difficult, however, to quantify the outcomes of value associated with mandatory iodine fortification beyond success or failure. This difficulty extended to the monetarisation of the health impacts of mandatory iodine fortification, a substantial weakness that impacted on the CBA. Additionally, there remains a lack of knowledge about both the costs of monitoring and efforts to encourage iodine intake, undertaken by public health organisations, as distinct from monitoring costs incurred by the government.

7.2 Observations and AIHW recommendations

To gain the greatest usefulness from a CBA or economic evaluation, the broad analysis, synthesis and interpretation of findings should be determined prior to data collection. This ensures appropriate data collection is undertaken and should start with the identification of benefits. Benefits should not be restricted to the policy objectives but should extend to broader health gains, if health gains are intended to be assessed post-implementation.

Should a CBA be envisaged at a later stage, the broad outcomes to be monetarised in the economic evaluations should also be identified prior to the intervention and evaluation. Consideration of a reference model ex-ante to be used ex-post should be undertaken.

The AIHW report,[7] published in 2016, included twelve suggestions regarding the next steps in assessing the future health impact of the mandatory fortification initiatives. These are considered by the AIHW to be key data requirements for ongoing monitoring[7]:

1. Up to date data on the levels of folic acid and iodine in bread;
2. Investigation as to why current iodine levels in bread in New Zealand are less than anticipated;
3. Up to date data on the foods being consumed by the Australian and New Zealand populations;
4. Consistency between national nutrition surveys;
5. Better quantification of discretionary salt use;
6. Specific monitoring of subpopulations at risk;
7. Regular consumer attitudes survey regarding mandatory fortification;

8. Further analysis on folate status to determine whether if it can be used to compare against the cut-off for NTD-risk;

9. Assessment of the upcoming national nutrition survey data in New Zealand would provide a more complete picture of iodine intake and iodine status of New Zealand population;

10. The inclusion of NTD data for Victoria;

11. Ongoing monitoring of NTDs across all jurisdictions; and

12. Ongoing monitoring of iodine status in Australia and New Zealand

The AIHW's suggestions are logical and, if implemented, would address several of the problems identified in this Report. The national nutrition survey data for New Zealand (the MPI companion report[8]) was published prior to this Report and was included in this Report's evaluation in Section 6.

7.3 Recommendations

Recommendation 1: Robust ongoing monitoring should occur to ensure the continued effectiveness of the mandatory fortification initiative

Robust ongoing monitoring is required to:

- ensure an adequate folic acid and iodine status in the population;
- assess and evaluate evidence that mandatory fortification continues to be the most appropriate strategy; and
- develop epidemiological evidence to confirm or refute hypotheses of potential adverse effects.

Recommendation 2: The mandatory folic acid initiative should be reviewed using a complete national data set, and with a longer follow-up period.

The continued benefits of mandatory fortification can only be determined through ongoing monitoring.[18] As the total population reaches sufficiency in intake of iodine and folic acid, the identification of subgroups at risk becomes more important in ensuring equity. The monitoring framework should be able to identify these subgroups and monitor their folic acid and iodine status appropriately. The use of NTDs and MUIC may not necessarily be the most appropriate way to achieve this outcome in the future.

Any CBA is dependent on high quality data and assessment of the value of the outcomes. The data limitations described in Section 7.1 of this Report flowed through to the cost-benefit analyses.

Any future economic evaluations would benefit from having available data that facilitates a robust assessment of the magnitude of the difference between mandatory fortification initiatives and pre-mandatory fortification suite of policies.

Identifying the outcomes of interest for the CBA (not only the policy objectives) should be considered prior to data collection. The outcomes of interest should not be restricted to health-related outcomes. The issue of loss of consumer choice is particularly important when a population as a whole receives an intervention, but the benefit is confined to a narrower subgroup (as in mandatory folic acid fortification). Research and data collections may have to consider these larger issues.

Constructing an economic model prior to data collection would also facilitate identification of key data requirements. A reference model would allow comparison of the ex-ante predictions and the ex-post reality.

Four additional recommendations for mandatory folic acid and iodine fortification initiatives follow below.

Recommendation 3: Consider conducting periodic evaluations to ensure the mandatory folic acid fortification initiative continues to demonstrate effectiveness and value for money. An interrupted time series analysis would potentially be an appropriate design for such an evaluation.

Recommendation 4: Consider undertaking research into the changes in NTD rates by socio-economic status to inform the distribution of burden, post-mandatory folic acid fortification.

Recommendation 5: Consider research to establish the importance and magnitude of the loss of consumer surplus associated with restricted choice in mandatory folic acid and iodine fortification.

Recommendation 6: Consider research to establish the value for money of avoiding mild iodine deficiency in the Australian and New Zealand populations.

Eight additional recommendations for future evaluations of micronutrient fortification follow below.

Recommendation 7: Consider the requirement for comparable nationally representative data sets prior to the commencement of any future mandatory fortification initiative and ensure appropriate data are collected.

Recommendation 8: Consider the requirement for data on important or at risk subgroups prior to any future mandatory fortification initiative.

Recommendation 9: Consider the requirement for data on health-related outcomes, especially adverse effects in high-risk subgroups, prior to any future mandatory fortification initiative.

Recommendation 10: Consider the framework and requirements for data in the economic evaluation prior to introducing any future mandatory fortification initiative.

Recommendation 11: Consider whether a cost-benefit or a cost-effectiveness analysis is the preferred economic evaluation when deciding on evaluation criteria for any future mandatory fortification initiative.

Recommendation 12: If a cost-benefit analysis is the preferred type of economic evaluation of any future mandatory fortification initiative, consider the importance of non-health sources of value in the evaluation criteria.

Recommendation 13: Decide on how effectiveness should be assessed (including the statistical approach) prior to any future mandatory fortification initiative, and consider the issue of confounding and the weakness of a pre-post analysis prior to data collection.

Recommendation 14: Consider the use of an ex-ante model to allow comparison to the estimations prior to any future mandatory fortification initiative.

8 Supporting information

8.1 Folic acid and iodine

8.1.1 The importance of folate/folic acid for neural tube defect prevention

NTDs can be serious birth defects of the spine and brain.[33] These defects are caused by a disruption of the development of the spinal cord and brain. They include anencephaly, encephalocoele and spina bifida. Spina bifida is the most common of the NTDs. It occurs when the lower part of the neural tube fails to close completely during the development of the fetus. Encephalocoele and anencephaly are the results of the failure of the upper part of the neural tube (which develops into the brain) closing.

Neural tube defects can result in stillbirths and babies born with NTDs are at a high risk of infant mortality. Moreover, survivors often suffer a decrease in health-related quality of life and require lifelong health care and social care.[30]

A relationship between folate/folic acid and NTDs was recognised in the 1960s. To an extent NTDs are a preventable form of morbidity and mortality.[33] Estimates of the proportion of preventable NTDs range from 50% to over 70% and are based on randomised controlled trials (RCT) level evidence.[37] However, a proportion of NTDs are caused by genetic or other environmental factors and are not responsive to folic acid.[134]

8.1.2 Overview of situation leading to mandatory folic acid fortification in Australia

The majority of NTDs are potentially preventable with the use of supplementary folic acid prior to and during the early stages of pregnancy. However, women can have an inadequate folic acid intake at key fetal development times due to a range of factors. These factors include unplanned pregnancies and a lack of supplement use.

In Australia, the importance of folic acid in reducing NTD incidence has been promoted since the early 1990s. Several state-based awareness-raising campaigns were conducted at that time.

In 1994, a report from the expert panel on folic acid fortification found that there was sufficient evidence to recommend mandatory fortification of wheat flour (in biscuits as well as bread) and voluntary fortification in breakfast cereals, rice, pasta and fruit juices.[135] As a practical first step, the expert panel recommended voluntary fortification, with a review three years after introduction, and that state and territory health authorities consider education campaigns to inform the public and health professionals.[135]

The voluntary fortification of some food products was introduced in 1995, which saw a subsequent decrease in NTDs.[30,39] Additionally, long-standing recommendations existed about the requirements for folic acid supplementation during and prior to pregnancy.[38]

The current recommendations are for the use of a folic acid supplement one month prior to pregnancy and 3 months into pregnancy.[136]

The reduction in NTDs that resulted from the above measures was distributed unevenly within the population. Higher rates of NTD-affected pregnancies occurred in younger women, those living in relative disadvantage and Indigenous women.[30]

In 2004, FSANZ was asked to investigate the possibility of mandatory fortification to reduce the incidence of NTDs. An expert group reviewed the evidence at that stage.[29] It concluded that the evidence suggested that mandatory fortification would be the most effective strategy. In reaching this conclusion, the group noted the inequity in the distribution of NTDs. The expert group also noted that supplementation would need to be continued since fortification alone cannot achieve the levels required by pregnant women without exceeding the upper levels of intake for the population.

After consultation and consideration of the options, mandatory fortification of wheat flour for bread making with folic acid was selected as the preferred option to address this public health issue. From September 2009, Australia (but not New Zealand) mandated the use of folic acid in wheat flour for making bread (except for organic bread).

8.1.3 Standard 2.11

The Standard 2.1.1 is reproduced below
(from https://www.legislation.gov.au/Details/F2014C01190)

STANDARD 2.1.1

CEREALS AND CEREAL PRODUCTS

Purpose

This Standard defines a number of products composed of cereals and qualifies the use of the term 'bread'. It also requires the mandatory fortification of wheat flour for making bread with thiamine and folic acid (Australia only) and the mandatory replacement of non-iodised salt with iodised salt in bread in Australia and New Zealand.

In this Code –

bread means the product made by baking a yeast-leavened dough prepared from one or more cereal flours or meals and water.

flour products means the cooked or uncooked products, other than bread, of one or more flours, meals or cereals.

flours or meals means the products of grinding or milling of cereals, legumes or other seeds.

Wholegrain means the intact grain or the dehulled, ground, milled, cracked or flaked grain where the constituents – endosperm, germ and bran – are present in such proportions that represent the typical ratio of those fractions occurring in the whole cereal, and includes wholemeal.

wholemeal means the product containing all the milled constituents of the grain in such proportions that it represents the typical ratio of those fractions occurring in the whole cereal.

1A Definition of bread for certain purposes

The definition of bread for the purposes of the mandatory addition of folic acid, thiamine and iodised salt to bread or wheat flour for making bread, does not include –

a) pizza bases;

b) breadcrumbs;

c) pastries;

d) cakes, including but not limited to brioche, panettone and stollen;

e) biscuits; or

f) crackers.

2 Composition of bread

Bread may contain other foods.

3 Use of the word 'bread'

This Standard does not prohibit the word 'bread' on the label of products that traditionally use that term.

Editorial note:

As an example, products are traditionally described by names such as 'shortbread', 'soda bread', 'pita bread' and 'crispbread'.

See Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations for requirements for declaring the presence of certain specified substances that must always be declared in the label of the food.

4 Wheat flour for making bread

Note: This clause does not apply in New Zealand.

It is the intention that a variation to this clause will be developed for New Zealand. In the interim, however, New Zealand has varied from this clause under Annex D of the Agreement between the Government of Australia and the Government of New Zealand Concerning a Joint Food Standards System, and has issued a food standard under section 11C of the New Zealand *Food Act 1981*.

1) Subclause 1(2) of Standard 1.1.1 does not apply to this clause.

2) Wheat flour for making bread must contain –

   a) no less than 2 mg/kg and no more than 3 mg/kg of folic acid; and

   b) no less than 6.4 mg/kg of thiamine.

3) For the purposes of this clause wheat flour includes wholemeal wheat flour for bread making.

4) Subclause 4(2) does not apply to wheat flour for making bread, which is represented as organic.

5) Paragraph 4(2)(b) does not apply to wheat flour for making bread sold or prepared for sale in, or imported into, New Zealand.

Editorial note:

The maximum limit for folic acid given in paragraph 4(2)(a) ensures the addition of folic acid to wheat flour for making bread in Australia is in controlled amounts to provide for a safe population intake of dietary folic acid. Paragraph 4(2)(a) will be reviewed, when sufficient monitoring data are available to assess the impact of this mandatory requirement.

Paragraph 4(2)(b) will be reviewed to assess the future need for this mandatory requirement.

Standard 1.3.2 regulates the voluntary addition of folate to both cereal flours and bread. These permissions will be retained to enable manufacturers to fortify specialised non - wheat flour and breads, such as, gluten free bread.

5 Mandatory addition of iodised salt to bread

1. Subclause 1(2) of Standard 1.1.1 does not apply to this clause.
   (2) Iodised salt must be used for making bread where salt would otherwise be used.

2. Subclause (2) does not apply to –

   a. bread which is represented as organic;

   b. the addition of salt (for example rock salt) to the surface of bread; or

   c. the addition of other food containing salt during the making of bread.

Editorial note:

The intention of clause 5 is to require the replacement of non-iodised salt with iodised salt where it is used as an ingredient in bread.

Clause 5 will be reviewed when sufficient monitoring data are available to assess the impact of this mandatory requirement.

Standard 2.10.2 sets out the compositional requirements for iodised salt.

8.1.4 Folic acid metabolism and measurement

Folic acid is the synthetic form of folate. Folate is the vitamin found in food, such as green leafy vegetables.[7] The different forms (folate and folic acid) have different bioavailability. This is further complicated by the bioavailability of folic acid changing depending on the other food that is taken at the same time. The bioavailability of folate is less than that of folic acid.

Once absorbed, folic acid is metabolised and then enters the folate pool.[137]

The dietary folate equivalent (DFE) combines the different forms of folate into a single measure.

1 microgram (µg) of DFE is equivalent to:

- 1 µg food folate; or
- 0.5 µg folic acid on an empty stomach; or
- 0.6 µg folic acid with meals.[7]

DFE intake estimation requires information on the numerous forms of folate present in food with an up to date database.[32]

There are nutritional guidelines about the amount of folate and folic acid which is appropriate to be consumed. The estimated average requirement (EAR) is the daily level estimated to meet the requirements of 50% of healthy individuals of a particular life stage and gender (such as pregnant women). The EAR is used to assess the prevalence of inadequate intake.[7] The EAR is expressed as DFEs and includes folate as well as folic acid added to the diet as supplements or via fortification.

The Upper Level of Intake (UL) is the highest average intake of folic acid likely to pose no adverse health effects for the population. Note that the UL is for folic acid intake only, not total folate intake and is expressed as folic acid and not DFE. It is used a measure of adverse effects in the AIHW report.[7]

In 2006, the Australian NHMRC and the New Zealand Ministry of Health published joint nutrient reference values for Australia and New Zealand. The upper level of intake for folic acid was 1 000 µg/day. The EAR is higher in pregnant and breastfeeding women than the general population .[32]

Folate has a key role in normal development, growth, and maintenance of health.[35] Essential through life; it is particularly important in the early stage of human development. It has an essential role in DNA, RNA and protein synthesis.[35] Without folate, living cells cannot divide.[32]

Inadequate intake is the main reason for folate deficiency. Other reasons include increased demand due to pregnancy or malabsorptive conditions (such as inflammatory bowel disease). Additional reasons include the use of anti-folate medication. Chronic alcoholism is linked to severe folate deficiency with a combination of poor diet and poor absorption.[35]

Folate insufficiency in an adult follows a path of a decrease in serum folate, then an increase in plasma homocysteine, then a decrease in red cell folate. This is followed by changes in bone marrow and rapidly dividing cells and the development of large (megaloblastic) cells and anaemia.

There is increasing evidence that genetics plays a large part in folate metabolism. Some individuals may have a genetic requirement for more folate.[32]

There are several different biomarkers that can be used to assess folate status. These include red blood cell folate, serum folate and homocysteine. Folate derivatives can also be measured in the urine.[36] The different assays used for the measurement of folate status have not been standardised and may produce different results.[36]

Red blood cell folate (RBC folate) is considered the most robust measure of folate status.[35] It is less sensitive to dietary fluctuations than serum folate and therefore more representative of folate status.[7]

The WHO recommends, given the limitations of the evidence, that for women of childbearing age the red cell folate level is kept above 400 ng/mL. It also recommends that the proportion of the population below that level be regarded as a measure of folate insufficiency at a population level.[36].

There is a two-step pathway for folic acid to enter the body folate pool.[138] The first step (conversion of folic acid to dihydrofolate) is easily saturated.[138] Therefore, unmetabolised folic acid can appear in the blood after folic acid intakes of 200 mg in a single dose.[138]

8.1.5 The importance of iodine

Iodine is an essential element for growth and development. Iodine deficiency has been a problem for more than a century.[99] Iodine sufficiency is particularly important in pregnancy and for the neural development of the fetus. The use of iodine in the body is connected with the thyroid gland and the hormones it produces (including thyroxine). Iodine is essential for thyroid hormone production. Thyroid hormones regulate a wide variety of physiological processes.[100]

Iodine is found in the soil, but the content varies widely.[100] Low soil iodine content results in low concentrations in plants and animals, and therefore results in a low intake for humans. The majority of the world's population lives in areas poor with soil iodine.[100]

A deficiency of iodine can lead to a constellation of symptoms and diseases collectively referred to as the Iodine Deficiency Disorders (IDDs). The consequence of iodine deficiency varies by age.[100] IDDs include enlargement of the thyroid (goitre), a decreased ability to produce thyroid hormone (hypothyroidism), an autonomously functioning thyroid (multinodular goitre and hyperthyroidism) which have impacts during pregnancy.

Pregnancy increases the demand for iodine. A sufficient level of thyroid hormone is required for the normal development of the brain and nervous system of a fetus during pregnancy. At its extreme, severe iodine deficiency can result in cretinism and increased neonatal mortality.

Cretinism results in a combination of mental retardation, sensory issues (e.g. deafness) and physical abnormalities (e.g. unusually short stature). However, even without cretinism, mild to moderate iodine deficiency during pregnancy may reduce cognitive performance.

IDDs are a global problem and considered the largest preventable cause of mental impairment.[2] A widespread public health intervention involving iodisation of salt has been in place since the 1920s. Elimination of iodine deficiency by universal salt iodisation is suggested to be one of the most cost-effective public health interventions.[2,99]

Iodine measurement, physiology and estimation

The measurement of iodine status can be performed using different biomarkers. The selection of the biomarker depends on a number of factors including intended purpose, cost, discomfort, and comparability to other studies.

Among the biomarkers that may be used are urinary iodine concentration, thyroid stimulating hormone, thyroglobulin, thyroid hormone and thyroid gland size (assessment of goitre). Other more indirect measures include dietary assessment.[100]

Urinary iodine concentration and thyroglobulin are biomarkers in the AIHW report[7] for iodine status of a population. The other biomarkers are used in several of the articles referenced in this Report.

Urinary Iodine Concentration (UIC)

The majority of iodine is excreted in the urine and therefore urinary iodine is an indicator of recent urinary intake.[100] The estimation can be performed either on a spot urine test or on a 24-hour collection.

While Urinary Iodine Concentration (UIC) may not be a good measure of an individual's iodine status because of day-to-day variation, the median (MUIC) is used as an indicator of a population's iodine status. This is because the day-to-day variation within an individual's results is evened out by a large number of individual samples. It is suggested that multiple UIC would be required to estimate an individual's iodine status.

UIC's advantages include simplicity, cost, accessibility and comparability over time and between countries.[102] There are cut-offs to determine a population's iodine status, and additionally subgroup cut-offs for pregnant and lactating women. It does not give information about thyroid function but rather a population's risk of iodine deficiency.

The WHO has guidelines for the monitoring of iodine status in a population.[102] The current epidemiological criteria and cutoffs are listed in Table 90 for children (over the age of six) and adults who are not pregnant or breastfeeding. The cut-offs for pregnant or breastfeeding women are listed in Table 91. As well as the median (which by definition 50% of the population is above) there are criteria for the proportion of the population that can be below the 50 µg/L threshold. For the assessment of the population having no iodine deficiency, not more than 20% of the samples should be below the 50 µg/L threshold. The WHO uses the results of a sample of school-age children to extrapolate to the iodine status of the population.[32]

There is concern that criteria derived from children are applied to adults. The concern is that the larger urine volume of adults may result in lower concentrations and potentially overestimate deficiency. The population criteria were derived from school children with an average daily urine volume of one litre, and the larger urine volume of adults (which would result in a lower urinary concentration) may place some caveats on using the MUIC in adults as a measure of population sufficiency.[7]

Table 90: Criteria for assessment of iodine nutrition

Median urinary iodine concentration (µg/L)	Iodine intake	Iodine status
<20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Adequate iodine nutrition
200–299	Above requirements	May pose a slight risk of more than adequate iodine intake in these populations
≥300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)

Source: WHO/UNICEF/ICCIDD 2007[101]

Table 91: Criteria for assessment of iodine nutrition for pregnant women

Median urinary iodine concentration (µg/L)	Iodine intake
<150	Insufficient
150-249	Adequate
250-499	Above requirements
≥500	Excessive

Source: WHO/UNICEF/ICCIDD 2007[101]

Use of MUIC within the AIHW report and this Report

MUIC is used in the AIHW report [7] for both Australia and New Zealand as a measure of population iodine status. Separate results are reported for the subgroups of women of childbearing age, pregnant or breastfeeding women, and children. MUIC is the recommended indicator for monitoring iodised salt programs.[139] As suggested by the WHO, there is a two-part approach to assessing the population as adequate: an MUIC above the required amount and not more than 20% below the 50 µg/L threshold. Notwithstanding the concerns raised about the use of childhood-derived values in adults, this Report has used the WHO criteria as an accurate representation of population and subgroup iodine status.

Other measurements for iodine deficiency and thyroid function

Besides the MUIC, various other tests provide information about iodine sufficiency (see below). Outcomes of these tests were not used for the current review.

Thyroid Stimulating Hormone

TSH is secreted in response to the levels of thyroid hormone. The level of TSH generally increases when the level of thyroid hormones falls. As a lack of iodine can lower the circulating thyroid hormones, it can increase the TSH. It is a potentially useful measure for neonatal iodine deficiency but less useful for school children and adults.[101] It is used for assessment of thyroid function in clinical situations. TSH can be measured in neonates routinely to detect congenital hypothyroidism.

Thyroglobulin

Thyroglobulin (Tg) is a precursor to the synthesis of thyroid hormone. It is detectable in the blood. The growth of the thyroid gland and goitre that occurs with iodine deficiency increases the level of thyroglobulin. It reflects the iodine nutrition over a longer period than the UIC.[101] There are no cut-off levels to define different epidemiological iodine deficiency levels (e.g., mild, moderate and severe).

Thyroid hormones

Thyroid hormones (T3/T4) are a direct reflection of thyroid function and are relatively preserved until severe iodine deficiency occurs.[100] Therefore, they are not a useful monitoring biomarker for iodine deficiency. Thyroid hormones are used for the investigation of patients in clinical situations.

Thyroid size evaluation

Thyroid Size evaluation using ultrasound (rather than palpation) is preferable for assessing the size of thyroids.[101] While useful for assessing baseline status, the lack of adaption of the size of the thyroid makes it less useful for monitoring current iodine status.[101] As with urinary iodine concentration, the population can be graded into assessments of iodine deficiency based on the proportion of the population that has an enlarged or palpable goitre.

Dietary intake

Dietary intake assessment for iodine can be undertaken in a variety of ways, including food diaries, 24-hour intake recall, and food frequency questionnaires combined with a food composition database. They provide a broader picture of the consumption of iodine containing foods. They can be time consuming to collect and depend on up-to-date data on the iodine content of specific foods. Recall is often inaccurate in measuring the amount of added salt (iodised or non-iodised) that is consumed.[100]

8.2 Review of Catalyst and AIHW reports

8.2.1 Introduction

The Catalyst report,[6] AIHW report[7] and the MPI companion report[8] were assessed against two criteria: reporting against their pre-specified requirements and the usefulness of the information for this Report.

8.2.2 Catalyst report

The report by Catalyst Ltd was finalised in 2015.[6] Its overall aim was to determine whether the mandatory fortification initiatives had been implemented as intended.

The Catalyst report aimed to review:

- the Australian milling industry's compliance with, and the Government's monitoring and enforcement of, mandatory folic acid fortification of wheat flour used in bread; and
- the compliance of the salt manufacturing and baking industries in Australia and New Zealand with the mandatory replacement of non-iodised salt with iodised salt in bread.

The report also considered the cost impacts on the food industry in complying with the regulations, and whether the dietary intake of folic acid and iodine had increased as a result of mandatory fortification.

Methods

The Catalyst report's approach comprised consultation with numerous organisations involved in producing and monitoring fortified bread. A pilot study was undertaken to gain an understanding of the issues. The results of the study were reviewed by the Commonwealth Department of Health and then structured interviews were undertaken. The results from those interviews were transcribed, collated and summarised.

Catalyst report findings and conclusions

Thirty-three organisations were interviewed or surveyed, including flour millers, salt manufacturers, bakers of bread, and compliance and enforcement agencies. The responses were collated according to type. Information about folic acid and iodine was sought where appropriate, for example, folic acid information from millers and iodine from salt manufacturers.

The response rate from the organisations approached to participate was high: between 50% for flour millers and 100% for compliance and enforcement agencies.

Compliance levels

For folic acid and iodine, the report found that millers, bakers and manufacturers had systems and documentation to ensure they complied with the relevant fortification standards. The regulators also had systems in place to enforce the relevant standards.

The report noted no evidence of ongoing interaction between enforcement organisations and the relevant industry group. The report considered this could potentially create a lack of timely information about non-compliance.

Compliance costs

Prior to implementation, it was estimated that there were substantial set up and ongoing costs associated with mandatory fortification. The actual costs, as assessed in the Catalyst report, were less than predicted. Notable set up (or one-off costs) were associated with the requirement to write-off the packaging.

The Catalyst report provided a breakdown of costs between the initial compliance costs and the ongoing direct costs of fortification for millers. Similar questions about the initial and ongoing costs were asked of wholesale suppliers of packaged goods, salt manufacturers and bakers. Results were presented as costs per tonne of wheat flour for millers and per tonne of salt for salt manufacturers. Industry-wide costs were reported for salt manufacturers, millers and bakers.

Impact of implementation

The impact of the implementation of mandatory fortification was, as intended, an increase in the provision of dietary folic acid and iodine. The Catalyst report estimated an increase to the food supply of between 2.42 and 2.68 tonnes of folic acid per annum and an increased provision of iodine through bread of between 300kg and 455kg per annum. In New Zealand, where the use of iodised salt in the manufacture of bread was already mandated, mandatory fortification resulted in an addition of approximately 88kg of iodine per annum to the New Zealand food supply.

Quality assurance, monitoring and enforcement

For folic acid, millers, bakers and compliance and enforcement agencies were consulted. All millers were subjected to third party audits of their systems. All bakers reported quality management systems for flour and the procurement of folic acid flour was a contractual requirement. There was testing of the final product by some bakers for verification. Compliance monitoring was delegated to a local government level.

For iodine, salt manufacturers, bakers and enforcement agencies were consulted. For salt manufacturers, the addition of iodine was automated and could only be changed by the Quality Manager. Bakers all identified appropriate procurement as an important issue. All bakers had in place a quality management system that specified the requirements for iodised salt. There were internal and external audits of the final product. Similar to folic acid, the compliance monitoring was delegated to a local government level in Australia. New Zealand has a third party audit system in place; the MPI being informed of any critical instance.

The Catalyst report noted that there were no specific resources or budgeting associated with the compliance or monitoring program within the enforcement agencies. No compliance investigations were carried out in the three years prior to interviews for either folic acid or iodine. For folic acid, this was said to be partly because the 2010 survey revealed good systems and processes.

Other concerns

Three specific issues were identified within the report as being consistently raised by industry:

1. Accuracy of testing;
2. Potential legal liability; and
3. The effectiveness of fortification.

8.2.3 Assessment of Catalyst Report

The Catalyst report's conclusions that mandatory folic acid fortification and mandatory iodine fortification implementation occurred as intended are justified by the evidence presented. This conclusion refers only to the first step in the monitoring framework of implementation (i.e. changes in nutrient availability). The differences between New Zealand and Australia in monitoring systems were highlighted.

The majority of the compliance costs were incurred by industry. There is a lack of disaggregation and sensitivity in the costs that is understandable given multiple quality assurance processes were occurring simultaneously.

The enforcement and compliance costs met within existing budgets do not indicate the displaced activities or reduced capacity that may have occurred within the relevant enforcement or compliance organisations. The current enforcement costs for government were low at the time of the report, partly due to conformity with the relevant standards. The reliance on questionnaires for events that have occurred in the past introduces the possibility of recall bias. Several respondents reported that they were managing the costs within their usual business practices. This suggests that the reported costs may be underestimated.

The costs reported in the Catalyst report are used as the basis of the costs of fortification used in this Report's economic evaluations. However, there are limitations to these data, such as a lack of disaggregation and a lack of information about the compliance, monitoring and enforcement costs. The approach taken in the Catalyst report potentially underestimated the opportunity costs associated with mandatory fortification's introduction.

8.2.4 AIHW report

The AIHW report assessed the population health effects of the policy of mandatory fortification.[7] It focused on changes in nutrient intake, nutrient status, and health effects prior to, and after, September 2009. The AIHW report also commented on other aspects of the monitoring framework.[7]

The method employed by the AIHW was to use nationally representative data sources to answer each of the monitoring framework questions. These data were compared in the pre and post-mandatory fortification periods. One nationally representative data source was not always available. Therefore, additional sources were used to complement the primary data source.

Sub-national surveys were used to supplement the data in the baseline monitoring reports and some, such as the NSW 45 and up study were identified as being potentially useful with regard to health condition data post-mandatory fortification.[26] However these were not considered in the final AIHW report due to funding constraints.[7]

The key findings of the AIHW report are as follows:

- For folic acid fortification in Australia, there was a statistically significant (14.4%) decrease in the rate of NTDs. This was based on analysis undertaken by Hilder.[12] The decreases were largest for Indigenous women and teenagers;
- For iodine fortification in Australia, the population consumed sufficient iodine to address the re-emergence of mild iodine deficiency as estimated by MUIC.

For iodine fortification in New Zealand, there was an improvement in iodine intake but not sufficient to completely address the re-emergence of mild iodine deficiency in all population subgroups. The subgroup of children had an MUIC of 113 µg/L and thus was no longer considered iodine deficient. The subgroup of women of childbearing age, however, had an MUIC of 68 µg/L and thus remained mildly iodine deficient. These results were replaced by the MPI companion report.[8]

The AIHW had also been commissioned to prepare the baseline data for assessing mandatory fortification and produced three reports.[25,26,30] Two were baseline monitoring reports[25,26] and one a report on the pre-mandatory fortification NTD rates.[30] This work informed the AIHW's consideration of the differences that occurred from pre-mandatory fortification to post-mandatory fortification.

Overview of the monitoring framework questions

The AIHW report specifically addressed a number of questions arising from the monitoring framework (see Section 2.2, Table 2 and Table 43).

For some of the monitoring framework questions, proxy measures were used. Notably, for assessing adverse effects caused by iodine and folic acid fortification, the AIHW used the proxy measure of the proportion of the population that consumed more than the daily upper level of iodine or folic acid. A second proxy measure for adverse effects in folic acid fortification was the meta-analysis of cancer risk in studies of folic acid supplementation.

The AIHW report listed the key mandatory fortification outcomes in New Zealand. These are reproduced below in Table 92. The results for folic acid and iodine in Australia are reproduced in Table 3 and Table 44. The original table for the iodine results in New Zealand is reproduced below (this was altered for Section 6).

Table 92: Key mandatory iodine fortification outcomes in New Zealand

Key monitoring question and measurement	Pre-mandatory fortification	Post-mandatory fortification	Outcome
Has the level of iodine in our food supply increased? *Mean iodine level of bread*	<2 µg/100 g (mean)	28–49 µg/100 g (median)	Desired outcome achieved
Are the food industries adequately complying with the mandatory fortification standards?	Not applicable	Salt manufacturers and bakers have systems in place to ensure compliance.	Desired outcome achieved
Have iodine intakes in the population increased, particularly in women of childbearing age and young children? *Mean iodine intakes*	Women aged 16–44: 99 µg/day Children aged 5–14: 45 µg/day	Women aged 18–44: 108 µg/day Children aged 5–14: 93 µg/day (48 µg/day increase)	Partial achievement
Proportion of the population with iodine intakes below the EAR	Women aged 16–44: 68% Children aged 5–14: 95%	Women aged 18–44: 39% Children aged 5–14: 21%	Partial achievement
Has the iodine status of the population improved, in particular in women of childbearing age and young children? *Median urinary iodine concentration (MUIC)*	Women aged 18–44: 48 µg/L Children aged 8–10: 68 µg/L	Women aged 18–44: 68 µg/L Children aged 8–10: 113 µg/L	Partial achievement for women between 18-44 Desired outcome achieved for children
Does mandatory iodine fortification result in adverse health effects for the population? *Proportion of the population with iodine intakes above the UL*	Adults: 0% Children aged 5–14: <1%	Adults: Not applicable Children aged 5–14: <1%	Not applicable

Abbreviations: MUIC, median urinary iodine concentration; UL, upper level (of intake)
Source: AIHW Report 2016[7]; Table S.3

The AIHW estimation of post-mandatory fortification iodine intake was lower than expected and appeared to have a follow-on effect on the population's iodine status. For example, it a 73 µg/day increase in the intake by women aged 18-44 was expected, but the actual intake was lower (approximately 9 µg/day).

The conclusion reached by the AIHW about adverse effects was that it was unlikely the upper level for iodine intake would be exceeded after the implementation of mandatory fortification because of the lower than expected increase in intake. No information was provided about what proportion of the adult population had iodine intake above the upper level post implementation in the AIHW.[7]

For the purposes of this Report, the results from the AIHW Report on the iodine status of the population were replaced by those from the MPI companion report[8] and from Jones et al.[31] Consequently, the outcomes in this Report and the AIHW report are not congruent.

Assessment of AIHW report

The comparability of the pre-mandatory fortification and post-mandatory fortification periods was limited for all the mandatory fortification initiatives. These are well documented in the AIHW report in Table 1.1, Table 1.2 and Table 1.3 on pages 9-11.[7] This assessment is also discussed in the Sections evaluating the implementation of each mandatory fortification initiative.

Attributing the difference between the pre-mandatory fortification period and the post-mandatory fortification period to the mandatory fortification intervention remains an assumption and requires that confounding is absent. The impact of the omission of sub-national surveys on the AIHW's findings is not known.

In the AIHW report, adverse health effects were not directly estimated in the Australian and New Zealand populations. However, two approaches were used to assess the potential health effects. The first approach was to estimate the proportion of the Australian adult population that exceeds the relevant UL for folic acid and iodine, using the FSANZ dietary intake assessment. The second approach was to include a meta-analysis undertaken by Mackerras et. al.[13] on cancer risk and all-cause mortality with folic acid supplementation. The effect of exceeding the upper level in childhood was not considered by the AIHW to be a health risk because aging lowered the proportion of the subgroup who exceeded the upper level.

The AIHW report acknowledged that literature was available on folic acid and non-cancer effects. These effects were, however, not assessed by the AIHW because the monitoring framework agreed by the then Ministerial Council selected outcomes for cancer as the main indicator for monitoring adverse effects of folic acid fortification,[7] although the reasons for this choice are not clear. The choice of cancer as the only potential health effect was, and remains, a limitation, as more clinical evidence is available about neurological abnormalities as adverse effects of excess folic acid intake and low levels of B_{12}. The method of the selection of the meta-analysis was also not articulated. The potential for adverse effects to occur in high-risk individuals under the upper level was not quantified.

The estimation of the portion of population exceeding the UL was mostly (not for New Zealand adults) based on the DIAMOND program which accessed food consumption data from the 1995 NNS for Australian adults and the 2007 ANCNPAS for Australian children) and its representativeness of the current population is uncertain, especially those who may use supplements. The lack of inclusion of supplements is a weakness in the use of the 1995 NNS. This would result in a bias towards underestimating nutrient intake in adults.

Given the low number of adults who exceeded the upper level in the dietary intake assessment and the lack of inclusion of supplements, the potential bias is one of underestimation (as it is bounded by zero).

8.2.5 MPI companion report (New Zealand)

Although not included in the AIHW report, the MPI companion report is cited as a more representative and larger data source, than that used within the AIHW report for the outcomes of the mandatory iodine fortification program in New Zealand.[8] These results have now been published on the MPI website, and a pre-publication version was made available for this Report. The available methodology and results are reported below.

Methods of data collection

Spot urine samples were collected from 4997 respondents aged 15 years and over as part of the 2014/15 New Zealand Health Survey. These samples were used to measure urinary iodine concentration using Inductively Coupled Plasma-Mass Spectrometry.

Results

The results of the New Zealand Health Survey demonstrated that the population aged over 15 years had an MUIC of over 100 µg/L. This is greater than seen in the AIHW report. Less than 20% of the population recorded an MUIC of less than 50 µg/L. However, 21% of women of childbearing age recorded an MUIC of less than 50 µg/L. This is slightly higher than the recommendation of less than 20% suggested by the WHO for iodine sufficiency.

The results for the key monitoring question will be placed in the supplement to the AIHW report and are reproduced below.

Key monitoring question:
Has the iodine status of the population improved, in particular in women of childbearing age and young children?

Data sources:
MPI report

Key findings:
Post-mandatory fortification:

- The MUIC of NZ population aged 15+ years was 103 µg/L, with concentrations higher in males than females (110 µg/L vs 91 µg/L)
- The MUIC of all women of childbearing age (16-44 years) was 104 µg/L
- The MUIC was highest in Pacific, followed by Māori and the European/Other ethnic group

Assessment of MPI companion report results

The 2014/2015 New Zealand Health Survey, discussed in the MPI companion report, is a nationally representative data source for the iodine status of adults in New Zealand. It is superior in size and applicability for adults than the alternatives used in the AIHW report.

The major limitation in the applicability of the New Zealand Health Survey, as it is used in this Report, is the lack of inclusion of children.

There have been other studies involving children in New Zealand. The AIHW report references Skeaff and Lonsdale Cooper (2013).[140] This study contained 147 children aged 8 to 10 recruited from two cities (Dunedin and Wellington). The results of the study suggested the subgroup of children were no longer iodine deficient (based on their MUIC). They also measured blood tests of thyroid function, serum thyroglobulin and total thyroxine. The results of those tests suggested the possibility of mild iodine deficiency.

A more recent publication by Jones et al.[31] found a very similar MUIC, of 116 µg/L (as opposed to 113 µg/L) but had a larger sample size and a more nationally representative ethnic makeup.[31] It sampled children in two different New Zealand cities, Auckland and Christchurch. Four hundred and fifteen children were included in the analysis. Jones et al.[31] also undertook blood tests. These blood tests showed an adequate iodine status.

In this Report, the AIHW report finding for the iodine status and health impacts of the iodine fortification were replaced with the updated results from the MPI companion report and the results from Jones et al.[31]

8.2.6 Conclusions

The Catalyst report reviewed the compliance and monitoring of millers, salt manufacturers, bakers, and enforcement and compliance agencies. It concluded that the implementation of the mandatory fortification initiatives had occurred as planned. The amount of additional micronutrients estimated to be delivered in bread was consistent with those predicted prior to the implementation by FSANZ. Significant audit and quality assurance programs were found to be associated with the production of flour, salt and bread.

The Catalyst report included a breakdown of costs from industry and enforcement agencies. The costs to industry were lower than predicted prior to the introduction of mandatory fortification. Costs associated with the enforcement and monitoring of the programs were considered low. The cost of folic acid is likely to be variable.[141]

There are limitations in the results of the Catalyst report as they are applied to this Report. The main limitations were.

- The costs are subject to some uncertainty. They do not include estimation of costs of public health units, were subject to recall bias and several respondents reporting that they had managed the costs within usual business practices. The bias would be expected to underestimate costs.

In this Report the costs reported by the Catalyst report are used in the economic evaluations. For mandatory iodine fortification in Australia, a threshold analysis is undertaken for the use of public health resources.

The AIHW report demonstrated that the folic acid mandatory fortification program had been associated with a reduction in NTDs in Australia. These results should be considered in the context of the short study period post-mandatory fortification and the relative rarity of NTDs both of which contribute to variability in NTD rates. Ongoing monitoring of Australian NTD rates is required to confirm whether these reductions will be sustained. The estimation of the other implementation outcomes of the mandatory folic acid program (food composition, nutrient intake, nutrient status and adverse health effects) were assessed as being satisfactory as the desired outcomes had been achieved.

The AIHW report found the iodine mandatory fortification initiative was associated with an improvement in the iodine intake to adequate levels in Australia. In Australia, the MUIC for children and adults had improved past 100 µg/L and thus, at a population level, Australia was no longer iodine deficient. The subgroup of pregnant and breastfeeding women did not have a sufficient iodine intake following mandatory fortification, as expected, and will continue to require supplementation. The AIHW assessed as satisfactory or non-applicable the other outcomes of the mandatory iodine fortification program in Australia (food composition, nutrient intake and adverse health effects) were all assessed as being satisfactory.

The New Zealand Ministry for Primary Industries published an MPI companion report to the AIHW report, specifically addressing the iodine status of the population of New Zealand adults using the 2014/15 New Zealand Health Survey data and other sources.[8]

The results and the conclusions of the previous reports are used in this Report. In particular, what is drawn upon is the description of the mandatory fortification initiatives' implementation and their expected health benefits, the assessment of mandatory fortification against the stated policy objectives, and as input for the CBA.

There are limitations in the results of the AIHW report as they are applied to the evaluation undertaken for this Report. The main limitations were.

- There were limitations in the data sources that flowed through to their use in this Report. These included low sample size, lack of comparability between periods, limited representation of the entire population and a short follow-up time. Additionally, the use of earlier food composition surveys is a limitation. These limitations mean that the differences found cannot always be confidently attributed to the mandatory fortification initiatives. Confidence decreases when different analytical methods and samples are used in the pre-mandatory fortification and post-mandatory fortification periods.

- The use of the upper level of intake as a proxy for the assessment of adverse health impacts may not be a valid measure of adverse effect impacts experienced by the population. The lack of data on Australian and New Zealand health impacts is a significant weakness in both the AIHW report and this Report.

- The AIHW acknowledged that voluntary folic acid fortification, supplementation programs and other factors were causing a continuous downward trend in NTD rates and that the combination of these, together with mandatory fortification, were expected to result in a 4-14% reduction in NTDs. Therefore, the change cannot be confidently attributed to mandatory folic acid fortification, and the exact effectiveness of mandatory folic acid fortification is not known with certainty.

The pre-post structure of the AIHW report is a limitation for the attribution of the observed changes to the mandatory fortification initiatives.

This Report replaced information in the AIHW report for the New Zealand mandatory iodine fortification initiative as discussed above. Additionally, published comparative information was included in the discussion of each evaluation. A background rate in the rate of NTDs was included to establish the impact attributable to the mandatory folic acid fortification initiative, as opposed to the use of the difference observed in the AIHW report.

8.3 International experience of mandatory fortification

This Section updates the international experience of mandatory iodine and folic acid initiatives. FSANZ undertook a prior review of this international experience.[10]

An increasing number of countries are engaging in mandatory fortification with folic acid and iodine.

8.3.1 Search strategy

Search terms: food fortification, fortified food, folic acid, iodine

All searches were conducted from 2007 (inclusive) onwards. Searches were conducted in several electronic databases to identify relevant studies. These databases included the Cochrane Library, EMBASE, MEDLINE, WHO Global Health Library regional databases, and WHO International Clinical Trials Registry Platform databases.

The following grey literature was searched including the international websites of:

- WHO;
- Iodine Global Network (IGN, formally International Council for Control of Iodine Deficiency Disorders (ICCIDD) Global Network); and
- Food Fortification Initiative.

The key national website searched was FSANZ.

The exclusion criteria for the search included non-English language articles, editorials, letters and conference abstracts.

The search returned 1 131 articles after 851 duplicates were removed. From the review of titles and abstracts, 1 105 articles were excluded. The full-text review consisted of 26 articles. Sixteen were included (13 for folic acid fortification and three for iodine fortification). Ten articles were excluded for the following reasons; five were not relevant; four were editorial/letters and one was excluded based on year of data (pre-2007).

8.3.2 Folic acid fortification

Since 2007, the number of countries with mandatory folic acid policies has increased.[16,142-149] As of January 2016, 79 countries had mandatory folic acid fortification of flour: Table 93 [Data request from Food Fortification Initiative Network, 21 January 2016, Food Fortification Initiative website].

In 2007, FSANZ reported that Canada and the United States had policies in wheat and wheat and maize flour, respectively and other grain product.[9]

In 2007, the UK and Ireland were reportedly considering mandating folic acid fortification of wheat flour. As at 2016, neither the UK nor Ireland had implemented mandatory folic acid fortification of flour [UK folic acid decision]. No country in the European Union has legislated mandatory fortification with folic acid.

Table 93: Countries with mandatory fortification of flour with folic acid in 2016

Country Name (N=79)	Current Folic Acid Fortification Level (mg/kg)	Year Folic Acid Added	Year Adopted
Antigua and Barbuda	-	-	1992
Argentina	2.2	2002	2002
Australia	2.0-3.0	2009	2009
Bahamas	-	-	1992
Bahrain	1.5	2001	2006
Barbados	-	-	1992

Country Name (N=79)	Current Folic Acid Fortification Level (mg/kg)	Year Folic Acid Added	Year Adopted
Bolivia, Plurinational State of	1.5	-	1996
Brazil	1.5	2006	2002
Belize	1.8	-	1998
Solomon Islands	2	2010	-
Burundi	1.1-3.2	2015	2015
Cameroon	2.6	2011	2011
Canada	1.5	1998	-
Cape Verde	2.6	2014	2014
Chile	1.0-2.6	-	1996
Colombia	1.54	1996	1996
Costa Rica	1.8	-	-
Cuba	1.8-1.9	-	-
Benin	2.6	-	2012
Dominica	-	-	1992
Dominican Republic	1.8	-	-
Ecuador	1.7	-	1996
Egypt	1.5	-	2008
El Salvador	1.8	-	2002
Fiji	1.6	2005	1993
Djibouti	1.3	2013	2013
Ghana	2.1	2007	2010
Grenada	-	-	1992
Guatemala	1.8	-	2001
Guinea	1.4	-	2005
Guyana	-	-	1992
Haiti	-	-	1992
Honduras	1.8	-	-
Indonesia	2	2001	-
Iran Islamic Republic of	1.5	2007	2001
Iraq	-	-	2006
Cote d'Ivoire	2.6	-	2007
Kazakhstan	1.5	-	2005
Jamaica	-	-	1992
Jordan	1	2006	2002
Kyrgyzstan	1.5	-	2009
Kenya	0.5-2.5	2012	2012
Kuwait	1.5	2001	2001
Liberia	-	-	2013
Malawi	1.3-3.3	2015	2015
Mali	2.6	-	2012
Mauritania	2.6	-	2010
Mexico	2	1999	1996

Country Name (N=79)	Current Folic Acid Fortification Level (mg/kg)	Year Folic Acid Added	Year Adopted
Morocco	1.5	2009	2005
Republic of Moldova	1.4	2012	2012
Nepal	1.5	2011	2011
Nicaragua	1.8	-	-
Niger	2.6	-	-
Nigeria	2.6	-	2002
Panama	1.8	2002	1997
Paraguay	3	2002	1998
Peru	1.2	1949	2004
Rwanda	1.1-3.2	2013	2013
Saint Kitts and Nevis	-	-	1992
Saint Lucia	-	-	1992
Saint Vincent and the Grenadines	-	-	1992
Saudi Arabia	1.5	2000	1978
Senegal	2.6	-	2009
Sierra Leone	-	-	2011
South Africa	2	-	1972
Suriname	-	-	1992
Turkmenistan	1.5	2006	1996
Tanzania, United Republic of	1.0-5.0	2011	2011
Togo	2.6	2009	2012
Trinidad and Tobago	-	-	1992
Oman	1.5-2.0	1996	1997
Uganda	1.1 - 3.2	2012	2011
United States of America	0.946-3.08	1996	1993
Burkina Faso	2.6	-	2012
Uruguay	2.4	1949	2006
Uzbekistan	1.5	-	2005
Yemen	1.6	2009	2000
Palestine Occupied Territory	1.0-2.5	2006	2006
Kosovo	1.5	2013	2012

Note: '-' indicates data not available.
Data was provided in parts per million (PPM), converted to mg/kg by assuming 1 ppm = 1000 ug/kg
Source: Data request from Food Fortification Initiative Network, 21 January 2016, http://www.ffinetwork.org/global_progress/index.php

Atta et al.[16] undertook a systematic review and meta-analysis of the prevalence of spina bifida by folic acid fortification in 2016. The results indicate that regions with mandatory fortification in place had a lower prevalence of births with spina bifida compared to regions with voluntary fortification (33.86 vs. 48.35 per 100 000 live births).

International experience demonstrates the requirement to consider targeting of specific high-risk subgroups with fortification of additional foodstuffs. For example, in the United States, where there is mandatory fortification of cereal grain products, racial disparities in NTDs lead to fortification of corn masa flour.[17,150]

8.3.3 Iodine fortification

FSANZ undertook a review of the international experience of iodine fortification programs in 2007 (Table 94).[10] Since then, there has been an increase in the number of countries with iodine fortification. The potential for re-emergence of mild iodine deficiency internationally has been noted elsewhere (e.g. United Kingdom).[151]

As of 2007, 20 American, and Western & Central European countries had salt iodisation initiatives in place: eight of these had voluntary initiatives, and the remaining 12 had mandatory initiatives. Of the 12 countries that had mandatory legislation, eight included salt iodisation in the food industry. The review also noted that some countries with mandatory iodisation had achieved iodine sufficiency. These include Switzerland, the Netherlands (mandatory, now voluntary) and Denmark.

Numerous countries have adopted iodine fortification. The IGN published a Global Iodine Nutrition Scorecard and noted the proportion of households consuming iodised salt and country iodine status.[152] Mandatory iodine fortification of salt in bread has occurred in countries as diverse as Denmark and China.[153] Nazeri et al.[154] reported that of 29 European countries with data, 13 had mandatory policies.[101,154] Of the ten ASEAN countries, six (Cambodia, Indonesia, Laos, Myanmar, Philippines and Thailand) have mandatory policies for salt iodisation.[153,155]

Minimising the burden of non-communicable diseases requires both a reduction in salt and the elimination of iodine deficiency diseases. The requirement to coordinate these strategies has been recognised.[151]

The reliance on salt as the vehicle for dietary intake of iodine and the decreasing use of salt may require an altered level of fortification. This will require monitoring of populations and adjustment of the level (and scope) of fortification. Strategies for ensuring iodine sufficiency should be locally tailored.

The universal iodisation of salt has been advocated internationally.[151] The fortification of salt with iodine has been credited with decreasing the number of countries that are iodine deficient.[2] There has been a change in emphasis in some countries from eliminating iodine deficiency to sustaining gains.[2] In industrialised countries, it is recognised that the majority of salt consumed is in processed foods. Therefore, it remains critical to convince (or regulate) the food industry to use iodised salt in production processes.[19]

Table 94: International iodine fortification policies

Country	Y/N	Year	Conc (ppm)	Mandatory/Voluntary	Household	Food Industry	Animal Feed	Monitoring	Iodine nutritional status
Austria	yes	1963/90	20.0	Mandatory	yes 0.95	No	yes	regular	sufficient
Bosnia	yes	2001	/	Mandatory	yes 1	Yes	yes	regular	sufficient
Bulgaria	yes	1994	/	Mandatory	yes 1	Yes	no	regular	sufficient
Canada	yes	1949	76.0	Mandatory	yes 1	No	no?	none	sufficient
Croatia	yes	1996	25.0	Mandatory	yes 0.9	Yes	yes	regular	sufficient
Czech	yes	1950	20-34	Mandatory	yes 1	Yes	yes	regular	sufficient
Denmark	yes	2000	13.0	Mandatory	yes >90%	yes, baking	no	yes	sufficient, regional variation
France	yes	1952	10-15	Voluntary	yes 0.55	No	yes	no	deficient
Germany	yes	1991	20.0	Voluntary	yes 0.84	yes, 30-35%	yes	yes	some deficient areas
Italy	yes	2005	30.0	Mandatory	yes 0.03	No	no	planned	deficient
Macedonia	yes	1999	20-30	Mandatory	yes 1	Yes	yes	regular	sufficient
Netherlands	yes	1968	50.0	Voluntary	yes 0.65	bread, some crackers	no	none	sufficient
Poland	yes	1935/97	20-40	Mandatory	yes 0.9	Recommended	planned	planned	some deficient areas
Romania	yes	1956	15-20	Voluntary to mandatory	yes 0.25	Yes	yes	planned	deficient
Slovak Rep	yes	1966	19.0	Mandatory	yes 0.85	Yes	no	regular	sufficient
Slovenia	yes	1953	20-30	Voluntary	yes	Yes	no	regular	deficient
Switzerland	Yes	1922	20.0	Voluntary	yes 0.94	bread, cheese	yes	regular	sufficient
Turkey	Yes	1999	40.0	Mandatory, not enforced	yes 20-64%	Yes	no	planned	deficient
Yugoslavia	Yes	1951	12-18	Mandatory	yes 0.73	Yes	yes	planned	regional variation
USA	No	1920	76.0	Voluntary	yes 0.7	Some	yes	none	sufficient

Abbreviation: ppm, part per million

Source: FSANZ, "Table 1 of attachment 3: International experience with iodine fortification programs, Consideration of mandatory fortification with iodine for New Zealand, 2008[10]

8.4 Consumer understanding, acceptance and awareness

This Section comprises a literature review of the level of consumer understanding, acceptance and awareness of the mandatory fortification initiatives.

8.4.1 Aim

The aim of this literature review was to identify studies specifying or describing the level of understanding and acceptance in Australia and New Zealand of the mandatory fortification initiatives.

8.4.2 Search strategy

The search terms used in the PubMed database were: folic acid, folate, folacin/iodine, iodised salt, sodium chloride, in combination with fortified food, fortification and consumer/patient (acceptance, knowledge, attitude, awareness, preference, satisfaction, willingness to pay, purchase intention, information, health behaviour). Search terms used in EBSCOhost were similar to those used in PubMed.

Publications selected for inclusion in this Report were based on the following criteria:

1. People living in Australia and New Zealand; and
2. Intervention: food fortification programs: Folic acid or iodine

The search of PubMed and EBSCOhost returned 325 papers after removal of duplicates. References in the publications selected for inclusion were reviewed to identify additional studies. Round 1 excluded papers based on title alone. These papers were related to the prevention of neural tube defects, salt fortification with iodine, and international studies. Round 2 excluded articles following a title and abstract scan. The excluded articles included papers on medical supplementation, vitamin intake, deficiency, related diseases, and deficiency in other ages (children and elderly).

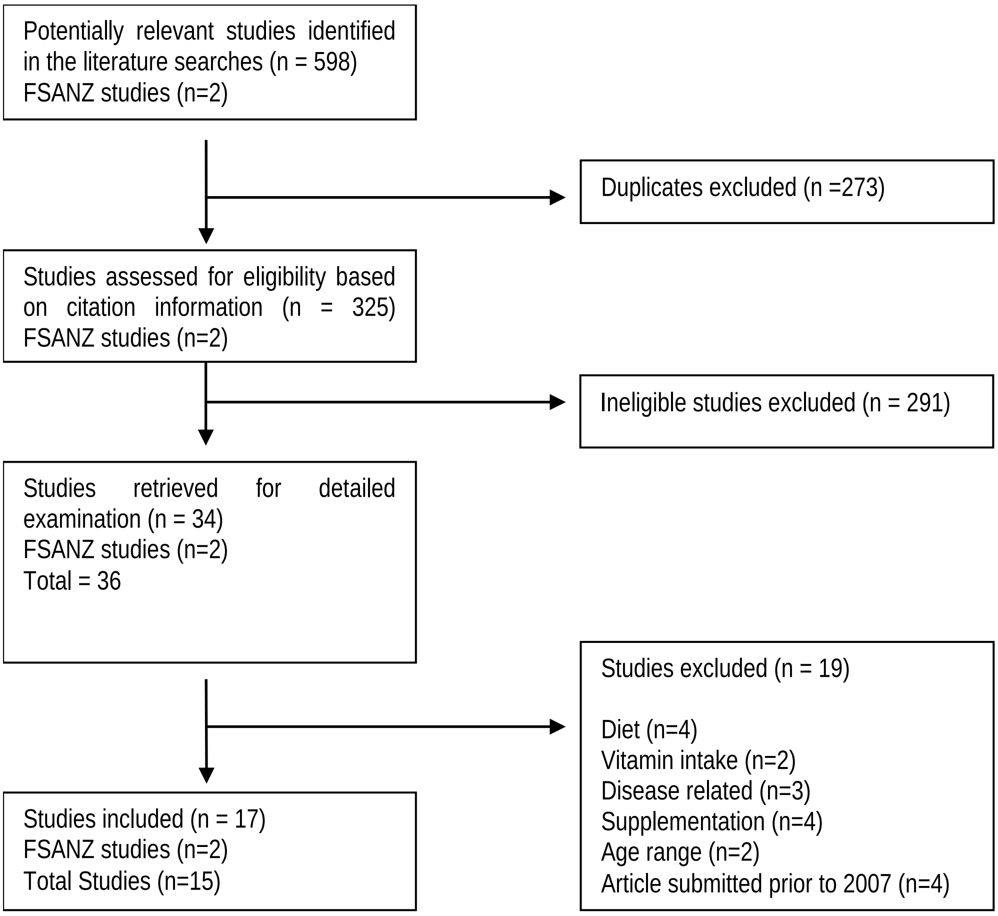
All searches were conducted from 2007 onwards. Results were not limited by study methodology, as a range of qualitative and quantitative studies may support this Report's findings. The results were limited to studies published in English and in human study populations.

The full articles were retrieved, and hand-searched according to the inclusion criteria developed by the reviewers. Papers were given a 0 1 ranking to determine if they addressed any of the research questions. Articles that returned a sum of 0 were excluded from the review.

8.4.3 Literature search results

Figure 7 summarises the process used to identify and select the studies included in this literature review.

Figure 7: PRISMA flow chart for consumer understanding



After review of the title and abstracts, 34 articles were identified as potentially having either direct relevance or being able to address research questions. Two papers were identified in the grey literature, published by FSANZ.

The literature searches for articles concerning consumer awareness of food fortification and the levels of folate and iodine in population resulted in 16 articles across Australia and New Zealand. Four articles were removed from the final list as the analysed data sets related to years ranging from 1994 to 2007. The 15 remaining articles comprised two studies on iodine fortification in New Zealand, six studies on iodine fortification in Australia, three studies on folic acid fortification in New Zealand (which were not reviewed) and four studies on folic acid fortification in Australia. One article reported the cost-effectiveness of folic acid and was reviewed in Section 8.6.[45] Hence, three of the studies on folic acid fortification in Australia are reviewed in this Section.

Table 95: Recovered literature for consumer awareness

Publication	Fortification program	Population	Sample size	Study type (Area)
FSANZ 2010[23]	All fortification initiatives	Adults	95 adults	10 focus groups and 8 shopping trips (Australia and New Zealand)

Publication	Fortification program	Population	Sample size	Study type (Area)
FSANZ 2013[20]	All fortification initiatives	Adults (16 years or older)	1602 adults (800 Australian and 802 New Zealand)	Telephone survey (Australia and New Zealand)
Charlton et al. (2013)[108]	Iodine in Australia	Pregnant women	291 women	From antenatal clinics (Wollongong)
Charlton et al. (2012)[113]	Iodine and folic acid in Australia	Pregnant, breastfeeding and other women	421 women	Multiple places of recruitment
Charlton et al. (2010)[112]	Iodine in Australia	Pregnant women	139 women	From antenatal clinics (Wollongong)
Charlton et al. (2010)[156]	Iodine in Australia	Non-pregnant women	78 women	From convenience sample (Wollongong)
Axford et al.[157]	Iodine and folic acid in Australia	Breastfeeding women	60 women	Early childhood centres (Wollongong)
Yeatman et al.[22]	Iodine in Australia	Women	20 women	Focus group (Wollongong)
Parkinson et al.[21]	Folic acid in Australia	Adults	207 adults	Online poll
Molster et al.[158]	Folic acid in Australia	Adults	1000 adults	Western Australia phone survey
Molster et al.[159]	Folic acid in Australia	Adults	1000 adults	Western Australia phone survey
Nithiananthan et al.[160]	Iodine in New Zealand	Health care workers & pregnant and lactating women	72 adults	Identified by authors
Brough et al.[130]	Iodine in New Zealand	Pregnant and lactating women	127 women	Community and local maternity service providers (Palmerston North)
Mallard et al.[161]	Folic Acid in New Zealand	Post-partum women	758 women	Birthing centres and hospitals (Nationwide)
Mallard et al.[162]	Folic Acid in New Zealand	Post-partum women	758 women	Birthing centres and hospitals (Nationwide)
Mallard et al.[163]	Folic Acid in New Zealand	Post-partum women	758 women	Birthing centres and hospitals (Nationwide)

Several of the publications included survey results that were reported in other papers meaning the results are not independent.

The majority of the studies included from the literature search of folic acid and iodine fortification focused on women of childbearing age or pregnant or breastfeeding women.

8.4.4 Review of consumer acceptance literature

FSANZ commissioned two reports (FSANZ 2010[23] and FSANZ 2013[20]) to gain an understanding of and quantify consumer knowledge and the level of understanding, awareness, and acceptance of folic acid and iodine mandatory fortification initiatives. These are outlined below after which this Section then reviews the 15 recovered articles.

FSANZ 2010

The first study used qualitative methods involving group discussions, and people were accompanied on group shopping trips (FSANZ 2010.[23]). Ten group discussions and eight shopping trips occurred. As a qualitative study, it was not randomised or powered to find a specific study outcome. The main purpose of the study technique was to elicit key themes, issues, patterns and points of contention that arose during the course of the discussion, and to elicit views about mandatory fortification from a wide range of participants.

The study found:

- recognition of the term "fortification" was low. However, the concept of adding vitamins and minerals to food was known;
- a risk that fortification (especially voluntary fortification) could be viewed as a marketing strategy (the study noted that the fact that regulations originate with an independent Government body might mitigate this concern);
- price is an important part in food purchasing decisions;
- a strong objection to mandatory fortification was raised on the grounds of restricting choice; and
- a trend that, once discussion began, more negative views were aired.

Both positive and negative consumer attitudes were present (Table 96).

Table 96: Consumer attitudes from FSANZ 2010

Positive	Negative	Neutral
• obtaining vitamins and minerals that otherwise would not have been consumed; • value for money with the inclusion of vitamins and minerals; • provision of a palatable vehicle for children to consume vitamins and minerals; • replacing vitamins or minerals which may have been eliminated from foods due to modern farming or processing of foods.	• scepticism regarding the health value of fortified foods; • mistrust in the motivations of food manufacturers in including vitamins and minerals into foods; • fortification used as a technique to market unhealthy foods as healthy. • mistrust of all non-natural ingredients in food, including preservatives, flavourings, colours and artificial sweeteners. Vitamins and minerals were sometimes included in this category of unhealthy ingredients. • fortified foods were generally perceived to be more expensive than non-fortified foods. • most participants found labelling confusing in regards to fortification, and were often unable to determine whether vitamins and minerals in foods were added or naturally occurring.	• indifference to whether food is fortified; • questions about the necessity of purchasing fortified foods; • concerns about the effectiveness of fortification.
Positive Perceptions	**Negative Perceptions**	**Neutral Perceptions**
In New Zealand and Tasmania, there were strong positive perceptions among participants regarding iodine	*For these participants' mandatory fortification represents a loss of choice, exacerbating dissatisfaction with the*	*Among those generally stating neutral opinions, they*

Positive	Negative	Neutral
fortification. It was considered the addition of iodine to salt is necessary due to perceptions emphasised in the media. [And participants aged ≥ 36 years]	*concept of fortification in general.*	*questioned the necessity of adding vitamins and minerals.*
Reasons for positive perceptions in the fortification of foods	**Reasons for negative perceptions in the fortification of foods**	**Reasons for neutral perceptions in the fortification of foods**
The main negative perception about vitamin and mineral supplements being 'unnatural' was not directly applied to folic acid. This was likely due to doctors recommending folic acid be taken for a specific purpose. *Following a discussion on the benefits of iodised salt some participants mentioned they would purchase the fortified product rather than other types of salt.*	*An influential source of negativity arose from the mistrust in health information disseminated through the media. Healthy food recommendations change regularly and are often overturned. Thus, when new information is disseminated, there is a high level of scepticism.* *A high level of mistrust was also associated with food producers and manufacturers in relation to their motivations for fortifying foods.*	-

FSANZ 2013

The study commissioned by FSANZ in 2013 was a population survey administered through computer-assisted telephone interviewing (CATI).[20] The results from the qualitative study (FSANZ 2010)[23] were used to develop the population survey questionnaire.

The research objective included understanding and quantifying:

- consumers' awareness of food fortification, and specifically whether they were aware of mandatory fortification and voluntary fortification;
- consumers' awareness and understanding of mandatory folic acid and iodine fortification in Australia and New Zealand;
- consumers' acceptance of mandatory folic acid and iodine fortification in Australia and New Zealand;
- consumers' awareness and attitudes towards the fortification of foods with low nutritional value with vitamins and minerals;
- consumers' understanding of voluntary fortification, including their ability to identify fortified foods;
- whether, and to what extent, consumers make purchasing decisions based on the presence of added vitamins and minerals in food; and
- how consumers use foods fortified with vitamins and minerals in their diet.

The population aged 16 years and above in Australia and New Zealand was the target group. A questionnaire was developed with slight differences between Australia and New Zealand because of food regulation differences. After pilot testing, the survey was conducted in June 2011 and July 2011. Landline phone numbers were randomly selected stratified by area. The results were weighted to the population norms.

The response rate was 9% for Australia and 11.1% for New Zealand, with a refusal rate was 58% in Australia and 42% in New Zealand. Eight hundred respondents in Australia and 802 from New Zealand completed the survey.

The results revealed that only a small proportion of respondents were aware that, for some foods, the government makes it compulsory for manufacturers to add particular vitamins or minerals.

The survey concluded that based on the responses:

- Australians and New Zealanders had a high awareness of voluntary fortification (>75%);
- a much lower level of awareness existed of mandatory fortification (19.2% for Australia and 23% for New Zealand);
- only 34% of Australians knew bread was mandatorily fortified (24% for New Zealand);
- more New Zealanders were aware of the benefits of iodine fortification than Australians (33% versus 19%);
- almost half of those surveyed favoured mandatory iodine fortification in Australia (49.5%) and New Zealand (47.3%);
- a substantial minority supported mandatory folic acid fortification (43% in Australia and 37% in New Zealand);
- a substantial minority believed some foods should not have vitamins or minerals added to them (41% in Australia and 42% in New Zealand); and
- consumption of fortified bread was high (over 88%).

There were some limitations associated with the survey methodology, especially the use of landlines. Mobile-only households would be excluded. This may bias against younger people. Additionally, the low response rate typical of phone surveys raises questions about representativeness.

Iodine fortification in Australia

Eight publications retrieved from this literature search provided information about consumer awareness, behaviour and outcomes associated with iodine in Australia.

Table 97: Australian literature for consumer awareness for iodine

Publication	Knowledge	Behaviour (Food frequency)	Urinary iodine
Charlton et al. (2013)[108]	Yes	Yes	Yes
Charlton et al. (2012)[113]	Yes	Yes	No
Charlton et al. (2012)[156]	Yes	Yes	Yes
Charlton et al. (2010)[112]	Yes	Yes	Yes
Axford et al.[157]	Yes	Yes	No
FSANZ 2013[20]	Yes	Yes	No
Yeatman et al.[22]	Yes	No	No
FSANZ 2010[23]	Yes	Yes	No

The literature searches for consumer awareness of iodine food fortification in Australia located six publications (in addition to the FSANZ publications). Several of these publications included previous surveys in their results. Accordingly, their results should not be considered independent of each other.

In Australia, a number of studies published between 2010 and 2013 explored respondents' understanding and knowledge of iodine fortification before and after the mandatory fortification of salt for use in bread.[22,108,112,113,156,157] Several studies undertook measurement of urinary iodine via the collection of urine samples. Some studies used a self-administered iodine specific food frequency questionnaires (FFQ), which allowed modelling of the daily intake of iodine per participant. These studies then compared the results of the FFQ with the survey responses on the perceived levels of iodine intake (Table 97).

The results indicated a poor awareness of intake and the benefits/risks of iodine in the diet. However, the studies concluded that knowledge related to iodine intake during pregnancy has improved between 2007 and 2012.

Yeatman et al.[22] undertook a pilot study involving four focus groups with twenty women (aged 20-49 years). The participants were recruited from three worksites/educational facilities. The study concluded that the women were unaware of the role of iodine in ensuring good health.[22] There was a degree of concern about the loss of choice and the participants suggested a mandatory education program should accompany mandatory fortification to explain its purpose and benefits.[22]

Charlton et al.[156] undertook a study of 78 non-pregnant women recruited from workplaces prior to mandatory iodine fortification. A 24-hour urine collection and a spot UIC was included in the study. Iodine intake was calculated from the 24-hour urine collection. Approximately 25% had an estimated iodine intake of less than 100 µg/day, and the results of the UIC showed a median UIC of 56 µg/L, indicating mild iodine deficiency in the population. The level of knowledge about iodine deficiency being a health problem was low. Approximately 50% supported fortification as a strategy to address iodine deficiency.

Charlton et al.[112] also undertook a study of 139 pregnant women recruited pre-mandatory fortification. This study found that knowledge of the adverse health effects of inadequate iodine intake was poor. Approximately half the participants identified fish (58%) and iodised salt (51%) as good sources of iodine. Only a small number of participants (11%) reported they had intentionally changed their diet to increase iodine intake during pregnancy. Fifty-nine per cent of women indicated supplement use during their pregnancy, of which 35% contained iodine. Twenty per cent of women were confident that their intake of iodine was adequate, 6% knew their diet did not provide enough iodine, and 74% did not know. Only 17% of participants indicated that they received sufficient information to make informed decisions regarding iodine. However, the result of the urine test (n=110) from the participants indicated that only 14.5% of women had UIC values of 150 µg/L and 15% had UIC values, below 50 µg/L. In addition, those who were taking supplements that contained iodine had significantly higher UIC levels (MUIC 139.1 µg/L) than those who were not (90.8 µg/L).

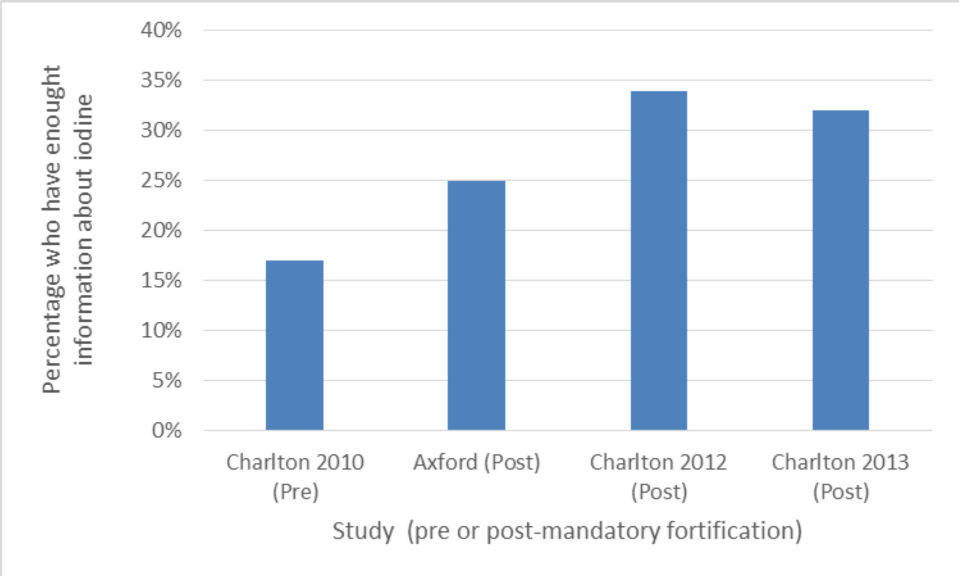
Axford et al.[157] undertook a survey of 60 breastfeeding mothers recruited from early childhood centres in the Illawarra region of NSW after mandatory fortification's introduction. The majority of those recruited had university degrees. The knowledge of adequate iodine intake from diet was poor (Figure 8). A series of questions about knowledge of iodine and a self-administered food frequency questionnaire was undertaken. Only half of women were taking supplementation and 36% of women were estimated as being below the EAR for iodine.

Charlton et al.[113] also undertook a comparative study of the knowledge among Australians of iodine fortification of bread before (2007-2008) and after mandatory fortification, (2011-2012). This study involved three cohorts of women: pregnant women (2007-2008), women not pregnant (2007-2008), and pregnant and lactating women (2011-2012). The comparison included results from the surveys used in the research conducted by Charlton in the pre-mandatory fortification period[113,156] and the post-mandatory fortification research from Axford .[157]

Only 5% of women in the 2011-2012 survey identified bread as a legal food fortified with iodine. The mean intake of iodine is increased with fortification. The proportion of pregnant and lactating women below the EAR post-mandatory fortification was 35% and 60% respectively. An increased proportion of pregnant women identified that they had changed their diet for iodine post-mandatory fortification compared to pre-mandatory fortification[113](22% versus 11%).

An article by Charlton et al.[108] presented a review of the data collected from pregnant women in 2008, 2011 and 2012, on mandatory iodine fortification's impact on UIC results in Australia. The study also reported that knowledge of iodine deficiency as a public health problem was poor (78%). Only 3.7% knew of mandatory fortification of bread, and 39-49% (across three surveys) were aware of using iodised salt for cooking.

Figure 8: Knowledge to make decisions involving iodine during pregnancy



Several studies examined if women believed they had received sufficient information about iodine (amongst others) to make an informed decision within their pregnancy (Figure 8). The knowledge about iodine in Australia is increasing, albeit from a low base. The majority of the peer-reviewed literature related to pregnant women from specific geographic locations.

Folic acid fortification in Australia

The literature searches for consumer awareness of folic acid food fortification in Australia identified four publications. Two studies presented the results of surveys conducted before or up to 2007 and are reviewed below. Several articles included in for iodine in Australia have also been included in this Section. This is because these articles reported results about the information provided to pregnant women about folate/folic acid.

Two studies were based on a cross-sectional telephone survey conducted in Western Australia in 2007 using a random sample of 1000 participants. This survey was conducted prior to the introduction of mandatory folic acid fortification of bread in September 2009.[158,159]

Of the 1000 respondents, 53% were aware of folic acid/folate fortification in bread (which was voluntary at that point in time) and 13% were concerned about it. In relation to food fortification. Approximately 10% agreed with a statement that 'folate should not be added to foods,' 43% disagreed with the statement and 42% were unsure. Most respondents indicated they would neither buy foods specifically for the added folate (60%) nor avoid foods with added folate (63%).

Only one in ten respondents indicated they would avoid foods with added folate, while around a quarter of respondents were uncertain. On average, however, 36% of respondents agreed with the benefits of fortifying/eating foods with folate, 17% would buy foods specifically for added folate, and 60% agreed that adding folate to food has health benefits for most Australians as well as personal health benefits. The survey indicated that more than 50% of respondents accepted bread fortification with folate, but 76-79% indicated that they needed more information on benefits/risks, and 47% said they were confused about the benefits of added vitamins. The authors concluded that the community was more likely to support than oppose fortification of foods with folate.[159]

Another publication using the same dataset, Molster et al.[158] assessed self-reported knowledge about folate. Almost half of women (ages 18-44) (N=263) 'know a small amount about folate' and 32% knew nothing. However, 94% of the respondents had heard or read about folate/folic acid. Women of childbearing age were more likely than other adults to know about the association between folate intake and birth defects (82% v 56%) when prompted. Unprompted awareness of the link between folate and birth defects was 33% among women of childbearing age and 22% among other adults. Forty-one per cent of women of childbearing age did not know that folic acid should be consumed periconceptionally to reduce the risk of spina bifida.

Overall, half the respondents did not take mineral or vitamin supplements, and two-thirds of the respondents did not know if the products they ate were fortified with folic acid. Less than 10% consumed fortified products specifically because they contained 'added folate.' One-third of women of childbearing age (39%) reported a preference for supplements rather than fortified foods while 36% did not prefer supplements and 25% were unsure or had no opinion. Only 5% of the women aged 18-44 years reported consuming food fortified with folate (2 weeks prior to interview). However, 23% reported consuming fortified foods but not specifically because of added folate.

Parkinson et al.[21] aimed to explore the utility impact of a loss of consumer choice from implementing mandatory health programs based on the case study of folic acid fortification of bread-making wheat flour. The study concluded that respondents were less likely to prefer an initiative if it was introduced on a mandatory rather than voluntary basis and would require some compensation for folic acid fortification. However, when given a choice, respondents were also more likely to prefer an initiative that produced a higher number of NTDs avoided and a lower incidence of neurological problems due to B_{12} deficiency masking.

Axford et al.[157] and Charlton et al.[113] reported the results of surveys of pregnant and breastfeeding mothers. These surveys assessed the percentage of respondents that reported having enough information to make decisions for a variety of different nutrients and risks. Seventy per cent of the 60 breastfeeding women reported having enough information with regards to folic acid/folate.[157] . In 2008, 78.5% (in 2011 72%) of pregnant women reported having enough information regarding folic acid/folate.

Iodine fortification in New Zealand

The literature searches for consumer awareness of iodine food fortification in New Zealand identified two publications in addition to the FSANZ reports.

Nithiananthan et al.[160] reported the results of a 2013 questionnaire on iodine status in New Zealand and awareness of current recommendations for iodine supplementation. The respondents (N=72) included healthcare workers (n = 25) (10 pharmacists, 9 midwives, six hospital nurses) and (n=47) and a sample of women who were not health care professionals (n=37 pregnant, n=10 breastfeeding) recruited in antenatal, postnatal and outpatient clinics. All the healthcare professionals were aware of dietary iodine supplementation through bread fortification compared to 72% of women. The majority of those surveyed were aware of iodine fortification of bread. The method of survey was a paper-based questionnaire which was asked to be completed "on the spot".[160]

Brough et al.[130] recruited women (n=127) at two points in time: in 2009 before mandatory iodine fortification (pregnant (n=25), breastfeeding (n=32)) and in 2011 post-mandatory iodine fortification (pregnant (n=32) pregnant, breastfeeding (n=36)). The participants completed a questionnaire and provided a urine sample. This study is also discussed in Section 6.4.

Brough et al.[130] reported low awareness of iodine deficiency and mandatory iodine fortification of salt to bread (15-22%). There was also a low awareness of the problem of iodine deficiency.[130]

Over half (56%) of pregnant women and 28% of breastfeeding women were aware of government subsidised iodine supplementation initiatives (subsidies at the pharmacy or the point of purchase). Forty-one (41%) of pregnant women and 19% of breastfeeding women were using these initiatives, respectively. Estimated mean daily iodine intake from the FFQ was 217 µg/day, with 74% of women in this study having achieved EAR for iodine compared to 20% in 2009.

The studies are convenience studies with a low sample size. They suggest an improvement in knowledge of iodine fortification over time.

Folic acid fortification in New Zealand

The literature searches for consumer awareness of folic acid food fortification in New Zealand identified three publications. Around half to two-thirds of women were aware of folic acid food fortification and approximately a sixth supported mandatory fortification prior to the mandatory folic acid fortification of bread in New Zealand.[163]

A survey of postpartum women residents in maternity wards was conducted across New Zealand from March 2011 – April 2011[161,162] The aim of the survey was to investigate knowledge of current behaviour among pregnant New Zealand women prior to mandatory fortification's potential implementation in May 2012.

The self-administered questionnaire was completed by 758 women (78% of 968 women who were invited to participate). The total sample used was 723, as 35 women did not meet the inclusion criteria for maternal age or gestational duration. The study assessed knowledge of current folate recommendations, awareness, consumption, and opinion of folate-rich and folic acid fortified foods and dietary supplement use[163] The results showed that 56.2% of women were aware that folic acid is an important nutrient and 67.7% were aware that it should be taken periconceptionally. In this survey cohort, 56.7% of women had planned pregnancies. All women with planned pregnancies were aware of folic acid, but only 64% were aware that folic acid contributed to a reduced risk of birth defects. Although three-quarters knew the correct period for folic acid supplementation, only 54% took it as recommended. In comparison, women with unplanned pregnancies had a lower knowledge and uptake of folic acid supplementation.

Mallard et al.[163] reported the results of a survey of pregnant women (n=708) regarding their knowledge, opinion and periconceptional consumption of folic acid-fortified foods.[163] Half (54.6%) indicated that they were aware that folic acid was added to some foods, with 44.2% aware before conception and 10.2% became aware during pregnancy. Furthermore, around 27.3% of women noticed 'folic acid' on food labels, 9.8% first noticed it during pregnancy.

Half (49.7%) of women were aware that some bread is voluntarily fortified with folic acid, with 7.8% becoming aware during pregnancy. Among these women, only 1.6% intentionally bought folic acid fortified bread (periconceptionally) by inspecting the labels, and 6% (n=26) bought it sometimes. Nine per cent did not consume manufactured bread, and 82.6% did not (intentionally) purchase fortified bread. Of all the respondents, 14.6% indicated that folic acid fortification of bread should be mandatory and 35.3% preferred voluntary fortification of bread. Only 3.6% thought that folic acid should not be added to bread, with 46.5% remaining unsure. Of all the respondents, 85.5% did not intentionally consumer any folate-rich foods in the periconceptional period.

Conclusions

Several themes emerged from this Report's updated literature review:

- Knowledge of the importance of iodine in pregnancy was lower than that of the importance of folic acid in pregnancy.
- Among the general population, awareness of the mandatory fortification initiatives scheme was low.
- The importance of the potential for loss of choice due to mandatory fortification and the subsequent loss of utility was acknowledged, but the magnitude of any such loss cannot be known with certainty.
- When asked, a substantial minority of respondents supported mandatory folic acid fortification in Australia (43%) but less so in New Zealand (29%).
- When asked, almost half of respondents supported mandatory iodine fortification in Australia and New Zealand.
- The majority of the peer-reviewed literature has focused on the demands and requirements of iodine in the pregnant and breastfeeding stages of life.

8.5 Conducting a cost-benefit analysis

8.5.1 Overview

The purpose of a cost-benefit analysis is to ascertain if the community is better off with one scenario rather than an alternative scenario.[44] A CBA allows the consideration of all costs and benefits rather than making decisions based on selected outcomes.[44]

The Office of Best Practice outlines why a CBA is useful for decision makers facing policy decisions. It states that a CBA *"encourages decision makers to take account of all the positive and negative effects of a regulatory proposal, and discourages them from making decisions based only on the impacts of a single group within the community"* (page 115).[164]

Calculating the impact of regulatory change is acknowledged to be a difficult practice.[164] This Report aimed to determine the value for money of the mandatory fortification initiatives with the use of a CBA (see Section 2.3).

8.5.2 Steps in conducting a cost-benefit analysis

The Productivity Commission breaks the conducting of a cost-benefit analysis into three stages.[44]:

1. Scoping;
2. Analysis; and
3. Conclusion.

Scoping is determining the purpose of the evaluation, the nature of the problems, the objectives, the potential alternatives and the perspective of the CBA. The perspective of the analysis determines which costs or benefits should be considered. Aspects of the scoping could be determined when considering the evaluation criteria in commissioning the CBA (see Section 7.2).

Analysis consists of identifying, measuring or quantifying, and valuing the costs and benefits associated with each alternative. In some situations, specific costs and benefits may not be able to be measured or quantified. An example in this CBA is the loss of consumer choice associated with mandatory folic acid fortification. In these cases, the lack of ability to measure or quantify should be made explicit and the likely bias described.

In the final concluding stage, the net benefit of each alternative is calculated and the results compared.

8.5.3 Scoping considerations

This Report undertook a separate economic evaluation for each of the three initiatives:

1. An economic evaluation of mandatory folic acid fortification in Australia;
2. An economic evaluation of mandatory iodine fortification in Australia; and
3. An economic evaluation of mandatory iodine fortification in New Zealand.

For each economic evaluation, one alternative is the mandatory fortification initiative. The alternative is the pre-mandatory fortification suite of policies that existed prior to the introduction of each initiative.

The status quo was not a single policy but rather a collection of policies and behaviours that were engaged in prior to mandatory fortification. Different jurisdictions had different policies and different policy responses. For example, Tasmania pursued an intensive policy of voluntary fortification of iodine whereas Western Australia introduced a strategy of education about the risks of NTDs early in the 1990s.

Regional differences may be important in discussing both benefits and costs. This Report has drawn attention to these regional differences where appropriate, especially for mandatory iodine fortification in Australia.

The population of interest (or scope) for the economic evaluations was the Australian or New Zealand population, as one alternative in each of the evaluations was a mandatory fortification initiative affecting a widely consumed food. The economic evaluations did not consider the transient population visiting either Australia or New Zealand. The economic evaluations within this Report also did not consider exported foodstuffs that may have been affected by mandatory fortification as this was outside of scope for the economic evaluation. Less than one per cent of turnover was exported in 2001-2002, and there was little importation.[9]

8.5.4 Analysis considerations

Identifying costs and benefits

The first step was to identify the costs and benefits associated with the change from the alternative of no mandatory fortification to mandatory fortification. An example of the identification of benefits and costs associated with a reduction in NTDs is presented in Table 98.

There were several potential benefits identified for the individuals involved. These benefits included increased health, increased workforce participation and reduced burden of funding health care (out-of-pocket costs). Additionally, there were potential benefits identified for mothers and families with an NTD pregnancy. These potential benefits included a reduction in the number of terminations, a reduction in the time spent caring for an NTD-affected individual and decreased expenditure on health care. The potential benefits for those responsible for the provision of health and disability care included a reduction in the requirement to provide that care. Finally, the potential societal benefit of an increase in productivity was identified.

There are two common challenges in identifying costs and benefits. The first challenge is avoiding double counting of benefits and costs. The second challenge is taking account of transfer payments, whereby individuals are made better or worse off, but there is no associated increase in production or generation of household income. A common example of a transfer payment is an unemployment benefit.[164]

Double counting refers to valuing the same benefit or cost in several different ways. An example might be valuing the health gain of not having an NTD for an individual, and then also for that individual's family, the government and society overall.

Changes in transfer payments (such as unemployment benefits) may not be associated with productive activities. The gains (for individuals) and losses (for the government) balance each other out. So while these transfer payments have been identified in the table below, they are neither measured (quantified) or valued. This is because their net measurement and valuation are zero. There is a distributional impact from these transfers, but these have not been included in this Report's analysis.

Table 98: Identification of benefits for reduction in NTD

Potential Benefit	Potential recipient(s) of benefit
Better health.	Individual who otherwise would have been impacted.
Improved workforce participation.	Individual who otherwise would have been impacted by increased income, society through increased taxes and production.
Reduced health care requirement.	Various departments of health and other funders of health care. Individuals and families who have to fund the care
Reduced terminations associated with NTDs.	Families and the individuals involved.
Reduced caring burden.	Increase in leisure time and potential working time for families involved.
Reduced transfer payments (unemployment pensions and disability	Governments and families but these are balanced against each other as these are transfer payments.

Potential Benefit	Potential recipient(s) of benefit
pensions).	

Measuring and monetarising costs and benefits

There are three levels for which identified costs and benefits can be reported.

1. The costs and benefits can be monetarised (that is, converted into a numerical monetary value). An example in this Report is the cost of health care associated with the treatment of NTDs in the folic acid fortification.

2. The costs and benefits can be measured but not monetarised (that is the magnitude of the cost or benefit is identified). An example relates to the health impacts of folic acid fortification in terms of Quality-Adjusted Life Years (QALYs), which was used in this Report's cost-utility analysis.

A QALY is a measure which combines the quantity of life (life years) weighted by the value of the health state that time is spent in (the quality).[165] Better health states are more highly valued and have a higher weighting. Death is a health state with a value of zero, and full health is a health state with a value of one. The health difference between having an NTD and not having one can be measured by the difference in the QALYs between the two health states.

3. The costs and benefits can be identified but neither measured nor monetarised. This means the cost or benefit is described in qualitative terms. Examples in this Report include the loss of consumer choice or the IQ impact on productivity in the iodine fortification CBA.

There are several reasons why an identified benefit may be neither measured nor monetarised.

In some circumstances, measurement and monetarisation may result in additional uncertainty for the decision maker. An example is the added productive value associated with improving human capital as a result of successfully addressing iodine deficiency's re-emergence. The actual value of this added productive value was found in this Report to be highly uncertain in Australia and New Zealand. There is no consistent evidence that iodine fortification in mildly deficient countries improves human capital.

In other circumstances, such as the case with the loss of consumer surplus, it is currently not known if this loss is greater than zero. So, measuring and valuing the cost of a loss of consumer surplus may give it a greater emphasis than appropriate.

This Report discusses when these circumstances occur in the relevant section. This uncertainty is the major reason for this Report's construction of the base case cost-effectiveness analysis and the extended CBA.

The policy objective of mandatory iodine fortification was to address the population's iodine deficiency. This deficiency was determined by the median UIC. This was quantified in this Report using two different measures: the percentage of the population over the relevant MUIC threshold, and per million individuals or tests that moved from below to above this threshold.

This outcome was not quantified as QALYs nor monetarised (for the QALY changes and the productivity changes). It was not converted into QALYs because of uncertainty about the population health effects of iodine sufficiency. It was not monetarised because of uncertainty associated with the productive impact of increased iodine sufficiency in Australia and New Zealand.

Discounting

In economic evaluations, it is conventional to apply discount rates to costs and outcomes that occur beyond the first year of the analysis.[93] Typically, the same discount rate is applied to both costs and outcomes. This takes into account the distribution of costs and benefits over time. This is because, usually, it is preferable for benefits to be received now and costs to be deferred until later. This is known as time preference.[93]

The calculated value of costs and benefits is reduced when they occur in the future. Usually, this calculation is undertaken using a net present value calculation:

$$Present\ Value = X/\ (1 + r)^{t}$$

Where X is the cost or outcome of interest (for example QALY), r is the discount rate (5% in this Report), and t is the number of years in the future. In the evaluation of mandatory folic acid fortification, both the costs occurring in the future (health care costs) and the benefits (QALY gains) were discounted. This Report discounted these costs and benefits heavily as they occur a long way into the future.

8.5.5 Interpreting the results

The relevant measurement used in this Report was the incremental change between the two policy alternatives (mandatory fortification versus the prior status quo).

Cost-effectiveness analysis

In the base case for each of the three economic evaluations, not all of the costs and benefits are monetarised, as discussed. Therefore, these alternatives can be – and were - compared in an Incremental Cost Effectiveness Ratio (ICER):

$$ICER = \frac{Cost_A - Cost_B}{Effectiveness_A - Effectiveness_B}$$

This type of economic evaluation is termed a cost-effectiveness analysis. The results are produced by calculating the difference in the costs divided by the difference in the outcomes. The ratio is the cost per outcome.

Evaluating mandatory folic acid fortification's value for money compared to the no mandatory iodine fortification, the outcome of interest was NTDs avoided. Thus, the ICER represented the cost per NTD avoided.

Evaluating mandatory iodine fortification's value for money compared to the no mandatory iodine fortification, the outcome of interest was the proportion of the population that moved from below to above the MUIC threshold. Thus, the ICER represented the cost per percentage of the population moved from below to above the MUIC threshold.

Cost-utility analysis

When the outcome is measured in QALYs, the analysis is termed a cost-utility analysis. This is the character of the base case economic evaluation undertaken for mandatory folic acid fortification in Australia in this Report.

In general, two results are produced by an economic evaluation considering two alternatives.

- One result can both generate more health and cost less than the other. That is, one alternative is better in all ways than the other. In this situation, decision-making is considered to be relatively simple. The cheaper, more effective alternative should be chosen. Technically, in this situation, one alternative dominates the other. This is the case with mandatory folic acid fortification. So, in this case, reporting the ICER is of limited value.

- The other result is that one alternative is both more expensive and more effective than the other. Then a decision must be made about whether the additional cost is worth the additional benefit. The lower the cost associated with each unit of additional benefit (the lower the ICER), the more likely it is to be considered worthwhile. Therefore, the decision to be made is about the value of the outcome relative to the cost of the outcome. This is the case with mandatory iodine fortification. It is more expensive and more effective than the alternative of no mandatory fortification.

Each outcome may have a different value of societal acceptability. For example, the cost per NTD avoided that is acceptable to society may differ from the cost per percentage improvement in iodine sufficiency. The costs are thus not comparable.

8.6 Previous economic evaluations of mandatory folic acid fortification

8.6.1 Review of the economic literature

This Report undertook a systematic literature review. Articles were retrieved if they met the inclusion criteria outlined below. The bibliographies of all retrieved publications were hand-searched for any relevant references missed in the database search (pearling).

8.6.2 Search strategy

Search terms: fortification, fortified food, folic acid, folic, economic evaluation, cost effectiveness analysis, cost-benefit analysis, cost utility analysis, costs and cost analysis.

The search was restricted to human studies and English language articles.

Searches were conducted in several electronic databases to identify the relevant studies. These databases included PubMed (Medline and PreMedline), EMBASE, the Cochrane Library, the Centre for Reviews and Dissemination (CRD) databases (Database of Abstracts of Reviews of Effects (DARE), the National Health Service Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database.

Study inclusion and exclusion criteriaTable 99 details the inclusion and exclusion criteria used. Additional papers were identified by hand-searching the reference lists of those studies meeting the inclusion criteria.

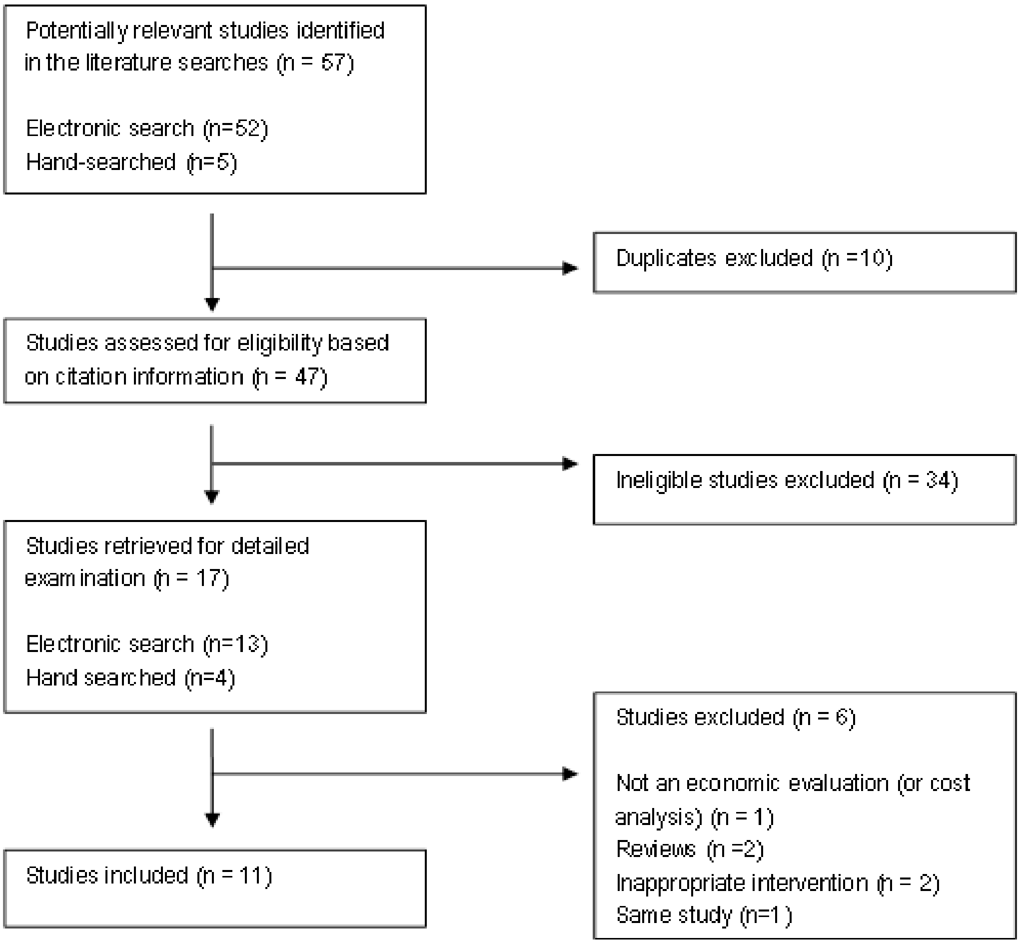
Table 99: Selection Criteria

Inclusion criteria	Exclusion criteria
Economic Evaluation (CUA, CEA) or cost analysis	Not an economic evaluation or cost analysis
Intervention: mandatory fortification of foodstuff with folic acid	Inappropriate intervention
English full-text papers	Papers published in non-English language without an English abstract
Systematic Literature review and unique studies	Editorials, comments, letters, conference abstracts

Abbreviations: CEA, cost-effectiveness analysis; CUA, cost-utility analysis

The search returned 57 articles (52 from electronic searches and 5 from other sources). From this initial result, 10 duplicates were removed with 47 articles remaining (see Figure 9). Following a review of titles and abstracts, 32 articles were excluded, and two trials were excluded. The full-text review thus consisted of 17 articles (13 from the search and four hand-searched from reference lists). Six articles were excluded for the following reasons: two were reviews; two were inappropriate interventions, one was not an economic evaluation and one was the same study as another paper.

Figure 9: PRISMA flow chart for economic literature search



De Steur et al.[166] was excluded as it was an economic evaluation of the multi-micronutrient biofortification (crop breeding) of rice. Hertrampf and Cortes[167] presented the results from the same study for the fortification of bread in Chile.

The review of the literature identified a systematic literature review.[72] This review included seven relevant economic evaluations.[46,96,168-172] Another review by Pachón et al.[173] cited Yi et al.[72] and the most recent Australian study Rabovskaja et al.[45] Hand-searching of the literature revealed a book chapter by Kelly et al.[174]

The search of the grey literature identified two studies: a cost-benefit analysis and a cost analysis of fortification of bread-making flour with folic acid by Access Economics for FSANZ.[70,175]

8.6.3 Studies of mandatory folic acid fortification of flour used in bread making

A total of 11 studies met this Report's criteria. A summary of study characteristics is presented in Table 100.[45,46,67,96,168-172,174] Four of the 11 studies performed ex-post evaluations of mandatory initiatives in the USA, Chile and South Africa.[46,168,170,172] Four studies were found examining the ex-ante cost of mandatory fortification of bread making flour in Australia. There are three such studies for New Zealand. Therefore, there are no ex-post economic evaluations of the mandatory folic acid fortification of bread making flour in Australia. Bentley et al.[46] found that fortification was predicted to be cost saving and provided positive net QALY gains at all fortification levels.

There was a consistent approach in the literature to including the benefits associated with a reduction in NTDs. There was, however, an inconsistent approach in the literature to including potential health risks associated with mandatory fortification. Neurological disorders were the most commonly included health-related adverse effect.

The majority of the economic evaluations found mandatory fortification to be superior to the alternatives to it.

Table 100: Included studies and summary study characteristics

Study	Analysis	Country	Type	Health outcomes	Unit of utility	Findings
Bentley, 2009	Ex post	USA	CEA/CUA	NTD; MI; Vitamin B_{12} masking; Colon Cancer	QALY	Dominant
Dalziel, 2010	Ex ante	AU/NZ	CEA/CUA	NTD	DALY	AU: Uncertain cost-effectiveness, NZ: not cost-effective
Grosse, 2005	Ex post	USA	CBA/CEA	NTD; neurological damage	NA	Dominant
Jentink, 2008	Ex ante	Netherlands	CEA/CUA	NTD [Anencephaly and cervical lesion; spina bifida (thoracic lesion, lumbar lesion and sacral lesion)]	QALY	Dominant
Llanos, 2007	Ex post	Chile	CEA/CBA	Anencephaly; spina bifida (all births); All NTDs; fetal death and infant death	DALY	Dominant
Rabovskaja, 2013	Ex ante	AU	CEA/CUA	NTD; severe neuropathy	QALY	Cost-effective at $AUD 11 485 per QALY gained

Study	Analysis	Country	Type	Health outcomes	Unit of utility	Findings
Romano, 1995	Ex ante	USA	CBA/CEA	Spina bifida; Anencephaly	NA	Benefit-to-cost ratio 4.3:1 (140 µg/100g grain)
Sayed, 2008	Ex post	South Africa	CBA	NTD (Spina bifida, anencephaly); oro-facial clefts;	NA	Cost-benefit ratio 46:1
Kelly, 1996	Ex ante	USA	CEA/CUA	NTD; Vitamin B_{12} related neurological complications	QALY	140 µg (cost saving, dominated by 350 µg/700 µg); 350 µg (cost saving, dominated by 700 µg); 700 µg (dominant)
Access Economics, 2006a	Ex ante	AU/NZ	CBA	NTD (Spina bifida, anencephaly, encephalocoele)	NA	Ratio of benefits to cost 8.4:1 (100 µg); 20.1:1 (200 µg) for Australia Ratio 1.5:1 (100 µg); and 3.2:1 (200 µg) for New Zealand
Access Economics, 2006b	Ex ante	AU/NZ	CA	NA	NA	NPV industry ($AUD 18.9 million); NPV government ($NZD 4.5 million) over 15 years

Abbreviations: AU, Australia; AU/NZ, Australia and New Zealand; CA, cost analysis; CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DALY, disability-adjusted life year; NTD, neural tube defect; NPV, net present value; MI, myocardial infarction; QALY, quality-adjusted life year

8.7 Iodine status, IQ/human capital and productivity

8.7.1 Introduction

Extrapolation of the iodine deficiency status to the societal benefit via changes in IQ/human capital required a series of linked associations to be modelled as outlined below between the parameters:

- Iodine sufficiency and changes in IQ/human capital; this is the first linked extension in Section 5 and Section 6.
- IQ/human capital and wages/productivity; this is the second linked extension in Section 5 and Section 6.
- Wages and societal benefit; this has been assumed in Section 5 and Section 6.

This Section evaluates the level of uncertainty and confidence held in each of these associations. The substantial uncertainty and limited evidence are the reasons why this Report recommends not using the results of the cost-benefit analysis for decision-making purposes.

8.7.2 Association between addressing mild iodine deficiency and IQ improvement

The relationship between addressing and improving mild iodine deficiency and IQ/human capital improvement is the first of the linked extensions discussed in the economic evaluations in Section 5 and Section 6.

Various figures have been cited for IQ improvement if iodine deficiency is reduced. An oft-quoted figure is a difference of between ten and thirteen IQ points.[176] Similar results have been found in other meta-analyses.[15,177] At the most severe end of the continuum, treating severe iodine deficiency will reduce the incidence of congenital cretinism.[15] At a population level, the link between treating severe iodine deficiency and improvement in IQ has been demonstrated.[15] However, a link between reducing mild-moderate iodine deficiency and improved cognitive functioning at a population level is less well established.[176]

Zhou et al.[176] conducted a review of RCTs of the effect of iodine supplementation during pregnancy on child development. They noted that there were no trials conducted in mild-moderate iodine deficient populations that reported childhood development outcomes. The authors were critical of the quality of the evidence of the effect of iodine supplementation on the cognitive function of children. They also noted future trials were unlikely. Therefore, only lower grade evidence is available to be assessed. A recent discussion of the consequences of iodine deficiency and excess in pregnant women concluded well-designed prospective RCTs of iodine supplementation in mild-moderately iodine deficient pregnant women are urgently needed.[178]

One trial listed in the international Clinical Trials database is assessing the impact of iodine supplementation during pregnancy in mild-moderate iodine deficient populations. This trial has finished recruiting, but the results are not available at the time of review (Clinical Trials Link). Participants were recruited from India and Thailand.

Several observational studies have demonstrated adequate iodine levels are associated with IQ, and literacy and numeracy skills, that are important in considering the impact of iodine deficiency on human capital development. It has also been suggested that iodine deficiency can impair fine motor skills .[179] A 2012 systematic review of studies concluded that the evidence was suggestive of a relationship between improved thyroid function during pregnancy and cognitive function in the offspring.[180] However, no conclusion could be drawn about iodine supplementation and cognition function in children who reside in a mildly iodine deficient area.[180]

Previous work has demonstrated that the chance of a child being in the lowest quartile for achievement (for IQ, literacy and numeracy) increases with decreasing maternal urinary iodine, even when adjusted for confounders.[181] This has been demonstrated in both Australia and overseas in mild iodine deficient countries.[182] However, this association has not always been demonstrated in countries that are iodine replete.[117] A series of observational studies conducted in OECD countries are presented in Table 101.

The groups being compared are the offspring of mothers whose maternal urinary iodine concentration were greater or less than 150 μg/L. For each measure, it has been standardised to a scale with a mean of 100 and a standard deviation of 15 by use of z-scores. This is the same mean and standard deviation as IQ scores.

Some of these observational studies, including those conducted in Australia, the UK and the Netherlands, adjusted for a range of confounders. The results of these studies indicate that an improvement in iodine intake was usually (but not always) associated with an improvement in the outcome measure used. These studies used control variables to eliminate the potential for omitted variable bias. However, the potential for endogeneity between maternal urinary iodine concentration and cognitive outcomes remained.

Table 101: Cognitive Impact of low maternal urinary iodine concentration

Source	Age of child review	Intellectual measure	Country	Confounders adjusted	Statistical difference	Assumed changes
Bath et al.[c,181]	8	Wechsler Intelligences Scale for Children	UK	Health and Social factors	1.35 OR of being in lower quarter	**2.5**
Bath et al.[c,181]	8	Wechsler Intelligences Scale for Children	UK	Health and Social factors	2.2 points	**2.2**
Ghassabian et al.[117]	6	Snijders-Oomen Niet-verbale intelligentie Test-Revisie	Netherlands	Health and Social factors	No statistical difference	**0**
Hynes et al.[c,182]	9	Naplan Spelling portion	Australia	Health and Social factors	38.6 decrease	**1.4**[a]
Hynes et al.[c,182]	9	All Naplan domains	Australia	Health and Social factors	Using the average z-score of all domains	**3.2**[b]
Rebagliato et al.[183]	1	Bayley scale of infant development	Spain	Maternal health factors	No statistical difference	**0**

[a] It is assumed that all domains contribute equally, but only one was different from zero
[b] All domains contribute but at their point estimates
[c] Studies listed more than once have assessed multiple measures of neurocognitive impact.
[d] Assumed change is mapped to a scale of 100
Note: the mean the studies was 1.1625 (adjusting for multiple outcomes in a study), and the median was 1.15 (adjusting for multiple outcomes in a study)
Source: http://reports.acara.edu.au/Home/Results#results, year=2010, jurisdiction of Tasmania

Some of the included studies attempted to correct for confounders, such as birth factors and socio-economic factors.

In the study by Hynes et al.[182] conducted in Tasmania, voluntary iodine fortification was introduced immediately after the cohort was born. Therefore, the differences noted may represent only differences in maternal iodine, as children had adequate iodine status after the introduction of voluntary fortification[11]. In Ghassabian et al.[117] the environment was iodine replete. Thus, the lack of an observed difference between groups in Ghassabian et al.[117] may be partly due to this factor.

An RCT, undertaken in Spain, randomised 131 pregnant women into three groups: use of iodised salt or one of two levels of supplementation.[184] The results indicate no differences between the groups in terms of the neurocognitive development of the children. The mean urinary iodine level in the group randomised to iodised salt was less than 150 µg/L.

Studies have partially addressed whether there is the potential to reverse iodine deficiency in children who may have experienced this deficiency in utero and early development. A New Zealand study by Gordon and colleagues[185] involved an RCT of children of 184 aged 10-13 years who were randomised to receive either a placebo or iodine (150 µg was used). The study was undertaken between 2007-2008. The Wechelser Intelligence Scale for children was used as an outcome measure. Urinary iodine concentration showed an improvement from a mean of less than 100 µg/L to a mean of over 100 in the intervention group. Overall, cognitive scores improved by 0.2 of a standard deviation (3 points for a standard deviation of 15).

The evidence related to the association between improvements in mild-moderate iodine deficiency and changes in IQ/human capital is of a lower level of evidence, mostly coming from non-experimental observational studies with generalisability issues. The evidence is also inconsistent. There is an RCT of supplementation in childhood in New Zealand, but this provides indirect evidence for the outcomes associated with iodine fortification.

There is also difficulty in assessing the relative impact of adequate iodine levels during pregnancy compared to adequate iodine levels in childhood. The lack of direct RCT evidence and the reliance on observational trials introduces a degree of uncertainty in assessing benefit. The evidence does suggest that exposure to iodine may improve cognition, this improvement can be seen with exposure prenatal, as an infant or in childhood. In order to monetarise the improvement in IQ/human capital, the benefit associated with an improvement in IQ/human capital has to be calculated.

8.7.3 Association between IQ and productivity changes

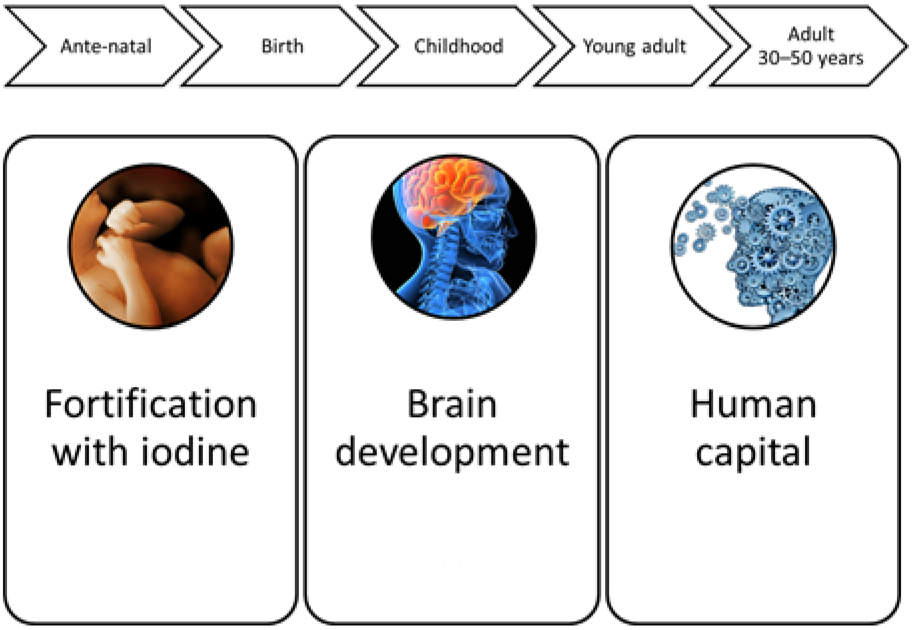
A key uncertainty in the cost-benefit analysis of iodine fortification is the relationship between the change in IQ/human capital and any subsequent improvement in productivity. This is the second linked extension discussed in Section 5 and Section 6.

Due to the association between intelligence and nutrition/health, it has been suggested that food fortification can increase individual IQ/human capital and thence income, and contribute to improved economic productivity. Health is considered a crucial determinant of cross-country income inequalities.[186] Extending the definition of health to include cognitive ability means that a reduction in this ability could significantly reduce the quality or quantity of human capital.[116] Most of the brain's development occurs from half way through pregnancy until a child reaches the age of two, which is the time considered most important for cognitive development.[186]

A substantial body of research is available that associates improvements in human capital to improvements in productivity (

Figure 10). Much of the research focuses on developing countries and suggests that mandatory food fortification initiatives have significant economic impacts based on health and monetary outcomes. A review of CEA and CBA by Horton et al.[187] found that fortification with iron, iodine, and potentially zinc provides significant economic benefits and results in large cost-benefit ratios. The unit cost of food fortification is low, and the effects via cognition were very important for iron and iodine. The value of the cost-benefit ratio was 6:1 for effects on physical productivity and increased to 36:1 if cognitive benefits were also included.[99]

Figure 10: Relationship over time between iodine and human capital



Aim

This Section reviews the literature that links cognitive functioning to productivity, aiming to:

- assess the impact on future earnings of differences in IQ as a proxy for cognitive functioning; and/or
- quantify the magnitude of impact on human future earnings for a change in IQ point.

IQ was selected as an appropriate measure to represent human capital because these scores are more readily available than other standardised test scores. Much of the empirical and clinical literature focuses on IQ scores. The purpose of this Section was to extend the results of the cost-effectiveness analyses in Section 5 and Section 6 and place a monetary value on the societal benefit of mandatory iodine fortification.

Search strategy

Several economic studies have investigated the impact of IQ on earnings. For this reason, a targeted review of the literature was undertaken to identify studies that link IQ to future earnings.

There has been an increase in the economic literature pertaining to intelligence and income over time. The targeted review was based on a narrative methodology, ensuring that only the most relevant literature was reviewed. Only articles pertaining to populations similar to Australia and New Zealand, or global studies including populations similar to Australia and New Zealand, were included. The cost-benefit analysis conducted by Access Economics in 2006[70] was used as an initial point of reference in identifying the available literature.

The literature search was conducted in the PubMed and Econlit databases, with the aim of identifying studies or analyses measuring the relationship between iodine and the impact on changes in IQ on wages or productivity. A search of the grey literature was also undertaken.

The reference lists of systematic reviews identified during the search were reviewed to include any relevant studies and analyses published in the years between 1990 and 2006. The search strings used in the databases were:

- Pubmed using the terms: *(((((IQ) OR intelligence) OR "intelligence quotient") OR intelligence test[MeSH Terms])) AND ((((income[MeSH Terms]) OR "human capital") OR productivity[MeSH Terms]) OR earnings) Sort by: Relevance Filters: published in the last 10 years*

- Econolit using the terms*: ((iq or intelligence quotient or intelligence)) AND ((income or earnings or productivity)).*

- The grey literature was searched using Google and the terms *"cost benefit analysis" AND "food fortification*". Only the first 10 pages were reviewed for relevance in these searches.

The titles and abstracts of each citation identified were reviewed for possible inclusion. Articles were then retrieved if they met the inclusion criteria outlined below:

- Studies reporting outcomes in a general human population in a developed country.

- Study linking IQ in adolescence or childhood to income or earnings i.e. economic evaluations or econometric studies using data from longitudinal studies were included. The studies needed to have their variables clearly defined and their method of evaluation specified.

- Systematic reviews identifying studies linking adolescent or childhood IQ to income or earnings i.e. general review papers were excluded. The method in which the systematic review was conducted was to be specified in the publication.

- Study outcomes reported were monetary and stated the year of study conduct and currency.

- The publication was in English.

The bibliographies of all retrieved publications were hand-searched for any relevant references missed in the database search (pearling). The search of the databases for PubMed and Econlit were combined in EndNote for overall review. The literature searches were conducted between 29 February 2016 and 11 May 2016.

Data extraction

To enable a comparison of the relevant studies data and information were extracted from the publications. It was expected that the studies identified would have considerable differences in their aims and reported other outcomes than the monetary value of one IQ point. Only information pertaining to analyses or assumptions linking IQ to earnings was extracted.

The key findings and conclusions reported in the table are only those that are pertinent to this literature review. The method used to assign a monetary value to an IQ point was of key interest.

The following information and data were extracted from the publications:

- objectives;

- study design;

- population;

- location and time;
- variables included in the analysis;
- outcome: specifically reporting a dollar value for an incremental change in IQ; and
- key findings/conclusions.

For any systematic reviews identified during the targeted search, data were only extracted if it reported an updated calculation of the monetary value of an IQ point. Otherwise, only the primary study was reviewed for adequacy of data extraction.

Results of the targeted literature search

A summary of the results of the literature search is presented in Table 102. After removal of duplicates from the EndNote database, a total of 22 publications were identified for detailed review. A list of the full citations of the included publications is provided in Table 103. Of the 22 publications identified:

- seven were economic evaluations using a cost-benefit analysis (Monahan et al.[188]; Perera et al.[189]; Bellanger et al.[190]; Pizzol et al.; Access Economics; Salkever[191]; Schwartz[192]);
- thirteen were econometric analyses using data from longitudinal studies (Spengler et al.[193]; Bergman 2015[194]; Bergman 2014[195]; Fletcher[196]; Rinderman et al.[197]; Jones and Schneider 2010[198]; Judge et al.[199]; Zagorsky[200]; Mueller and Plug[201]; Jones and Schneider 2006[202]; Zax and Rees[203]; Johnson and Neal[204]; de Wolf and van Slippe[205]);
- one was a revealed preference study (Lutter[206]); and
- one was a systematic review (Salkever[191]).

Table 102: Search strategy and results

Database	Search strategy	Date of search	Citations retrieved	Relevant citations
Econlit	(iq or intelligence quotient or intelligence) AND (income or earnings or productivity) Filter: published from 2006	10 Mar 2016	276	8
PubMed	(((((IQ) OR intelligence) OR "intelligence quotient") OR intelligence test[MeSH Terms])) AND ((((income[MeSH Terms]) OR "human capital") OR productivity[MeSH Terms]) OR earnings) Sort by: Relevance Filters: published in the last 10 years	06 May 2016	667	7[a]
Google	"cost benefit analysis" AND "food fortification" AND "IQ" AND income AND earnings AND productivity	29 Feb 2016	NA[b]	1[c]
Manual search	NA: review of references from relevant publications	11 May 2016	NA	9
Total relevant citations [after removal of duplicates]	NA	NA	NA	22[d]

a There were three duplicate citations from identified from the Econlit database.
b Only the first 10 pages were reviewed in the Google search.
c The report by Access Economics was identified in the Google search.
d Two publications are not included in the data abstraction presented in Individual studies included in the review presented by Salkever are presented in the table to avoid duplication. The Bergman 2014 and 2015 publications are presented as one, and de-Wolf and van Slippe is not presented due to the age of the publication. The citations of all publications are presented in Table 103.

Figure 11: PRISMA flow chart for IQ and earnings

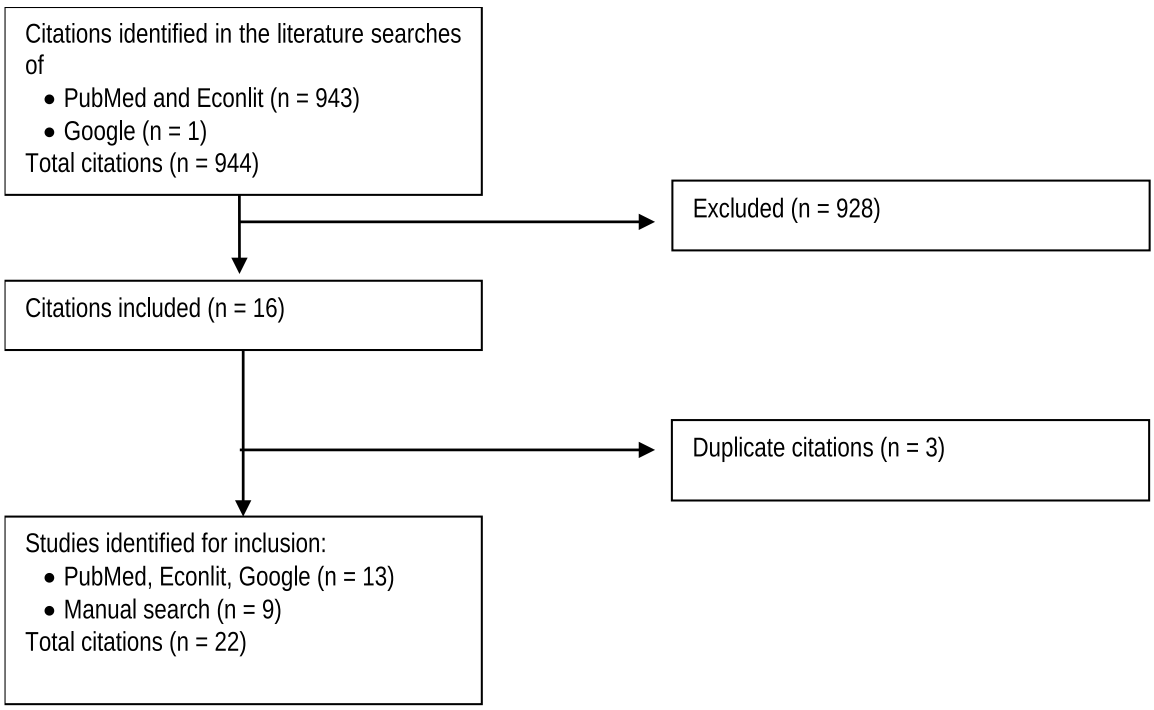


Table 103: Master list of included studies at Level II full-text review

Articles for inclusion
Access Economics for FSANZ (2006)[70] “Cost benefit analysis of fortifying the food supply with iodine” Accessed on the 29 Feb 2016, 10.40AM from URL: https://www.foodstandards.gov.au/code/proposals/documents/P230%20Iodine%20Fortification%20DAR%20Attach%2011%20FINAL.pdf
Bellanger, M., C. Pichery, D. Aerts, M. Berglund, A. Castaño, M. Čejchanová, P. Crettaz, F. Davidson, M. Esteban, M. E. Fischer, A. E. Gurzau, K. Halzlova, A. Katsonouri, L. E. Knudsen, M. Kolossa-Gehring, G. Koppen, D. Ligocka, A. Miklavčič, M. F. Reis and P. Rudnai (2013)[190] "Economic benefits of methylmercury exposure control in Europe: Monetary value of neurotoxicity prevention." Environmental Health: A Global Access Science Source 12(1): 1-10.
Bergman, L. R., L. Ferrer-Wreder and R. Žukauskienė (2015)[194] "Career outcomes of adolescents with below average IQ: Who succeeded against the odds?" Intelligence 52: 9-17.
Bergman, L. R., J. Corovic, L. Ferrer-Wreder and K. Modig (2014)[195] "High IQ in Early Adolescence and Career Success in Adulthood: Findings from a Swedish Longitudinal Study." Research in Human Development 11(3): 165-185.
de Wolff, P. and A. van Slijpe (1973)[205] "The relation between income, intelligence, education and social background." Europ Econ Rev 4: 235–264.
Fletcher, J. (2014)[196] "Friends or family? Revisiting the effects of high school popularity on adult earnings." Applied Economics 46(20): 2408-2417.
Johnson, W.R.,Neal,D. 1998[204]Basic skills and the black–white earnings gap. In: Jencks, C., Phillips, M.(Eds.), The Black–White Test Score Gap. Brookings Institution Press, Washington, DC
Jones, G. and W. J. Schneider (2006)[202] "Intelligence, Human Capital, and Economic Growth: A Bayesian Averaging of Classical Estimates (BACE) Approach." Journal of Economic Growth 11(1): 71-93.
Jones, G. and W. J. Schneider (2010)[198] "IQ IN THE PRODUCTION FUNCTION: EVIDENCE FROM IMMIGRANT EARNINGS." Economic Inquiry 48(3): 743-755.
Judge, T. A., R. L. Klinger and L. S. Simon (2010)[199] "Time is on my side: time, general mental ability, human capital, and extrinsic career success." J Appl Psychol 95(1): 92-107.
Lutter, R. (2000)[206] "Valuing Children's Health: A Reassessment of the Benefits of Lower Lead Levels." AEI-Brookings Joint Center Working Paper No. 00-02,
Monahan, M., K. Boelaert, K. Jolly, S. Chan, P. Barton and T. E. Roberts (2015)[188] "Costs and benefits of iodine supplementation for pregnant women in a mildly to moderately iodine-deficient population: a modelling analysis." Lancet Diabetes Endocrinol 3(9): 715-722.
Mueller, G. and E. Plug (2006)[201] "Estimating the effect of personality on male and female earnings." Industrial and Labor Relations Review. (60): 3–22.
Perera, F., K. Weiland, M. Neidell and S. Wang (2014)[189] "Prenatal exposure to airborne polycyclic aromatic hydrocarbons and IQ: Estimated benefit of pollution reduction." Journal of Public Health Policy 35(3): 327-336.
Pizzol, M., M. Thomsen, L. M. Frohn and M. S. Andersen (2010)[207] "External costs of atmospheric Pb emissions: valuation of neurotoxic impacts due to inhalation." Environ Health 9: 9.
Rindermann, H. and J. Thompson (2011)[197] "Cognitive capitalism: the effect of cognitive ability on wealth, as mediated through scientific achievement and economic freedom." Psychol Sci 22(6): 754-763.
Salkever, D. S. (1995)[208] "Updated estimates of earnings benefits from reduced exposure of children to environmental lead." Environ Res 70(1): 1-6.
Salkever, D. S. (2014)[191] "Assessing the IQ-earnings link in environmental lead impacts on children: Have hazard effects been overstated?" Environmental Research 131: 219-230.
Schwartz, J. (1994)[192] "Societal benefits of reducing lead exposure." Environ Res 66(1): 105-124.
Spengler, M., R. I. Damian, R. Martin, M. Brunner, O. Lüdtke and B. W. Roberts (2015)[193] "Student Characteristics and Behaviors at Age 12 Predict Occupational Success 40 Years Later Over and Above Childhood IQ and Parental Socioeconomic Status." Developmental Psychology 51(9): 1329-1340.
Zagorsky, J. L. (2007)[200] "Do you have to be smart to be rich? The impact of IQ on wealth, income and financial distress." Intelligence 35(5): 489-501.
Zax, J. S. and D. I. Rees (2002)[203] "IQ, ACADEMIC PERFORMANCE, ENVIRONMENT, AND EARNINGS." Review of Economics & Statistics 84(4): 600-616.

8.7.4 Included studies data extract

Table 104: Extracted data from the included studies

Source	Study design / Sample	Measures and objectives	Results
Monahan et al.[188]	**Locations** UK **Time of conduct** 2013 [Currency £GBP in 2013]	**Objectives** To investigate the cost-effectiveness of iodine supplementation versus no supplementation. CBA using a societal perspective was undertaken as a second analysis [using the value of an IQ point]. **Variables in analysis** None [systematic review was conducted to identify original studies that measured the value of one IQ point]. **Outcomes** • £GBP per IQ point derived from earnings. • WTP £GBP for an additional IQ point [Currency in 2013 pounds]	**Key findings/conclusions** • Eight economic publications that derive the value of one IQ point were identified in the systematic review (Fletcher[196]; Lutter[206]; Mueller and Plug[201]; Salkever[208]; Schwartz[192]; de Wolff and van Slijpe[205]; Zax and Rees[203]; Zagorsky[200]) • Most of the studies valued an IQ point based on its effect on an individual's income. The value of one IQ point derived from the systematic search and applied to the unborn cohort was £GBP 3 297 (range £GBP 1 319 to £GBP 11 967) [discounted lifetime value, adjusted with life tables] (p5)
Perera et al.[189]	**Design** Cost-benefit analysis of the effect of polycyclic aromatic hydrocarbons using data from CCCEH cohort study. **Population** Children of non-smoking African-American or Dominican-American women and their children from New York City, USA.	**Objectives** To estimate the costs of IQ loss associated with polycyclic aromatic hydrocarbons exposure. **Variables in analysis** NA. [Assumption used for the value of an IQ point and the relationship between earnings and IQ (earnings - IQ slope)]. **Outcomes**	**Key findings/conclusions** A modest reduction in ambient concentrations of PAH is associated with substantial economic benefits to children. The gain in lifetime earnings due to IQ increase for a single year cohort was estimated to be: • $USD 215 million; or • $USD 43 million (using more conservative assumptions) The value of 1 IQ point in $USD (year 2000) was assumed to be [Table 1 p331]:

Source	Study design / Sample	Measures and objectives	Results
	Locations USA **Time of conduct** 2000	The gain in lifetime earnings (discounted).	• Best estimate: $USD 3 887; and • Lower estimate: $USD 3 004 [for an individual] The gradient of the relationship of the earnings-IQ was assumed to be: • Best estimate: 1.1; and • Lower estimate: 0.85

Bellanger et al.[190]	**Design**
	Cost-benefit analysis of the effect of global mercury pollution using cross-sectional survey of pollution exposure (DEMOCOPHES).
	
	Population
	Children aged 6–11 years and their mothers (child-mother pairs).
	
	Locations
	17 European countries.
	
	Time of conduct
	• DEMOCOPHES sampling: September 2011 to February 2012.
	• Estimate of €EUR /IQ point is from 2008
		Objectives
		To assess the economic benefits of prevented developmental neurotoxicity.
		
		Variables in analysis
		Estimated value of an IQ point takes into account:
		• labour costs;
		• productivity; and
		• assumes IQ deficit are permanent (from preschool to age of 7 years).
		
		Outcomes
		Lifetime earnings loss per person.
		Economic cost (million/year) for each country, then Europe.
			Key findings/conclusions
			• Avoided lifetime costs were calculated by using the value of €EUR 17 363/IQ point (2008 estimate) as a basis to calculate €EUR /IQ point for each European country and adjusted for purchasing power parity (PPP) and Gross Domestic Product (GDP)/capita (in reference to the USA) (source from Additional file 1; Table 2 p6).
			• Average benefit: €EUR 13 579/IQ point
			• Total economic benefit for Europe:
			  • > €EUR 9 000 million/year [Table 2 p6]
			  • slightly less than €EUR 8 000 million/year when adjusting for productivity [additional file 3]
			Adjustment for productivity resulted in slightly lower total benefits.
			• The economic estimates were highly influenced by uncertainties regarding the dose-response relationship. A logarithmic response curve resulted in 4-fold higher benefit estimates.

Pizzol et al.[207]	**Design** Cost-benefit analysis of effect of atmospheric lead (Pb) emissions	**Objectives** To estimate the relationship between Pb emissions in the air to related impacts on Pb	**Key findings/conclusions** The study used the same methodology to derive the value of one IQ point as outlined by Salkever et al. (1995). The value of one IQ

Source	Study design / Sample	Measures and objectives	Results
	using data from the NLSY1979. **Population** Children in Denmark aged 0 to 3 years. **Locations** Denmark **Time of conduct** 2006	blood concentration and implied loss in earnings. **Variables in analysis** Assumptions in model include: • Annual productivity growth of 1% per annum; • Lifetime incomes are gender specific; and • The impact of IQ loss is expressed differently for men and women. **Outcomes** Monetary loss (€EUR) per one IQ point.	point for a Danish citizen in 2006 was estimated as: • Base case: €18,918 (using discount rate of 3%); • Sensitivity: €37,069 (discount rate of 1.4%) (p5, Table 2 p6)
Access Economics[70]	**Design** Cost-benefit analysis of mandatory iodine fortification of salt in bread using longitudinal survey data from the WLS to estimate the increase in earnings per IQ point (Zax and Rees[203]). **Population** • Children (aged 0 - 3), • Women of childbearing potential (WOCBP) • Australian and New Zealand population aged > 2 years **Locations** Australian and New Zealand	**Objectives** To compare the benefits of avoiding cognitive harm caused by iodine deficiency, with the costs to industry and government associated with mandatory fortification. **Variables in analysis** • The increase (%) in earnings per IQ point [assumption in model i.e. not an outcome explicitly stated by the authors]. **Outcomes** Mean productivity gain ($AUD or $NZD) for: • Australia; and • New Zealand	**Key findings/conclusions** • The increase (%) in earnings per IQ point was assumed to be 0.9% (range: 0% to 3.5%) (Table 1.4 p9 based on the study by Zax and Rees[203]). The net benefits for the cost-benefit analysis were estimated to be (Table 1:7 p15): • Australia: $AUD 1.8 billion (range: -9.8M to 7.3B); and • New Zealand: $NZD 2.65 million (range: 910M to 1.0B)

Source	Study design / Sample	Measures and objectives	Results
	Time of conduct 2006		

Salkever[208]	**Design**
	Cost-benefit analysis of reduced exposure to environmental lead using longitudinal data from the National Longitudinal Survey of Youth 1979.
	
	Population
	Men and women aged 14-22 in 1979 and 25 to 33 in 1990.
	
	Locations
	USA
	
	Time of conduct
	• Initial survey conducted in 1979 [Follow-up surveys carried out annually.]
	• Data on educational attainment and annual income was obtained from a survey conducted in 1990.
		Objectives
		To provide updated estimates of earnings benefits of reduced exposure of children to environmental lead.
		
		Variables in analysis:
		• Direct IQ effects;
		• Indirect IQ effects;
		• Participation (working or not working); and
		• Loss per IQ point $USD 5 307 (based on Schwartz's value of earnings of $USD 301 000).
		
		Outcomes
		• Log of annual earnings
		• Earning losses avoided (net) includes the:
		  • Loss in earnings for those that do not work; and
		  • Reduced participation rate.
			Key findings/conclusions
			The loss of one IQ on lifetime earnings (for men and women aged 25 to 33 in 1990) was:
			• 1.24% for men;
			• 1.40% for women; and
			• 1.32% for men and women.
			(Source: Table 1 p3)
			
			Including participation effect as a variable, the loss of one IQ point (direct and indirect) on lifetime income/earnings:
			• 1.9% for men;
			• 3.2% for women; and
			• 2.6% for men and women.
			(Source: Table 2 p4)
			
			The total earnings losses (%) per additional IQ point (IQ direct and indirect effects, probability of participation, and schooling)
			• 2·09% for men; and
			• 3·63% for women;
			(Source: Table 2 p4)

Schwartz[192]	**Design** Cost-benefit analysis of reduction of lead exposure using data from the NLSY79. **Population**	**Objectives** [To determine the societal benefits of reducing lead exposure.] **Variables in analysis:** NA (includes participation effect)	**Key findings/conclusions** The effect of a one IQ point change on earnings was calculated as: • direct effect: 0.5%; • participation effect: -0.473%; and • direct effect + indirect effect: -1.286%

Source	Study design / Sample	Measures and objectives	Results
	Men in USA **Locations** USA **Time of conduct** 1989 [USD]	**Outcomes** Log of annual earnings.	The total effect was an increase of 1.76% in earnings per additional IQ point.
Spengler et al.[193]	**Design** Econometric analysis using longitudinal data from the Luxembourgish MAGRIP study. **Population** • Men and women in Luxemburg who were students in grade 6 in 1968; and • Students aged 12-years in grade 6 in Luxembourg in 2013. **Time of conduct** • Wave 1 original sample f in 1968 • Wave 2 follow-up in 2008 • Additional cohort of children aged 12 years, 2013.	**Objectives** To review the relation of different predictors on occupational achievement. On the basis of results from previous longitudinal studies, the authors predicted childhood IQ, parental SES, education attainment, and student characteristics and behaviours to predict occupational success independently. **Variables in analysis:** • Model A: IQ and SES; • Model B: additionally, included years of education and • Model C: additionally, included the MAGRIP personality scales (MPS) and teachers' ratings of studiousness. **Outcomes** At middle adulthood (age 52) • Occupational success • Income: participants selected from income range (scale ranging from < €EUR 150 to	**Key findings/conclusions** Regression models: Predictors of career success Three models were estimated for the independent outcome of individual income. The coefficients for the parameter of IQ were 0.26 (95% CI 0.19 – 0.33) for Model A; 0.13 (95% CI 0.06 – 0.2) for Model B and 0.15 (95% CI 0.07 – 0.24) for Model C. Only the IQ point estimate is reported. For the full set of results, please see publication. Source: Table 2 p7. • Childhood intelligence was significantly related to the outcomes (educational attainment, occupational success, income). • For childhood intelligence, more than half the effect was mediated by educational attainment.

Source	Study design / Sample	Measures and objectives	Results
		> €EUR 10 000 per month)	
Bergman et al. 2014[195] and 2015[194]	**Design** Econometric analysis using data from the Swedish longitudinal research program entitled Individual Development and Adaptation (IDA). **Population** Swedish adolescents (aged 10) in 1955 followed until mid-life (age 43 women, age 47 men). **Locations** Sweden **Time of conduct** From 1955 followed until *1998-2003*	**Objectives** To determine the extent intellectually talented adolescents pursue educational and vocational careers that match their intellectual resources. **Variables in analysis** Models presented: • Model 1: IQ, high IQ; • Model 2: IQ, high IQ, school achievement and parent SES; • Model 3: IQ, high IQ and highest education. (Bergman 2014); • Gender; • Parents SES; and • Competence factors: IQ, high IQ, school achievement, task persistence, educational aspiration) **Outcomes** Career outcomes (dependent variables): • Education level • Income (log) • Occupational level	**Key findings/conclusions** • The differences in the income for males versus females was statistically significant ($p<0.001$) • The group with the lower IQ earns on average 15% less (men)/ 12% less (women) than the group with the average IQ (only significant for women). • Belonging to the high-IQ group increases income by 44% of the average monthly income for the total sample. *(Results are presented by IQ group*) *A currency value for an incremental IQ point increase is not reported, but the proportion is based on the average income in midlife for employed persons (as per Table 2 p13)]*
Fletcher[196]	**Design** Econometric analysis using data from longitudinal study (restricted version of the National Longitudinal Study of Adolescent Health (Add Health))	**Objectives** To measure the association between high school popularity and adult earnings (at ~age 30). **Variables in analysis:**	**Key findings/conclusions** When controlling for ability (PVT) in the model, PVT score at wave 1 was not statistically significant. *IQ has no effect on earnings.*

Source	Study design / Sample	Measures and objectives	Results
	Population Students in grade 7 to 12 in 1994-1995. **Locations** USA **Time of conduct** • Wave 1 in 1994-1995 • Wave 4 conducted 13 years later	High-school popularity, as measured by the number of nominations each individual received. Other covariates: family-level heterogeneity; academic achievement (GPA); education (at wave 4); personality traits (at wave 4); Peabody Picture Vocabulary Test (PVT) measured at wave 1, was used as a measure of ability (verbal IQ) in the regression. **Outcomes** Log of annual earnings. Earnings data were collected at Wave 4 (at ~age 30).	
Rinderman and Thompson[197]	**Design** Economic analysis using data from 90 countries **Population** Global population Not explicitly specified **Locations** Europe [Author's location] **Time of conduct** The analysis was based on data collected from 1995 to 2007.	**Objectives** To check the effect of cognitive ability levels on national wealth. **Variables in analysis** Covariates: • Economic freedom [property rights, rule of law, low customs, taxes, government spending ratio, and trade restrictions]; and • High achievement in STEM. **Outcomes** • The increase in average GDP for a one IQ point in the intellectual class, 95th percentile). • Increase in cognitive ability of the mean for one IQ point (mean)	**Key findings/conclusions** The intellectual class (cognitive ability in the 95^{th} percentile) determines the affluence of the nation. • An increase in one IQ point in the intellectual class increases the average GDP by $USD (2003) 468. • An increase in one IQ point increase in the cognitive ability of the mean increases the average GDP by $USD (2003) 229. The results obtained in this study are similar to another study (Murray 2002) where one additional IQ point produced an additional $USD (2000) 810/year by age 35. Authors note that using log GDP instead of GDP increases wealth at lower levels, which is more important that increasing wealth at higher levels.

Source	Study design / Sample	Measures and objectives	Results
		Wealth indexed by log GDP (1998 and 2003)	
Jones and Schneider[198]	**Design** Econometric analysis using data from: • IQ data from database of IQ from Lynn and Vanhanen 2002 • 1990 Census of Population and Housing (Hendricks 2002) **Population** Adult immigrants working in the USA. **Locations** USA **Time of conduct** Based on data collected from 1960 to 2000.	**Objectives** To determine is the country's average IQ is a useful predictor of the wages that immigrants from that country earn in the U.S. **Variables in analysis** • Immigrant wages • National average IQ is used to determine "unmeasured worker skill." **Outcomes** • Log adjusted earnings • γ, the IQ semi-elasticity of wages.	**Key findings/conclusions** • National average IQ predicts part of "unmeasured work skill." • A one-point increase in IQ is associated with 1% rise in immigrant wages. Source: Table 1 p19. • When IQ is added to the production function, the differences in national average IQ are quantitatively significant in explaining cross-country differences.
Judge et al.[199]	**Design** Econometric analysis using data from the NLSY1979. **Population** Men and Women in the USA **Locations** USA **Time of conduct**	**Objectives** Three objectives: To examine whether GMA is linked to the within individual change in extrinsic career success over time. To identify the mechanisms through which the intelligent might establish successful careers. To examine whether the dynamic processes through which the timing and quantity of educational attainment, job training, and job complexity are achieved can lead to accelerated career trajectories resulting in extrinsic	**Key findings/conclusions** GMA is positively related to the slope of time for income and occupational prestige. High-GMA individuals had higher levels of extrinsic career success in 1979 and success increased at a quicker rate. • As GMA increases the relationship between changes in income with education, training and job complexity becomes stronger and more positive. • In 1979: Individuals scoring above one SD above the mean on GMA made on average $USD 1 574.82 more than individuals scoring one SD below the mean on GMA. • By 2006: the difference increased more than 20-fold to

Source	Study design / Sample	Measures and objectives	Results
	From 1979 to 2006 [Retention rate: 85.4% by 2006]	cumulative advantages for the intelligent. **Variables in analysis:** • Educational attainment; • Training experience; • Job complexity; • General mental ability (GMA); and • Control variables: age, race, gender, SES. **Outcomes** Extrinsic career success as measured by: • income (pay); or • Occupational prestige (status).	$USD 38 819.43
Zagorsky[200]	**Design** Econometric analysis using data from the NLSY79. **Population** Men and women in the USA **Locations** USA **Time of conduct** 2004 [uses income data from this year]	**Objectives** To understand the relationship between intelligence and: • income; • wealth; and • financial difficulty **Variables in analysis** [Full list of variables are presented in Table 1 p493 of the original paper]. A summary of variables includes: • age; • labour market experience; • education; • family structure; • personal characteristics; and	**Key findings/conclusions** Depending on the method of analysis used and specific factors held constant an additional point increase in IQ is associated with an increase of $USD 202 to $USD 616 in annual household income. The average income difference between a person with an IQ score in the normal range (100) and someone in the top 2% of society (130) is currently between $USD 6 000 and $USD 18 500 per year.

Source	Study design / Sample	Measures and objectives	Results
		• IQ test score **Outcomes** Annual household income	
Mueller and Plug[201]	**Design** Econometric analysis using longitudinal survey data from the WLS. **Population** Men (N=2 424) and women (N=2 601) in employment in 1992. **Locations** Wisconsin, USA **Time of conduct** • Initial survey: 1957 • Follow-up in: 1964, 1975 and 1993.	**Objectives** To investigate the link between personality and earnings by incorporating traits from the five factor model (FFM) of personality structure. **Variables in analysis** Each model adds variables compared to the previous model: i) Personality traits (five independent variables); ii) General intelligence (Henmon-Nelson Test of Mental Ability) is added to the model; iii) individual characteristics (years of schooling, work experience), tenure, region and family characteristics added to the model; and iv) industry, occupation and job characteristics added to the model. **Outcomes** Log of hourly wages/earnings	**Key findings/conclusions** Regression models (point estimates for IQ) demonstrated an increased earnings with increases in IQ. For model ii, iii and iv for both males and females this increase was statistically significant at the 0.01 level. The coefficient of IQ for males was 0.179 in regression ii, 0.098 in regression iii and 0.065 in regression iv. For females, the coefficient for IQ was 0.127 in regression ii, 0.066 in regression iii, and 0.051 in regression iv. An increase of 0·69% and 0·48% in earnings per additional IQ point for men and women respectively (Monahan 2015 Appendix 1 Table 1). • The magnitude of the change in earnings induced by a one–standard deviation change in IQ scores is large (range: 7% to 17%) conditional on the particular set of covariates entered. • Personality does not predict as well as our cognitive ability measure. In isolation, the five personality measures explain about 5% of the variance in earnings. • The addition of IQ test scores improves the R2 by almost 10 percentage points.
Jones and Schneider[202]	**Design** Econometric analysis using data from: • Sala-i-Martin's "I just ran Two Million Regressions"; and	**Objectives** To evaluate the explanatory power of national average IQ **Variables in analysis:**	**Key findings/conclusions** • The correlation between national average IQ and log GDP per worker is 0.82. • A 1-point increase in a nation’s average IQ is associated with a persistent 0.11% annual increase in GDP per capita.

Source	Study design / Sample	Measures and objectives	Results
	• IQ data from database of IQ from Lynn and Vanhanen 2002 **Population** Global population Not explicitly specified **Locations** USA [Authors location] **Time of conduct** Based on data from 1960 to 1992.	• IQ; and • 3-variable combinations from Sala-i-Martin's top 21 growth variables (Full list of variables are provided in Table 1 p76). **Outcomes** Average annual increase in GDP per capita.	• IQ was found to be statistically significant in 99.8% of the same regressions; IQ is highly correlated with economic growth in the sample, showing it was the most robust human capital measure in the dataset. Lynn and Vanahan 2002: one additional IQ point is associated with a $USD 519 increase in GDP per capita in 1998.

Zax and Rees[203]	**Design**
	Econometric analysis using longitudinal survey data from the Wisconsin Longitudinal Study of Social Psychological Factors in Aspiration and Attainment (WLS).
	
	Population
	Males in 11th grade in 1957 in the (WLS).
	
	Locations
	Wisconsin, USA
	
	Time of conduct
	• Initial survey: 1957,
	• Follow-up in: 1964, 1975 and 1993.
		Objectives
		To estimate the effect of IQ measured at age 17, on earning at ages 35 and 53.
		
		Variables in analysis
		Covariates:
		• Model 1: none:
		• Model 2: adds conventional measures of family context; Household characteristics, fathers' education and mothers' education; and
		• Model 3: covariates as per Model 2 and adds variables for respondent and parental college aspirations.
		
		Outcomes
		Earnings (log) when subjects at age:
		• 35 years; and
			Key findings/conclusions
			
			It was estimated that a difference of 15 IQ points is associated with an earnings difference of:
			• At age 35:
			  • More than 11% in Model 1.
			  • Approximately 6% in Model 3.
			• At age 53:
			  • More than 21% [Model 1, table 5 p609].
			The magnitude of the relationship between IQ and subsequent income is reduced by the addition of other explanatory variables.
			The effect of true intelligence on earnings at age 35 lies between the coefficients of IQ in model 1 of table 3 and the 1974 models in table 8. That for earnings at age 53 almost surely lies between the coefficients on IQ in the 1992 models in table 5 and table 8.

Source	Study design / Sample	Measures and objectives	Results
		• 53 years.	
Johnson and Neal[204]	**Design** Econometric analysis using data from the NLSY79. **Population** Respondents born from 1962 to 1964 **Locations** USA **Time of conduct** 1993	**Objectives** To examine the relationship between basic skills and annual earnings **Variables in analysis** • Average respondents' inflation adjusted wages from 1990 to 1993; • IQ [AFQT]; • Worker age; • Race; • Gender; and • Education **Outcomes** Log wage rates ($USD 1993) [annual average earnings]	**Key findings/conclusions** • Skills are important determinants of wages and earnings. • The black-white gap in annual earnings is twice as large as the gap in hourly wages and not explained by skills. • There is a larger impact of an additional IQ point on the annual earnings for the subgroups, black males and females compared with white males.
Lutter[206]	**Design** Revealed preference study of reduction in blood lead. **Population** Parents in the USA. **Locations** USA **Time of conduct** 2000	**Objectives** To determine the marginal willingness to pay (WTP) for one IQ point gained in a child. **Variables in analysis** Not applicable. **Outcomes** Marginal WTP for one IQ point gained for a child.	**Key findings/conclusions** • Agee and Crocker reported that parental decisions to use chelation therapy imply an average WTP for a 1% reduction of child lead body burden of $USD 31 for parents on average or about $USD 210 for a reduction in lead in teeth of one part per million. • Lutter 2000 calculated an estimate of WTP between $USD 1 100 and $USD 1 900 per IQ point gained for the child. • The WTP estimates from Lutter are about a sixth of the earnings based estimate of $USD 8 800 per IQ point (based on a 3% discount rate) reported by the U.S. EPA in 1998.

Summary of the studies identified

Researchers have linked IQ to human capital using a variety of different methods. The results were diverse and ranged widely (Table 104;Table 105). For this reason, the results are described qualitatively throughout this Section. The value of one IQ point ranges from $USD 202 to €EUR 38 819. The majority of studies identified were either econometric analyses using data from longitudinal population studies or cost-benefit analyses that imputed the value of an IQ point based on values obtained from the literature.

One study[188] conducted a systematic review as part of a cost-effectiveness analysis of an iodine supplementation program in the UK; another revealed preference study measured the willingness to pay for an IQ point gained.[206] Although one publication identified was a general review and did not report original study results; it was retained because it provided an in-depth critique of the different methods of valuation found in the literature.[191]

The majority of the studies identified reported outcomes based on two datasets, either the National Longitudinal Survey of Youth 1979 (NLSY79)[192,199,200,207,208] or the Wisconsin Longitudinal Study of Social and Psychological Factors in Aspiration and Attainment (WLS).[70,188,201,203]

Systematic review

The review by Salkever et al.[191] was not a primary study publication. The authors compared a selection of studies reporting the impact of differences in childhood IQ on future earnings. Although this paper did not provide an updated calculation of the impact of IQ in childhood on earnings, the authors discussed how omission or inclusion of covariates in an analysis either attenuates or increases the magnitude of the effect on earnings. In more recent literature, it has been suggested that the magnitude of the effect of adolescent IQ has on future earnings is over-estimated. Salkever,[191] however, has contradicted this view. The studies Salkever[191] compared are included in the discussion.[192,203,204,208]

Salkever[191] argued that the studies supporting the notion that IQ has a weaker effect on future income have the following characteristics:

- not factoring in additional impacts, such as the inclusion of the participation effect that increases the magnitude of the results;
- the population is based on the earnings of Caucasian males, and less emphasis is placed on other demographic subgroups, where the IQ-earnings effect is potentially larger; and
- earnings gained are measured prior to 1990, whereas the demographics of the labour market have since changed.

The criticisms of the literature raised by Salkever[191] explain why there are variations in the results found in the literature search.

Cost-benefit analyses

Seven economic evaluations using a cost-benefit analysis[70,188-190,192,207,208] were identified in the literature review. A summary of the lifetime value of one IQ point calculated in these studies is presented in Table 105.

Access Economics cost-benefit analysis

The CBA conducted by Access Economics[70] assumed that mandatory iodine fortification would increase the average IQ of a proportion of the population, and result in an increase in average weekly earnings.

Iodine deficiency to earnings in two steps.

- The link between iodine deficiency and loss of IQ was based on a meta-analysis of 19 studies by Bleichrodt and Born,[209] which focused on regions of severe iodine deficiency. The meta-analysis reported that iodine deficiency is responsible for a mean IQ loss of 13.5 points among affected populations.[210]

- A link between IQ and earnings was based on the study by Zax and Rees[203] and assumed a 0.9% increase in earnings per IQ point gained for the entire population.

The Access Economics CBA[70] emphasised the high degree of uncertainty in quantifying the benefits arising from mandatory iodine fortification. The size of productivity gain resulting from mandatory fortification was estimated to lie within an interval of $AUD 44.9 million to $AUD 7.23 billion for Australia, and in the interval of $NZD 6.56 million to $NZD 1.14 billion for New Zealand. These were the 95% confidence intervals reported in the Access Economics report.

However, there were additional limitations in the literature used to inform the assumptions of the Access Economics[70] CBA, examples include;

- the increase in earnings was assumed to be the same for men and women, whereas the data from Zax and Rees[203] was based on Caucasian males only; and

- the authors assumed that the value of a one-point increase in IQ was meaningful, in that all individuals obtained a benefit from an IQ increase of one point. However, an increase of one IQ point may have a different impact depending on the IQ. The point at which a change in IQ has an effect on a change in earnings is still unknown. Only a small proportion of the population may reap the benefits of higher productivity gains associated with a one IQ point change. The value of the effect of an IQ point on the total population is potentially overestimated.

Other cost-benefit analyses

The systematic review conducted as part of the CBA by Monahan et al.[188] identified eight primary studies linking IQ to income. In common with the CBA undertaken by Access Economics,[70] the input of the value of one IQ point was based on Zax and Rees[203] with the results from Lutter[206] used in a sensitivity analysis. Monahan et al.[188] estimated that the monetary value of one additional IQ point for an unborn cohort had a discounted lifetime value of £GBP 3 297, range £GBP 1 319 to £GBP 11 967 ($AUD [2014] 7 111 range 2 845 to 25 810) (Table 105). This was an intentionally conservative analysis given that the improved IQ was not used to estimate benefits in the other ‘work’ types such as voluntary work or in activities undertaken after retirement. Monahan et al.[188] noted the exclusion of factors not traditionally associated with work limited their analyses, potentially leading to an underestimate of the value of an additional IQ point. This is similar to the argument by Salkever.[191]

Three of the cost-benefit analyses[190,192,208] based their estimates of the value of one IQ point on data from the National Longitudinal Survey of Youth in 1979. These cost-benefit analyses focused on estimating the cost of harmful effects of toxic pollutants (mercury and lead) in the environment. The results presented for each of these studies varied: the magnitude of the effect of one IQ point gain in earnings ranged from 1.76% to 2.09% for men and 3.63% for women. Differences in the estimated results presented by Salkever,[208] Schwartz[192] and Bellanger et al.[190] are partly due to the covariates included in their analyses, which may have had confounding effects or influenced IQ directly. The results they presented are consistent with the other studies in so far as the increase in IQ for an individual result in an increased lifetime income.

In the estimate calculated by Salkever,[208] the earning losses included a direct IQ effects, indirect IQ effects, and a participation effect. Salkever[208] posited that IQ has a direct compounding effect on participation in the labour market, and argued that exclusion of this factor would substantially underestimate productivity losses. Lifetime earnings were reported separately for males and females aged from 25 to 33 years, with impact estimates on projected earnings substantially higher for females compared to males.

Monahan et al.[188] did not use the results obtained by Salkever[208] or Schwartz[192] in their cost-benefit analysis study. They argued this was because the effects on future earnings were potentially overstated.

Bellanger et al.[190] applied the value of one IQ point to estimate the lifetime earnings loss for an individual and the economic costs for each country. Bellenger et al.[190] noted that benefits might be underestimated because not all costs linked to neurotoxicity and long-term disease risks were considered. For example, special education or other interventions were not included when calculating economic impact. This method of calculating the productivity potentially overstated the magnitude of impact.

Perera et al.[189] estimated the loss of productivity due to a loss of an IQ point, using a best-case estimate that assumed one IQ point resulted in a 1.1% increase in earnings. The gain in lifetime earnings due to an IQ increase for the cohort in a single year was estimated to be $USD 215 million, however using more conservative assumptions lowered the estimate to $USD 43 million.

Pizzol et al.[207] used the same methodology as Salkever[208] to derive the value of one IQ point. The value of one IQ point for a Danish citizen in 2006 was estimated as €EUR 18 918 in the base case and €EUR 37 069 in a sensitivity analysis. This estimate is much higher than that used by Perera et al.[189]

All CBAs identified in this literature review assumed that an increase in an individual's income would continue each and every year. That is, the differences in wages due to IQ are never mitigated. This is a significant assumption and is a key driver in the economic models.

Table 105: Lifetime earnings (per IQ point)

Study	Lifetime earnings (per IQ point)	Year	$AUD (2014)	$NZD (2014)
Monahan et al.[188]	£GBP 3 297 (range: 1 319 to 11 967)	2013	7 111	6 821
Perera et al.[189]	Lower estimate: $USD 3 004 Best estimate: $USD 3 887	2000	5 951	6 118
Bellanger et al.[190]	€EUR 13 579 [average benefit]	2008	29 176	28 733
Pizzol et al.[207]	Base case: €EUR 18 918 Sensitivity analysis: €EUR 37 069	2006	39 899	40 920
Access Economics[70]	0.9% (range: 0 - 3.5%)	2006	-	-
Salkever[208]	2·09% [Males] 3·63% [Females]	1990	-	-

Study	Lifetime earnings (per IQ point)	Year	$AUD (2014)	$NZD (2014)
Schwartz[192]	1.76%	1989	-	-

Values reported are variable for each publication. The values are reported as a monetary point estimate (currency £GBP, €EUR, $USD) or a proportion (%) of lifetime earnings. Conversion is undertaken using PPP from OECD[211] and CPI from Australia and New Zealand
Abbreviation: $AUD, Australian dollar; $NZD, New Zealand dollar

Econometric studies

Econometric analyses conducted on longitudinal studies support a temporal relationship between IQ and earnings for individuals over time. This type of analysis tests if a higher IQ in earlier life translates into higher earnings in the future. Understanding the relationship between childhood and adolescent intelligence with earnings provides some insight into the validity of the modelled assumption that IQ changes result in a change of wage.

The key limitations of this type of evidence are:

- The longitudinal studies are mature. The majority of the econometric analyses identified were based on data from earlier cohorts/populations at a particular point in time.

- There have been significant changes over time in the labour market, for instance, the participation of women has increased, and technology has improved significantly since these studies were conducted.

- The majority of econometric analyses were focused on changes at an individual level i.e. log income, adult earnings, and annual household income. It was unclear whether changes at an individual level would translate into a change for an entire population or have an aggregate effect on productivity. Only the study by Jones and Schneider[202] provided an estimate for the impact on a national level using Gross Domestic Product (GDP). All the other econometric studies reported outcomes for an individual adult.

- The longitudinal studies were observational, not experimental. They did not show that changing an individual's IQ resulted in improved wages for a specific individual.

Wisconsin Longitudinal Study of Social and Psychological Factors in Aspiration and Attainment

The Wisconsin Longitudinal Study of Social and Psychological Factors in Aspiration and Attainment was the basis for two econometric studies[201,203] Participants were enrolled in the WLS if they were senior students (aged 17 in 1957) attending high school in the state of Wisconsin, in the USA.

Wisconsin is considered to be a relatively rich state, where the high schools enrolled very few students from severely disadvantaged neighbourhoods. Participants were followed up in 1975 at age 35, and then in 1993 at age 53. The IQ of participants (n=10 317) were measured at age 17 using the Henmon-Nelson Test of Mental Ability. They were then surveyed at ages 35 and 53 to collate data on earnings. Other data collected included parental education, socio-economic status, family characteristics, years of education, and participant and parental college aspirations. The lack of disadvantaged areas in the study cohort severely limited its applicability to a national population.

Zax and Rees[203] presented three regression models. Model 1 was a simple regression of IQ on earnings (age 35). Model 2 added conventional measures of family context into the regression (household characteristics, father's education and mother's education). Model 3 included the same covariates as Model 2 and added variables for the participant and parental college aspirations. Zax and Rees[203] demonstrated that IQ was a predictor of future earnings (Model 1, 2 and 3). However, the influence of IQ attenuated, when additional covariates were included in the regression analyses (point estimate for respondent IQ decreases and R^2 increases with each model (Table 3 p605). The inclusion of other factors such as family context (Model 2) and personal characteristics (Model 3; respondent and parental college aspirations) attenuated the effect of IQ on future earnings. At age 35, a difference of 15 IQ points represented an earnings difference of more than 11%, whereas including family context variables and personal characteristics reduced the difference in earnings to 6%.

In the econometric study conducted by Mueller and Plug[201] covariates representing personality traits, individual characteristics such as education and work experience, and occupational characteristics were included in the regression analyses. Similarly to Zax and Rees[203] they found that a higher cognitive ability (IQ) predicted higher earnings. However, the magnitude of difference was conditional on the set of covariates included in the regression. The magnitude of change in earnings induced by a one standard deviation change in IQ score was large, ranging from 7% to 17%.

National Longitudinal Survey of Youth 1979 (NLSY79)

Three econometric analyses identified were based on data from the National Longitudinal Survey of Youth 1979.[199,200,204] The NLSY79 was a longitudinal study that followed the lives of Americans born between the years of 1957 and 1964. Participants were initially surveyed when aged between 14 to 22 years in 1979. The participants were more diverse in gender (50% males) and race/ethnicity (non-black/non-Hispanic, ≈60%) than participants in the WLS. The most recent survey of the NLSY79 was conducted in 2012 (round 25)[3].

The econometric analysis by Zagorsky[200] addressed the question of the impact of IQ on wealth, income and financial distress. In this study, income was not considered to be the sole determinant of financial success. Zagorsky[200] included covariates for age, education, family structure, personal characteristics and labour market experience in the regression analyses. Zagorsky found that a one-point increase in IQ was associated with an increase in income of $USD 234 to $USD 616 per year in 2004 in annual household income. The magnitude of the effect of IQ on income was dependent on the method of analysis used, and the specific covariates included in the analyses. The average difference in the income range depended on the range a person's IQ fell within. For instance, a person with a high IQ (130) in the top 2% of society had a higher income (ranging from $USD 6 000 to $USD 18 500 per annum) than a person with a normal IQ score (100).

Judge et al.[199] found that high general mental ability (GMA) individuals were able to attain a higher income or occupational status at an accelerated growth rate. This was because they attained more education, completed more job training and gravitated towards more complex jobs. GMA was positively related to income over time. Judge et al.[199] found that high-GMA individuals with a GMA score one standard deviation above normal made on average $USD 1 574.82 more than individuals scoring one standard deviation below the mean in the year 1979. By 2006, that difference increased to $USD 38 819.43.

Johnson and Neal[204] restricted their analyses to participants born from 1962 to 1964 to ensure only participants with an IQ score measured before the age of 19 were included. Participants with zero earnings were excluded from their analysis which overstated income gains attributable to IQ in their analysis. Johnson and Neal[204] sought to examine the relationship between basic skills and

[3]URL: NLSY79 Cohorts , accessed 2 June 2016.

annual earnings. The authors found that the impact of an IQ point on annual earnings of workers was 31% to 40% higher for males and females. They found that additional IQ points were more beneficial for "black males and females", compared with "white males". Johnson and Neal[204] concluded that skills are important determinants of wages and earnings. However, when reviewing differences in the wage gap by ethnicity and gender, they found the gap was not explicable by the differences in skills.

Although the NLSY79 data are more recent than the WLS data, a longitudinal study - NLSY97 – is currently ongoing for a younger cohort. Once its results are available, it would be useful to assess whether the outcomes for NLSY79 are similar to NLSY97.

The results of all the econometric analyses show that higher IQ is a predictor of higher future earnings; however, the magnitude of difference depends on covariates and other factors included in the regression models. Interestingly, an increase in monetary benefit is dependent on whether an individual is considered to have a high GMA or not. Consequently, a one-point increase in IQ may not be a significant change that results in higher income for an individual.

Econometric studies using other longitudinal datasets

Seven econometric analyses identified were based on data from various datasets.[193,194,196-198,202,205]

The results extracted from these studies are similar to those from the econometric analyses conducted using the WLS and NLYS79 data. Although each of the studies used different methods and cohorts, additional variables included in the regression analyses decreased the magnitude of the effect that childhood or adolescent IQ has on future earnings. For instance, the inclusion in the regression analysis of non-cognitive variables, such as high school popularity[196] or personality traits,[193,196] results in decreases in the coefficients of IQ. Cognitive ability or IQ was found to predict performance better in complex occupations compared to simple occupations.[202]

Although the majority of studies demonstrated that higher IQ was related to higher future earnings (except Fletcher[196]), the magnitude of difference was difficult to ascertain. This is because the analyses included different variables incorporating cognitive and non-cognitive skills and abilities. The results obtained by Bergman et al.[194] suggested that gender was a stronger predictor of future earnings than IQ.

The econometric analysis by Fletcher[196] was the only study to find that IQ has no effect on earnings. Conversely, Jones and Schneider[202] found IQ to be the most robust predictor of cross-country growth differences measured in GDP per capita. However, an investigation into the underlying cause of IQ variations was not explored.

Rinderman and Thompson[197] concluded cognitive ability was the decisive factor influencing human capital, and the intellectual class (defined as those with cognitive ability in the 95th percentile) determines a country's affluence. Rinderman and Thompson[197] found that an increase of one IQ point within the intellectual class increases the average GDP by $USD (2003) 468, whereas a one IQ point increase in cognitive ability of the mean (i.e. the mean IQ of a population increase by one point) increases the average GDP by $USD (2003) 229. This was the most conservative estimate of the monetary value of one IQ point among the studies identified in this Report's literature review.

Similarly to results published by Rinderman and Thompson,[197] Jones and Schneider[198] concluded that when IQ is added to the production function, the differences in national average IQ are quantitatively significant in explaining cross-country differences in GDP per capita.

The econometric analysis by de Wolff and van Slijpe[205] is dated, and studies on more recent cohorts have been published. Nonetheless, this study's results are consistent with many of the others. It was found that an additional IQ point increases earnings by 0·4%. Key covariates included in the regression analysis were social class, educational performance, and civil status.

Revealed preference study

Only one revealed preference study was identified in the search.[206] This is the only study that provided a direct link between the intervention and the cost of an IQ point. The study, conducted in 2010, aimed to determine parents' marginal willingness to pay (WTP) for a gain of one IQ point for their child. Parents were willing to pay between $USD 1 100 and $USD 1 900 per IQ point gained in their child.

However, the results of this study may not be applicable to the cost-benefit analysis in this Report because the results are based in the context of parental preferences for an intervention that reduced lead in blood. The preferences obtained from this study may be different to those obtained in the context of the introduction of mandatory iodine fortification. Although the monetary estimate for a one-point change in IQ is derived from this study, the same issues apply in using this parameter to generalise to an entire population remain (see discussion above).

Conclusions & Discussion

According to the literature, a higher IQ is associated with increased future earnings at an individual level. However, the magnitude of the increase varies widely. The impact of a change in IQ on an individual's income may be overestimated because of other influences that caused confounding in the analyses undertaken. These and other limitations discussed below impact on the certainty with which the results of the cost-benefit analysis conducted for the purposes of this Report can be regarded.

Individuals with high IQ scores had increased earnings both annually[192,199,200,204] and over their lifetimes.[201,203,208] Although IQ explained part of an individual's increased future earnings, it did not explain the whole story. A plethora of econometric regression analyses have been conducted using data from the WLS and NLSY79 cohorts, and on cohorts in other longitudinal studies. They all show that the impact of increased IQ at a younger age on future earnings varied according to which additional covariates were included in the regression.

For instance, Zax and Rees[203] concluded that cognitive ability alone is a poor predictor of earnings. Education, family background, and environment reduced the effect of IQ on future earnings and explained more of the variance in the models. Muller and Plug[201] found that cognitive ability was a stronger measure than personality in influencing an individual's wealth. There has, however, been a shift in the literature to include non-cognitive and social skills to explain the full effect of future earnings.[196,200] The econometric analyses also revealed that the value of one IQ point differed by gender and race/ethnicity.[194,204,208]

Monetarising lost cognitive ability in childhood is conducted by estimating the reduction of income in the future. Cost-benefit analyses identified in this targeted literature search commonly estimated the value of one IQ point based on published econometric analyses or using data from longitudinal studies. The estimated values derived from the analyses varied considerably, with sensitivity analyses providing a range in values from £GBP 1 319 to €EUR 37 069 ($AUD [2014] 2 845 to 78 179). This method assumes that an increase of only one IQ point is meaningful for all of the population, rather than a proportion of the population and always translates into increased earnings. It assumes that investments in education and utilisation of human capital will occur. It also assumes that observed differences represent the increase in income that will occur when an individual gains IQ points following an intervention such as mandatory iodine fortification.

The internal and external validity of the studies used in the cost-benefit analysis are also questionable. The internal validity is questionable because other unobserved characteristics may be associated with IQ and earnings. External validity to Australia and New Zealand is questionable because of the time and context in which the studies were conducted.

The influence of education, training and occupational complexity in explaining how higher IQ increases future income requires further consideration.[194,199,200,203] Judge et al.[199] posits that the career trajectory of most individual's progress upward over time, however, this depends on how time is invested i.e. with more education and training. Overall the tendency was for an individual to become more prosperous over time.

Labour force changes are another notable issue associated with using values from econometric analyses of longitudinal data. Female workforce participation has increased, technology has improved, and workers are more mobile today. The studies are dated and hence the relevance of the value of one IQ point from these studies is questionable.

Uncertainty also remains in identifying the size of the productivity gain due to a change in IQ because of the use of observational data. The potential for confounders that impact on both IQ and wages cannot be excluded.

8.7.5 Association between productivity and societal benefit

It was usually assumed that the benefit to IQ/human capital is manifested by an increase in productivity, which is often measured by increases in return for labour (wages). This assumption may be incorrect.

Societal benefit is equivalent to increased wages (productivity=wages)

One method of estimating a change in societal benefit due to the impact on IQ/human capital of a particular intervention is to estimate the changes that occur in an individual's wages as their IQ/human capital improves. This assumes that changes in the aggregated wage represent the societal benefit. That is, the increased wages of an individual whose human capital increases represents increased productivity for society.

This may or may not be the case. It is, however, the method that has been used previously in cost-benefit analysis. There is a consistent, but variable, relationship between increasing human capital as measured by IQ and the wages that accrue to an individual. The magnitude of the relationship decreases when adjustment is made for confounders, such as socio-economic status and education.

There are two alternative relationships between wages and national changes in income that could be considered. The first is that individual wages overestimate the societal benefit. The second is the societal benefit is greater than changes in individual wage.

Social benefit is less than wage changes (wages >productivity)

The short-run full employment model of the economy is a framework that supports individual wage changes not being reflective of societal benefit. In this model, an intervention would not change total employment, but the individuals who are employed may alter because improved cognitive functioning may improve an individual's chance of being employed. In this model, however, improved functioning delivers no benefit to society. Rather, it benefits the individual whose human capital improved as a result of the mandatory iodine fortification initiative.

Societal benefit is greater than wage benefit (productivity>wages)

Societal benefits may exceed wage changes because of the relationship between human capital and other forms of capital. The different forms of capital are interdependent; increasing human capital may increase the return from other forms of capital. It is possible that improved human capital may have an impact on national income but not an individual's income by improving the use of other forms of capital.

Whatever relationship holds between individual wages and national changes in income, using the individual wages of those who benefit from improved human capital to estimate societal benefit will be inaccurate. If the first relationship holds, the use of wage changes will over-estimate societal benefit. If the second relationship holds, the use of wage changes will under-estimate societal benefit.

Evidence from international studies shows that national intellectual performance is associated with national income.[186] Some studies argue that the differences between countries with regard to income are partly determined by cognitive ability. Using panel data from 81 countries, Jones and Schneider estimated a growth model that relates human capital increases to GDP. Measuring human capital increase using IQ score, they found that an average 1-point increase in IQ produced a 0.1% increase in GDP per capita for a country.

Despite the limitations and uncertainty surrounding this field, it is assumed that increases in productivity are manifested in wage increases.

8.8 Iodine fortification safety

The safety of iodine fortification of salt was studied as part of a systematic review by the WHO.[15] This Section updates this WHO review.

8.8.1 Methods

This update includes articles published from May 2011 until January 2016, in the English language. Randomised controlled trials (RCTs), non-RCTs, quasi-experimental studies, observational cohort studies and cross-sectional observational studies were included. The following sources were searched: The Cochrane Library, EMBASE and Pubmed. Table 106 provides the search strategy. Reference lists of identified papers were also hand-searched.

Table 106: Search strategy iodine fortification review

Unless otherwise stated, search terms are free text terms; MeSH = Medical Subject Heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.
#1 iodine deficiency disorders/[MeSH term, all subheadings included]
#2 goitre
#3 endemic goitre
#4 cretinism
#5 hyperthyroidism
#6 hypothyroidism
#7 #1~#6/OR
#8 iodized salt [in all fields]
#9 salt
#10 salt iodization
#11 iodine fortification
#12 #8~#11/OR
#13 #7 AND #12

As opposed to the WHO review, “elevated urinary iodine excretion” was not included as an adverse effect in this update.

8.8.2 Results

The search of electronic databases yielded 669 unique publications. 27 studies remained, after the exclusion of 122 non-English papers, 54 papers that did not contain original information (e.g. reviews, comments, editorials), three papers were published before May 2011, and 463 papers that did not provide quantitative data about the effect of iodine intake on at least one adverse effect. Hand-searching identified three additional articles. The results of the 30 included studies are presented in Table 107 and discussed per adverse effect.

Figure 12: PRISMA flow chart for iodine fortification safety

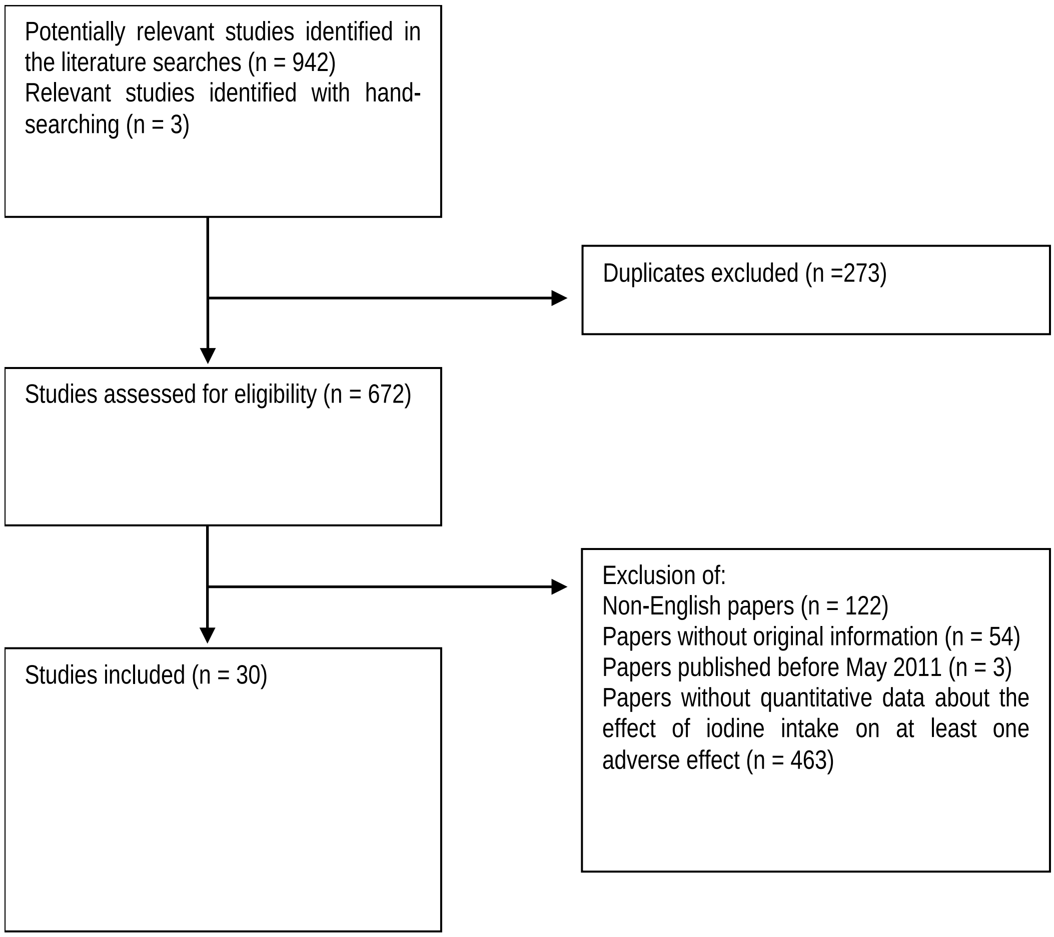


Table 107: Results of the safety review of iodine fortification (hypothyroidism)

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Aburto et al. 2014	Cohort	203 425 (4 studies)	All	WHO meta-analysis	NR	I2 = 91, Peto OR = 1.14 (0.84-1.53).
Aburto et al. 2014	Multiple cross-sectional	11 375 (4 studies)	All	WHO meta-analysis	NR	I2 = 90, Peto OR = 1.13 (0.94-1.36).
Latrofa et al. 2013[212]	Multiple cross-sectional	1 429	All	Iodised salt users and non-users from Italy completed questionnaires, had a thyroid ultrasound and provided urinary samples.	Iodised salt users: UIE 112.0 µg/L. Iodised salt nonusers: UIE 86.5 µg/L.	Frequency of hypothyroidism: 49/906, 5.4% (iodised salt users) vs 14/389, 3.6% (iodised salt nonusers), p=0.16.
Nepal et al. 2015[139]	Multiple cross-sectional	696	Infants	Household salt samples, venous blood samples and spot urine samples were collected from infants (6-24 months) from eastern Nepal.	Iodine-sufficient region, 20 years post-mandatory fortification. MUIC: 407 µg/L.	No significant difference in the prevalence of subclinical or overt hypothyroidism was found between infants with deficient (8.6% subclinical, 0% overt), sufficient (7.6% subclinical, 1% overt) or excess (7.4% subclinical, 0.8% overt) iodine intake (p = 0.7 subclinical, p = 0.7 overt).
Zimmermann et al. 2013[129]	Multiple cross-sectional	2 512	Children (6-12 years)	Urine and blood samples were obtained from primary school children in 12 countries.	MUIC ranged from 16 µg/L (Morocco) to 338 µg/L (Tanzania).	The prevalence of subclinical hypothyroidism was not significantly different between UIC groups: 1.8% (UIC <50), 0.3% (UIC 50-99.9), 0.5% (UIC 100-199.9), 0.2% (UIC 200-299.9) and 0.6% (UIC > 300). The prevalence of overt hypothyroidism was not significantly different between UIC groups: 0.7% (UIC <50), 0.0% (UIC 50-99.9), 0.0% (UIC 100-199.9), 0.0% (UIC 200-299.9) and 0.0% (UIC > 300).
Sang et al. 2012[213]	RCT	256	Adults	Euthyroid adults were randomly assigned to 12 intervention groups with various iodine	Initial MUIC (pre-supplementation): 291 µg/L.	Subclinical hypothyroidism appeared in the participants who took the 400 µg supplement (5%, total iodine intake of ~800 µg per day) and

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
				supplement doses ranging from 0 to 2 000 µg/d for 4 weeks in China.		500-2000 µg (15-47%).
Teng et al. 2011[214]	Multiple cross-sectional	3 813	Unknown	Urine and blood samples were collected, and thyroid ultrasounds were performed in two Chinese populations exposed to different levels of iodine intake.	MUIC 261 µg/L in Rongxing and 145 µg/L in Chengshan.	The prevalence of subclinical hypothyroidism was significantly higher for subjects who live in Rongxing than those who live in Chengshan (5.03 vs. 1.99, $p < 0.001$).
Du et al. 2014[215]	Multiple cross-sectional	2 147	Adults	Drinking water, salt, urine and blood samples were collected, and thyroid ultrasounds were performed in iodine excess, sufficient and deficient regions in China.	Regions varied from iodine deficient to iodine excess. The MUIC was 750.18 µg/L, 228.70 µg/L and 62.03 µg/L for iodine excess, sufficient and deficient groups, respectively.	The prevalence of subclinical hypothyroidism was 20.09%, 10.41% and 2.25% in the excess, sufficient and deficient iodine groups, respectively. The difference between the iodine excess and iodine sufficient group was significant ($p = 0.002$ for males and 0.001 for females). The prevalence of overt hypothyroidism was 2.56%, 1.18% and 1.05% in the excess, sufficient and deficient iodine groups, respectively. The difference between the iodine excess and iodine sufficient group was non-significant ($p = 0.082$).
Shi et al. 2015[216]	Multiple cross-sectional	7 190	Pregnant women	Pregnant women from China completed questionnaires and provided samples of spot urine and blood.	Iodine-excess region, 16 years post-fortification.	More-than-adequate iodine intake (UIC 250 – 499 g/L) and excessive iodine intake (UIC 500 g/L) were associated with a 1.72-fold and a 2.17-fold increased risk of subclinical hypothyroidism respectively (prevalence: 2.4% for women with adequate iodine intake, 4.2% for more-than-adequate ($p = 0.004$) and 5.7% for excessive iodine intake ($p = 0.004$)). No significant difference in the prevalence of overt hypothyroidism was found between women with more-than-adequate (1.2%, $p=0.17$) or excessive (0.9%, $p=0.67$) iodine intake compared to women with adequate (0.7%) iodine intake.

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Lombardi et al. 2013[217]	Multiple cross-sectional	2 559	All	Before and 5 years after voluntary iodine fortification of salt, Italian subjects completed questionnaires, had a thyroid ultrasound and provided urinary samples.	Before: UIE 55 µg/L. 5 years after: UIE 98.0 µg/L.	The prevalence of hypothyroidism was higher post iodine fortification, 5.0% vs 2.8% (P = 0.005), mainly because of an increased frequency of subclinical hypothyroidism in subjects younger than 15 years (7/83, 8.4% vs 0/419, 0.0%, P < 0.0001).
Cerqueira et al. 2011[218]	Cohort	~5 300 000	All	Nationwide incident use of levothyroxine to treat hypothyroidism was evaluated in Denmark during 1995-2009 (salt iodisation: 1998).	Aalborg: UIE from 53 µg/L (moderately deficient) to 93 µg/L (mildly deficient). Copenhagen: UIE from 68 µg/L (mildly deficient) to 108 µg/L (iodine sufficient). Before versus 11 years post-fortification.	The incidence rate increased by 75% in the moderately iodine deficient region (72.2 incident users/100 000 person-years in 1997 to 126.6 in 2008) and 87% in the mildly deficient region (86.9-162.9).
Teng et al. 2013[219]	Multiple cross-sectional	15 008	School-age children	Participants from ten cities in China were studied. Palpation and ultrasounds were performed, and urine and blood samples were collected.	Iodine excess.	The prevalence of subclinical hypothyroidism and overt hypothyroidism were significantly higher in regions with excessive iodine intake than in regions with adequate iodine intake.
Gaberscek et al. 2014[220,221]	Multiple cross-sectional	47 563	All	Records of all patients diagnosed with iodine induced hypothyroidism or iodine induced hyperthyroidism were collected in a hospital in Slovenia before (1998-1999) and after (2000-2009) an increase in iodisation of salt.	Before and 11 years post-fortification.	Significantly more patients presented with iodine induced hypothyroidism during 2000-2009 (157/40 818, 0.38%) than during 1998-1999 (5/6 745, 0.07%), p < 0.001.

Abbreviations: MUIC, median urinary iodine concentration; OR, odds ratio; UIC, urinary iodine concentration; UIE, urinary iodine excretion.

Table 108: Results of the safety review of iodine fortification (hyperthyroidism)

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Aburto et al. 2014	Cohort	202 848 (2 studies)	All	WHO meta-analysis	NR	I2 = 0, Peto OR = 1.36 (1.12-1.66).
Aburto et al. 2014[a,b]	Multiple cross-sectional	1 999 998 (5 studies)	All	WHO meta-analysis	NR	I2 = 89, Peto OR = 0.96 (0.92-1.00).
Nepal et al. 2015[139]	Multiple cross-sectional	696	Infants	Household salt samples, venous blood samples, and spot urine samples were collected from infants (aged 6-24 months) from eastern Nepal.	Iodine-sufficient region, 20 years post-fortification. MUIC: 407 μg/L.	No significant difference in the prevalence of subclinical or overt hyperthyroidism was found between infants with deficient (0% subclinical, 0% overt), sufficient (0% subclinical, 0% overt) or excess (1.3% subclinical, 0.2% overt) iodine intake ($p = 0.7$ subclinical, $p = 0.7$ overt).
Medici et al. 2014[222]	Cross-sectional	5 326 (urinary iodine for random subset of 1 154)	Pregnant women	Urine and blood samples from pregnant women in the Netherlands were collected in early pregnancy and newborn cord serum was collected at birth.	MUIC 222.5 μg/L (iodine sufficient).	There were no differences in the risk of maternal hyperthyroidism between mothers with urinary iodine levels >500 μg/L versus ≤500 μg/L ($p = 0.76$), neither after exclusion of TPOAb-positive mothers and adjustment for confounders ($p = 0.99$). There were significant differences in the risk of newborn hyperthyroidism between mothers with urinary iodine levels >500 μg/L versus ≤500 μg/L ($p = 0.02$), also after exclusion of TPOAb-positive mothers and adjustment for confounders ($p = 0.01$).
Du et al. 2014[215]	Multiple cross-sectional	2 147	Adults	Drinking water, salt, urine and blood samples were collected, and thyroid ultrasounds were performed in iodine excess, sufficient and deficient regions in China.	Regions varied from iodine deficient to iodine excess. The MUIC was 750.18 μg/L, 228.70 μg/L and 62.03 μg/L for iodine	The prevalence of subclinical hyperthyroidism was 0.58%, 0.20% and 1.95% in the excess, sufficient and deficient iodine groups, respectively. The prevalence of overt hyperthyroidism was 0.58%, 0.79% and 1.50% in the excess, sufficient and deficient iodine groups, respectively ($p = 0.166$). The prevalence of Graves' disease was 0.35%,

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
					excess, sufficient and deficient groups, respectively.	0.59% and 0.75% in the excess, sufficient and deficient iodine groups, respectively.
Zimmermann et al. 2013[129]	Multiple cross-sectional	2 512	Children (6-12 years)	Urine and blood samples were obtained from primary school children in 12 countries.	MUIC ranged from 16 µg/L (Morocco) to 338 µg/L (Tanzania).	The prevalence of subclinical hyperthyroidism was not significantly different between UIC groups: 0.2% (UIC <50), 0.3% (UIC 50-99.9), 0.3% (UIC 100-199.9), 0.0% (UIC 200-299.9) and 0.2% (UIC > 300). The prevalence of overt hyperthyroidism was not significantly different between UIC groups (all 0.0%).
Gaberscek et al. 2012[223,224]	Multiple cross-sectional	7 789	All	Retrospective record review of thyroid patients before (1998) and ten years after (2009) increase in mandatory salt iodisation in a hospital in Slovenia.	NR	In 1998, significantly more patients presented with thyroid autonomy than in 2009 (383/3 243, 11.8% vs 333/4 546, 7.3%), $p < 0.001$.
Gaberscek et al. 2013[225]	Multiple cross-sectional	7 789	All	Retrospective record review of thyroid patients before (1998) and ten years after (2009) increase in mandatory salt iodisation in a hospital in Slovenia.	Iodine sufficient after salt iodisation (MUIC in school children 148 µg/L).	The percentage of (overt and subclinical) hyperthyroid patients decreased from 10.1% to 5.0%.
Gaberscek et al. 2014[220,221]	Multiple cross-sectional	47 563	All	Records of all patients diagnosed with iodine induced hypothyroidism or iodine induced hyperthyroidism were collected in a hospital in Slovenia before (1998-1999) and after (2000-2009) an increase in iodisation of salt.	Before and 11 years post-fortification.	A similar number of patients presented with iodine induced hyperthyroidism during 2000-2009 (461/40 818, 1.1%) than during 1998-1999 (85/6 745, 1.3%), $p < 0.350$.
Teng et al.	Multiple	15 008	School-	Participants from ten cities in	Iodine excess.	The prevalence of overt hyperthyroidism was

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
2013[219]	cross-sectional		age children	China were studied. Palpation and ultrasound were performed, and urine and blood were collected.		significantly higher in regions with excessive iodine intake than in regions with adequate iodine intake.
Laurberg et al. 2012[226]	Multiple cross-sectional	143	All	Incidence and clinical presentation of moderate to severe Graves' orbitopathy was studied based on a Danish registry, before and after mandatory iodisation of salt.	During 9 years before (61 µg/L) and 9 years after (101 µg/L) salt iodisation.	No change in the incidence of moderate to severe Graves' orbitopathy was observed before and after salt iodisation (p = 0.35).

Abbreviations: MUIC, median urinary iodine concentration; NR, not reported; OR, odds ratio; TPOAb, thyroperoxidase autoantibodies; UIC, urinary iodine concentration

Table 109: Results of the safety review of iodine fortification (elevated thyroid autoantibodies)

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Aburto et al. 2014	Cohort	2 848 (1 study)	Adults	WHO meta-analysis	NR	Elevated TPOAb: Peto OR = 2.51 (1.93-3.27)
Aburto et al. 2014	Multiple cross-sectional	6 172 (2 studies)	All	WHO meta-analysis	NR	Elevated TPOAb: I2 = 96, Peto OR = 1.27 (0.94-1.71). Elevated TgAb: I2 = 97 Peto OR = 1.43 (1.08-1.89).
Latrofa et al. 2013[212]	Multiple cross-sectional	1 429	All	Iodised salt users and non-users from Italy completed questionnaires, had a thyroid ultrasound and provided urinary samples.	Iodised salt users: UIE 112.0 µg/L. Iodised salt nonusers: UIE 86.5 µg/L.	TgAb, and not TPOAb, was more frequent in iodised salt users: 18.9% vs. 13.6%, p=0.02.
Pedersen et al. 2011[227]	Multiple cross-sectional	8 219	Adults	Blood tests were performed on a Danish cohort before (MUIC 61 µg/L) and 4-5 years after (MUIC 101 µg/L) mandatory iodine fortification of salt.	Median UIE in Aalborg: 53 µg/L before, 93 µg/L after iodisation. Median UIE in Copenhagen: 68 µg/L before,	Antibodies were more frequent after iodine fortification: TPOAb > 30 U/ml, 14.3% vs 23.8%, p < 0.001; TgAb > 20 U/ml, 13.7% vs 19.9%, p < 0.001. TPOAb: OR 1.80 (1.59-2.04). TgAb: OR 1.49 (1.31-1.69).

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
					108 µg/L after iodisation.	
Bjergved et al. 2012[228]	Cohort	2 203	Adults	Physical examination, blood tests, a urine test and thyroid ultrasound were performed on a Danish cohort before (MUIC 61 µg/L) and 8.6 years after (MUIC 84 µg/L) mandatory iodine fortification of salt.	Before (MUIC 61 µg/L) and 8.6 years after (MUIC 84 µg/L) mandatory iodisation.	Antibodies were more frequent after iodine fortification: TPOAb > 30 U/ml, 16.1% vs 23.9%, p < 0.01; TgAb > 20 U/ml, 12.1% vs 21.5%, p < 0.01.
Lombardi et al. 2013[217]	Multiple cross-sectional	2 559	All	Before (MUIC 55 µg/L) and 5 years after (MUIC 98.0 µg/L) voluntary iodine fortification of salt, Italian subjects completed questionnaires, had a thyroid ultrasound and provided urinary samples.	Before: UIE 55 µg/L. 5 years after: UIE 98.0 µg/L.	The prevalence of serum thyroid autoantibodies was higher post iodine fortification, 19.5% vs 12.6% (P < 0.0001).
Teng et al. 2013[219]	Multiple cross-sectional	15 008	School-age children	Participants from ten cities in China were studied. Palpation and ultrasound were performed, and urine and blood were collected.	Iodine excess.	The prevalence of positive TPOAb and TgAb were significantly higher in regions with excessive iodine intake than in regions with adequate iodine intake.
Teng et al. 2011[214]	Multiple cross-sectional	3 813	Unknown	Urine and blood were collected, and thyroid ultrasounds were performed in two Chinese populations exposed to different levels of iodine intake (MUIC 261 µg/L in Rongxing and 145 µg/L in Chengshan).	MUIC 261 µg/L in Rongxing and 145 µg/L in Chengshan.	The prevalence of positive TPOAb and TgAb was significantly higher for subjects who live in Rongxing than those who live in Chengshan (TPOAb: 10.64 vs. 8.4%, p = 0.02; TgAb: 10.27 vs. 7.93%, p = 0.01).
Provenzale et al. 2012[229]	Cross-sectional	1 146	Unknown	Iodised salt users and non-users underwent a medical exam, thyroid ultrasound, measurement of thyroid hormones and UIE.	NR	In iodised salt users, positive thyroid autoantibodies were more frequent than in non-iodised salt users, both for TgAb (128/769, 16.6% vs 33/309, 10.7%, p = 0.01) and TPOAb (120/769, 15.6% vs 34/309, 11.0%), although in the last case this difference was not statistically significant (p = 0.05).

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Shi et al. 2015[216]	Multiple cross-sectional	7 190	Pregnant women	Pregnant women from China completed questionnaires and provided samples of spot urine and blood.	Iodine-excess region, 16 years post-fortification.	The prevalence of TgAb positivity was 10.1% in women with adequate iodine intake, 12.2% (p = 0.06) in women with more-than-adequate iodine intake and 13.5% (p = 0.10) in women with excessive iodine intake. The prevalence of TPOAb positivity was 7.1% in women with adequate iodine intake, 9.2% (p = 0.03) in women with more-than-adequate iodine intake and 10.0% (p = 0.11) in women with excessive iodine intake.
Zimmermann et al. 2013[129]	Multiple cross-sectional	2 512	Children (6-12 years)	Urine and blood samples were obtained from primary school children in 12 countries	MUIC ranged from 16 µg/L (Morocco) to 338 µg/L (Tanzania).	The prevalence of elevated TPOAb was not significantly different between UIC groups: 0.0% (UIC <50), 0.0% (UIC 50-99.9), 0.5% (UIC 100-199.9), 0.6% (UIC 200-299.9) and 0.5% (UIC > 300). The prevalence of elevated TgAb was not significantly different between UIC groups: 0.0% (UIC <50), 1.1% (UIC 50-99.9), 0.8% (UIC 100-199.9), 1.2% (UIC 200-299.9) and 1.0% (UIC > 300).

Abbreviations: MUIC, median urinary iodine concentration; TgAb, thyroglobulin autoantibodies; TPOAb, thyroperoxidase autoantibodies; UIC, urinary iodine concentration

Table 110: Results of safety review of iodine fortification (autoimmune thyroiditis)

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Lombardi et al. 2013[217]	Multiple cross-sectional	2 559	All	Before (MUIC 55 µg/L) and 5 years after (MUIC 98.0 µg/L) voluntary iodine fortification of salt, Italian subjects completed questionnaires, had a thyroid ultrasound and provided urinary samples.	Before: UIE 55 µg/L. 5 years after: UIE 98.0 µg/L.	The prevalence of HT was higher post iodine fortification, 14.5% vs 3.5% (P < 0.0001).

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Zaletel et al. 2011[230]	Multiple cross-sectional	7 923	Adults	Clinical examination, blood tests and thyroid ultrasound were performed to assess the incidence of thyroid disorders before (1999) and after (2009) an iodine increase from 10 - 25 mg of potassium iodide per kg of salt in Slovenia.	MUIC was 148 µg/L.	Incidence of HT increased strongly between 1999 and 2009, RR = 1.86 (1.64-2.12).
Du et al. 2014[215]	Multiple cross-sectional	2 147	Adults	Drinking water, salt, urine and blood samples were collected, and thyroid ultrasounds were performed in iodine excess, sufficient and deficient regions in China.	Regions varied from iodine deficient to iodine excess. The MUIC was 750.18 µg/L, 228.70 µg/L and 62.03 µg/L for iodine excess, sufficient and deficient groups, respectively.	The prevalence of autoimmune thyroiditis was 8.13%, 6.09% and 2.55% in the excess, sufficient and deficient iodine groups, respectively. The prevalence of HT was 1.05%, 0.39% and 0.0% in the excess, sufficient and deficient iodine groups, respectively. The prevalence of atrophic thyroiditis was 7.08%, 5.70% and 2.5% in the excess, sufficient and deficient iodine groups, respectively.
Miranda et al. 2015[231]	Multiple cross-sectional	206	Children	Schoolchildren from Brazil underwent a physical examination, blood tests, a urine test and thyroid ultrasound.	Urinary iodine was mean 165.1 µg/L.	Children without CAT had a mean urinary iodine concentration of 164.9 µg/L (sd 20.2) vs 168.3 (sd 27.5) for children with CAT (p = 0.598).

Abbreviations: CAT, chronic autoimmune thyroiditis; HT, Hashimoto's thyroiditis, MUIC, median urinary iodine concentration; SD, standard deviation; UIE, urinary iodine excretion.

Table 111: Results of safety review of iodine fortification (thyroid nodule and thyroid cancer)

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Chen et al. 2013[232]	Cross-sectional	9 412	Adults	Iodised salt intake, UIC and thyroid nodule (by ultrasound) were measured in Hangzhou, China.	MUIC: 172.6 µg/L.	Adults consuming non-iodised salt had an increased risk of thyroid nodule (OR 1.36, 1.01-1.83). An increased risk of thyroid nodule was observed among both pooled samples and women with low UIC.

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Blomberg et al. 2012[233]	Cohort	6 629	All	All newly diagnosed cases of thyroid cancer between 1943 and 2009 were identified from the Danish Cancer Registry.	UIE from 94 µg/day (1997-1998) to 145 µg/day (2004-2005).	Age-standardised incidence of thyroid cancer increased in both sexes, from 0.41 to 1.57 per 100 000 men and from 0.90 to 4.11 per 100 000 women. The strongest increase in incidence began in the years before implementation of compulsory iodine supplementation.
Harach et al. 2013[234]	Multiple cross-sectional	593	All	Undifferentiated thyroid cancer incidence (as a proportion of total thyroid cancer incidence) was assessed in one period before and two periods after salt iodination in Salta, Argentina.	Urinary iodine (µg/day) in 1960: 20.3, in 1975: 151.7 and in 1980-1981: 104.0.	The frequency of undifferentiated thyroid cancer decreased from 15.2% (9/59 cases) in the first period to 2.6% (10/381 cases) well after salt iodination ($p < 0.0002$), and the incidence from 1.4/106/year to 0.1/106/year ($p < 0.06$), respectively.
Dong et al. 2012[235]	Multiple cross-sectional	1 239	All	Incidence of thyroid cancer was analysed before and after universal salt iodisation in Shenyang, China, based on pathology reports.	NR	The total detection rate of thyroid cancer increased from 0.71% (85/11903) to 1.31% (1154/87911), $p < 0.001$. The detection rate of papillary thyroid carcinoma and medullary thyroid carcinoma increased, that of follicular thyroid carcinoma decreased, and that of undifferentiated thyroid carcinoma showed no change.

Abbreviations: MUIC, median urinary iodine concentration; NR, not reported; OR, odds ratio; UIC, urinary iodine concentration; UIE, urinary iodine excretion.

Table 112: Results of safety review of iodine fortification (goitre)

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
Lv et al. 2015[236,237]	Multiple cross-sectional	911	Children (8-10 years)	Thyroid volume was determined before and after removal of iodised salt in three high-iodine towns in China.	MUIC 518 µg/L in 2010 and 416 µg/L in 2013.	Goitre prevalence decreased from 24.56% (111/452) to 5.88% (27/459), $p < 0.001$ (first publication) and from 32.96% (149/452) to 6.54% (30/459), $p < 0.001$ (second publication).
Zaletel et al. 2011[230]	Multiple cross-sectional	7 923	Adults	Clinical examination, blood tests and thyroid ultrasound were performed to assess the incidence of thyroid disorders before (1999) and after (2009) an iodine increase from 10 -	MUIC was 148 µg/L.	The incidence of diffuse goitre significantly decreased to a more than 80% lower value, and the incidence of multinodular goitre and solitary nodules significantly increased to 55% and 72% higher values, respectively.

Author & Year	Study design	Sample size	Group	Study details	Iodine status	Main study results
				25 mg of potassium iodide per kg of salt in Slovenia.		
Lv et al. 2012[238]	Multiple cross-sectional	1 259	Children (8-10 years)	Iodine nutrition and goitre status were evaluated in 30 villages in China.	MUIC 418.8 µg/L.	There was no significant difference in the goitre rate between villages with median iodine content in drinking water <150 µg/L (45/416, 10.8%) and villages with median iodine content in drinking water >150 µg/L (93/843, 11.0%), p = 0.9. Within the group with water iodine >150 µg/L, goitre rate in the group with median salt iodine > 10 mg/kg was 12.1% compared with 8.6% in the group with median salt iodine <5 mg/kg (p = 0.094).
Hussein et al. 2012[239]	Multiple cross-sectional	280	Children (6-12 years)	UIC, visible goitre rate and iodine content of salt and fish were determined in two regions of Sudan.	The MUIC in children from Port Sudan and Jabal Awliya was 533 and 160 µg/L, respectively.	Goitre was detected in 17.1% of children from Port Sudan and 1.4% of children from Jabal Awliya.

Abbreviations: MUIC, median urinary iodine concentration; UIC, urinary iodine concentration.

Hypothyroidism

The WHO review of four cohort studies and four multiple cross-sectional studies found no evidence for iodine induced hypothyroidism (cohort: Odds Ration [OR] = 1.14 [95% CI 0.84-1.53]; cross-sectional: OR = 1.13 [95% CI 0.94-1.36]). In the subsequently published studies, the association between iodine and hypothyroidism differed.

Three studies[218-221] suggested a significant increase in the incidence of hypothyroidism with increased iodine intake. Two of these studies[219-221] (from China and Slovenia) were published as abstracts only and did not provide information about the levels of iodine intake. Therefore, it is not possible to evaluate the extent to which these studies are relevant to Australia and New Zealand. The third study (from Denmark) suggested a positive association between iodine intake and hypothyroidism. This study related, however, to the incidence of levothyroxine use, not hypothyroidism as such. The increasing use of levothyroxine since the iodisation of salt does not necessarily represent an increase in overt hypothyroidism. It may also be caused by increased diagnostic activity or increased treatment of subclinical hypothyroidism.[218]

Five other studies[213-217] (four from China, one from Italy) did not find an association between iodine and overt hypothyroidism but between iodine and subclinical hypothyroidism. Subclinical hypothyroidism occurs when serum TSH concentrations are raised but serum thyroid hormone concentrations are normal. The clinical significance of subclinical thyroid disease is controversial. Three studies[129,139,212] (one from Italy, one from Nepal and one study conducted in twelve countries) did not find any evidence for iodine-induced hypothyroidism, either overt or subclinical. The results from these studies did not find a significant difference in the prevalence of hypothyroidism between groups based on either iodine intake[212] or excretion.[129,139]

The WHO review as updated in this Report does not provide sufficient evidence to assume iodine fortification induces hypothyroidism in the population.

Hyperthyroidism

The meta-analysis of two cohort studies showed increased odds of hyperthyroidism associated with exposure to iodised salt (OR 1.36 [95% CI 1.12-1.66]). However, a meta-analysis of five multiple cross-sectional studies failed to find any relationship between exposure to iodised salt and hyperthyroidism (OR 0.96 [95% CI 0.92-1.00]). One study in the meta-analysis measured the incidence of hyperthyroidism as indicated by incident use of anti-thyroid medication in the Danish population, and included more than 5 million individuals, 4 821 of whom were incident users of anti-thyroid medication. All other studies measured low circulating TSH in samples of individuals as the outcome measure. Without the Danish study, the meta-analysis found that exposure to iodised salt reduced the odds of hyperthyroidism (OR 0.50 [95% CI 0.40-0.63]).

The majority of studies published after the WHO review[129,139,215,220,221,223-226,230] (from Nepal, Slovenia, China, Denmark and a combination of twelve countries) found either no effect or a preventive effect of iodine on hyperthyroidism. One study[219] found a significant difference in the prevalence of overt hyperthyroidism in Chinese regions with excessive iodine intake compared to Chinese regions with adequate iodine intake. This study was published as an abstract only and did not provide information about the levels of iodine intake in these regions. It is therefore not possible to evaluate the extent to which this study is relevant for Australia and New Zealand.

One study among pregnant women from the Netherlands[222] did not find differences in the risk of maternal hyperthyroidism between mothers with urinary iodine levels >500 µg/L versus ≤500 µg/L, but did find significant differences in the risk of newborn hyperthyroidism.

The WHO review as updated in this Report does not provide sufficient evidence to assume iodine fortification induces hyperthyroidism in the population.

Elevated thyroid autoantibodies

Although elevated thyroid autoantibodies do not necessarily cause symptoms, they are associated with thyroid diseases including Hashimoto's thyroiditis and Graves' disease. In the WHO review, one cohort study reported that consumption of iodised salt significantly increased the odds of elevated thyroperoxidase autoantibodies (TPOAb). There were two multiple cross-sectional studies with contradictory results. The meta-analysis of those studies detected no increased odds of elevated TPOAb with iodised salt. The WHO review only included one study about the effect of iodine on thyroglobulin autoantibodies (TgAb). This study showed an increased risk of elevated UIE with 10 years of exposure to iodised salt.

Most studies undertaken after the WHO review (in Italy, Denmark and China) found a positive association between iodine intake and elevated autoantibodies, both for TPOAb and TgAb[212,214,219,227,228,240] One study found a positive association between the use of iodised salt and thyroid autoantibodies (TgAb and TPOAb), although this was not statistically significant in the case of TPOAb[229] The opposite was true in the study by Shi et al. [216] among pregnant women. The prevalence of women with elevated TgAb was not significantly different between groups with different iodine intake, but the prevalence of elevated TPOAb was higher for women with more-than-adequate iodine intake compared to women with adequate iodine intake. One study[129] performed among school-children in 12 countries found no significant difference in either TPOAb or TgAb between groups with different UIC.

The apparently contradictory study results may be explained by the different durations of exposure to the increased iodine levels or the cut-off values used for the laboratory tests. Unfortunately, the study publications do not provide sufficient information to test these hypotheses.

Other adverse effects

The WHO review did not include autoimmune thyroiditis, thyroid cancer or goitre as adverse effects.

The thyroid gland has several mechanisms to keep its hormone secretion constant, despite varying iodine intake. Bürgi[241] published a paper explaining these control mechanisms. The most flexible and potent mechanism is provided by the sodium–iodide symporter, which controls the limiting step of thyroid hormone synthesis. Other mechanisms are "an immediate, albeit short-lived, block of iodine organification after a sudden massive iodine excess (the Wolff–Chaikoff effect), an equally short-lived arrest of thyroid hormone secretion from stores in the colloid, a preferential secretion of the less active T4 over T3, and dumping of excess iodine by secreting it in non-hormonal form". Although most people do not experience symptoms due to iodine excess, some develop thyroid dysfunction. In particular, infants, the elderly, pregnant and lactating women, and individuals with pre-existing thyroid disease are susceptible to adverse effects of excess iodine intake and exposure[241]

The WHO review as updated in this Report does not provide sufficient evidence to assume iodine fortification induces adverse effects at the population level.

8.9 Folic acid fortification safety

8.9.1 Introduction

FSANZ's 2006 safety review of folic acid identified several hypothesised risks without evidence of harm based on the folic acid intake expected with mandatory fortification.[9] These risks included masking of the diagnosis of B_{12} deficiency, cancer, unmetabolised circulating folic acid, multiple births and interactions with medications.[9]

Mandatory folic acid fortification is an initiative which has a specific target population, namely women of childbearing age. The safety of folic acid fortification should be considered in the target population and the non-target population, especially the young and the elderly.

The October 2006 FSANZ Final Assessment Report critiqued the safety of mandatory folic acid fortification.[9] It concluded that the proposed level of mandatory fortification did not pose a risk to public health and safety. The issue of B_{12} deficiency masking was considered, but there was no evidence to suggest existing fortification initiatives had resulted in increased adverse effects associated with B_{12} metabolism. Concern about the potential interaction between folic acid and cancer was noted, and a risk management approach was suggested. This risk management approach consisted of the inclusion of an upper concentration limit in the Standard (see Section 8.1.3), and the identification of a requirement to monitor potential health risks. The review of potential health benefits and risks were outlined in Attachment 6 of the Final Assessment Report.

This Report has assessed recent advances in knowledge about the safety of folic acid fortification by a review of the safety and toxicity of folic acid fortification. The meta-analysis conducted by Mackerras et al.[13] was required to be reviewed as part of this Report and was also discussed in the AIHW report.[7,13]

8.9.2 Review articles

There have been several review articles published about potential adverse effects associated with folic acid. This Report describes these articles and the broad areas of potential adverse effects below.

The WHO guideline for optional serum and red blood cell folate concentrations in women of reproductive age for prevention of NTDs commented that “high folic acid intake has not reliably been shown to be associated with negative health effects”.[36]

Selhub and Rosenberg[138] disputed the WHO comment in a review article published in 2016 which linked excessive folic acid intake to adverse health outcomes. The authors commented on the association between increased risk of cognitive impairment in seniors (aged >65 years) and the combination of high blood levels of folate and low blood levels of B_{12} which had been demonstrated in a cross-sectional study. The authors also highlighted the association of B_{12} deficiency and high folate levels in pregnant women with an increased risk of insulin resistance in their offspring. The authors discussed the results of studies where the presence of unmetabolised folic acid was associated with a reduction in the natural killer cytotoxicity.[138] Finally, the authors discussed genetic polymorphism in folic acid metabolism and the potential for some polymorphisms to be associated with an increased cancer risk when combined with high folate/folic acid intake.[138]

Colapinto et al.[242] conducted a systematic review of published literature which reported the results of studies investigating the association between high folate levels (in the blood) and adverse effects. Although the authors had intended to conduct a meta-analysis of the results, the heterogeneity in the studies meant they were unable to conduct it. The four adverse effects studied were cancer, cognitive impairment, cardiovascular disease and kidney disease. The majority of studies were observational and used different assays creating significant problems for comparison. The authors concluded that there was no consistent association between increased blood folate concentration (as opposed to intake) and adverse effects.

In 2016 the Food and Drug Administration (FDA) in the United States contemplated adding folic acid to corn flour.[17] As part of this process, it considered the evidence for safety and harm in seven broad categories of potential harms, namely: masking B_{12} deficiency; direct effect on B_{12} deficiency induced neurology and neurological decline; cancer; prenatal exposure and childhood health outcomes; hypersensitivity; reproductive effects, and folic acid drug interactions. The FDA concluded that no definite association exists between folic acid and adverse effects such as cancer, childhood health outcomes, hypersensitivity, reproductive effects and drug interactions.[17] Further research was recommended.

Choi et al.[137] published a review concentrating on areas of concern with regard to folate fortification. The review highlighted the positive benefits of improved folate status, notably a decrease in NTDs reported in Chile, Canada and the United States.[137] They listed the potential harms suggested as associated with mandatory fortification, discussed a possible biological mechanism and reviewed the evidence. Several of the issues covered by the authors were entirely biochemical in nature, without any evidence presented of occurrence in medical or public health practice. The central role of folate (and folic acid) in DNA synthesis and methylation was highlighted in this review. The associated potential harms were categorised as: the presence of unmetabolised folic acid in the blood; potential neurological adverse effects related to B_{12}; folate levels and central nervous system development; folic acid fortification and epilepsy; the efficacy of anti-folate medication; and photolytic conversion of folic acid into genotoxic products.

This Report identified seven potential/hypothesised classes of adverse effects based on the articles reviewed. These are as follows:

1. Increased cancer risk;
2. A relationship with B_{12} and neurological dysfunction, including masking B_{12} deficiency and accelerated cognitive decline;
3. Impact on medication use, especially anti-folate medication;
4. Unmetabolised folic acid in the blood and the postulated follow-on effects (potential impact on natural killer cells, interference with folate metabolism and photolytic conversion);
5. Reproductive impacts, notably increased twin births;
6. Impacts on offspring (including insulin resistance, autism spectrum disorder, wheezing, gene selection etc.); and
7. Folic acid hypersensitivity or allergy (not prenatally induced).

8.9.3 Methods

This Report undertook a review to establish the breadth of adverse effects and safety issues proposed and identified in the literature to date. This was not a systematic literature review of specific adverse effects.

Table 113: Search strategy folic acid fortification review

Unless otherwise stated, search terms are free text terms; MeSH = Medical Subject Heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.
#1 Food, Fortified/ or Flour fortification.mp.
#2 folic acid.mp. or Folic Acid/
#3 #1 AND #2

Non-English articles and articles from prior to 2007 were excluded.

The abstracts and titles were reviewed. If the abstract and title indicated that the article concerned the safety of folic acid, it was retained for full-text review.

This search was supplemented by a search of Google Scholar for national position statements from the Cancer Council, the Scientific Advisory Committee on Nutrition (SACN) and the United States FDA. Additionally, the top 30 google scholar hits for folic acid fortification safety were included.

A full-text review was undertaken. An article was excluded if it did not involve folic acid, did not involve folic acid safety or adverse effects, or if the article contained minimal information (it was in the nature of an editorial, letter etc.).

The recovered articles were then associated with one or more of the seven classes of adverse effects described above or included in an "other adverse effects" class. A single article could, therefore, be associated with multiple adverse effects. The recovered articles were then searched for references and 'pearl' searched for citing articles.

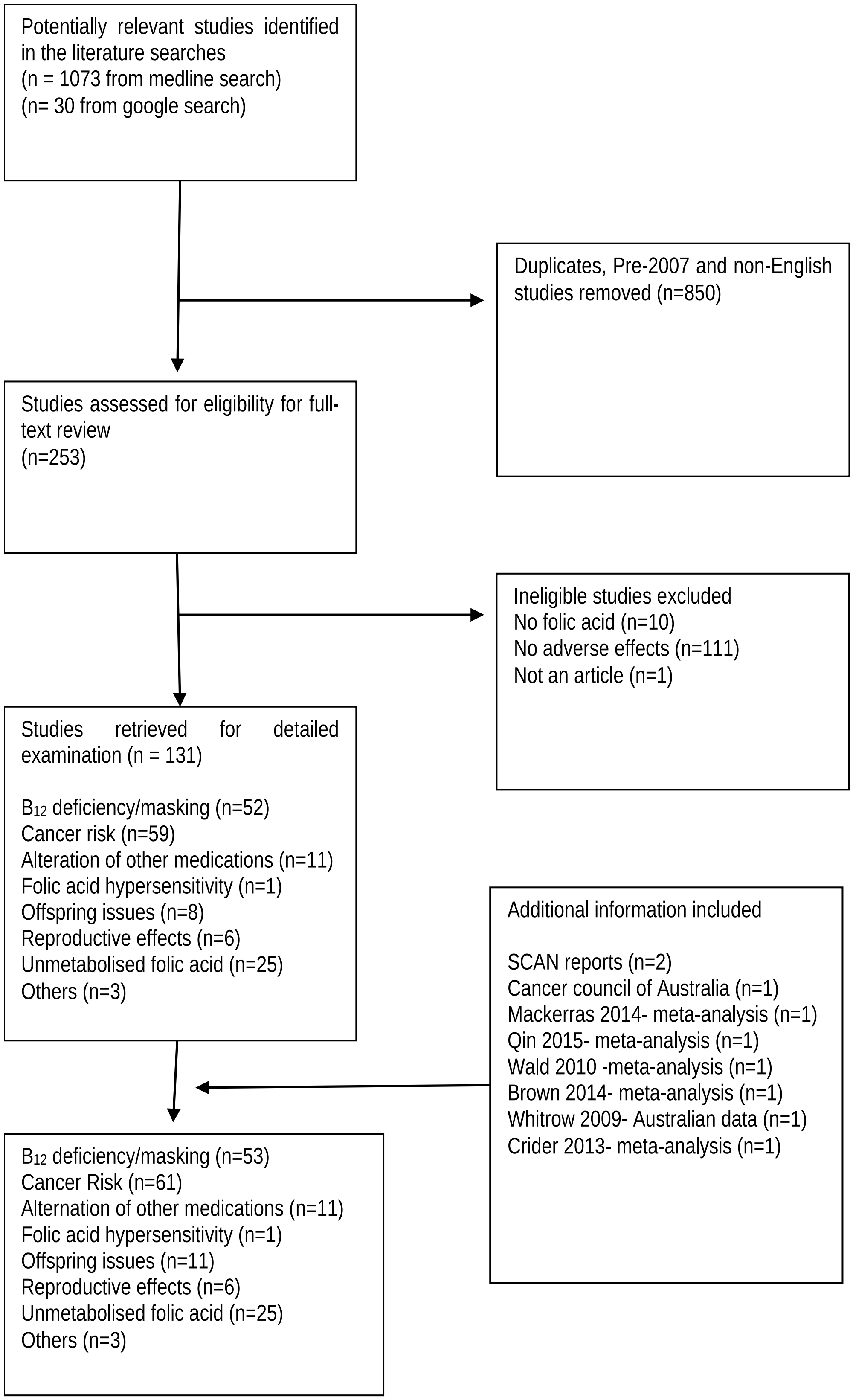
Information about the type of safety issue and the evidence to support it was extracted from each article. The studies were categorised according to the level of empirical evidence (I to IV) using the NHMRC grading system[243] and the highest level retained. Also included were systematic reviews that did not only include RCTs, which were included in the level I category.

The articles with the highest level of evidence for each adverse effect class were reviewed for quality, using CONSORT for RCTs,[244] PRISMA for meta-analysis and STROBE for observational studies.[245,246] The quality of the other studies was not assessed. The studies were not restricted to human studies because animal studies were considered potentially important in terms of hypothesis generation. The animal studies were included but not assessed for quality.

8.9.4 Results

There were 1103 articles recovered in the search of electronic databases. Of these, 850 were excluded for publication prior to 2007, duplicates and non-English language. There were 253 articles that were considered for full-text review (Figure 13). One hundred and twenty-two were removed. The main reason for their exclusion was the lack of reporting of adverse effects. Nine articles were included through pearl searching and the grey literature. The adverse effects most commonly included in recovered articles were cancer risk and the association between B_{12} and folate.

Figure 13: PRISMA flow chart for folic acid safety review



Folic Acid and B_{12} deficiency

Concerns have been raised that increasing amounts of available folate and folic acid could exacerbate the harmful health states associated with a B_{12} deficiency. B_{12} deficiency is associated with anaemia, neurological and psychological conditions.

There are two separate, but interrelated issues discussed further below. The first is masking of anaemia by folate/folic acid leading to a delayed diagnosis of B_{12} deficiency. The delayed diagnosis results in a worsening neurological dysfunction that may be irreversible. The second issue is that increased amounts of available folate result in the metabolism of B_{12} and the alteration of the natural history of neurological dysfunction.

Concern has been raised that the characteristic megaloblastic anaemia associated with B_{12} deficiency would be masked by the increase in folate/folic acid. That is, the anaemia would be resolved with the higher level of physiologically available folate. Therefore, the proportion of the population with B_{12} deficiency but no anaemia would increase.[247]

The issue identified is that the diagnosis of B_{12} deficiency would be delayed because the anaemia does not occur. This delay would allow the development of neurological disorders associated with B_{12} deficiency. As some neurological disturbances can be irreversible, this could be considered a potential adverse effect associated with increased folic acid intake. Serum B_{12} testing rather than examination of the blood film is a contemporary method of diagnosing B_{12} deficiency.[248]

A series of case reports between 1945 and 1954 chronicled the rapid progression of neurological dysfunction in patients treated with large doses of folic acid.[249] The authors claimed that the prevention of anaemia might delay the diagnosis of B_{12} deficiency. However, the neurological complications may occur with or without anaemia.[249] Folic acid was isolated and synthesised in 1945, vitamin B_{12} was isolated in 1948 but was not commercially available until 1972.[138] Therefore, between 1945 and 1972 patients with megaloblastic anaemia were often treated with large doses of folic acid and without vitamin B_{12}.[138] This is not the contemporary approach.

Owing to the concern associated with the potential of B_{12} deficiency masking and exacerbation of B_{12} neurological complications, it was estimated that the folic acid intake associated with an impact on neurological function B_{12} was 5 mg.[248,249] In a number of these cases larger doses of folic acid were given as treatment for the anaemia.[247] A safe upper intake level (UL) for folic acid of 1 mg was set with this issue in mind, being one-fifth of the 5 mg level[32]. Therefore, the upper intake level was set with a large margin of safety. This is discussed in Section 5.2 of the P295 final report.[9]

Some have argued that these complications may occur at lower levels of intake of folic acid than 5 mg and have advocated increased surveillance and treatment of B_{12} deficiency to remove this problem.[249]

Older people and vegans are at a higher risk of B_{12} deficiency and therefore are assumed to be at risk of masking of B_{12} associated with increased folic acid intake.[9] The assessment of the risk of masking conducted for FSANZ[248] confirmed that, in Australia, there is a higher prevalence of low B_{12} levels in those over 50 years of age, albeit in non-nationally representative studies.

The change in the proportion of the population with an intake of 1 mg of folic acid post-mandatory fortification was estimated as being a fraction of a per cent in Australia.[7] However, the confidence in this result is limited by the lack of inclusion of supplements in the calculations of the 1995 NNS in Australia (Section 3.4.2).

Selhub and Rosenberg argue that the association found in observational studies between low B_{12} and high folate status, and the prevalence of cognitive impairment required further investigation.[138] The United States FDA concluded that there was some evidence linking high folic acid intakes in adults to masking B_{12} deficiency and cognitive decline among those that are B_{12} deficient.[17]

Results from two groups of observational trials are quoted for the conclusion that there is an association between low B_{12} level, high folate levels and cognitive impairment. These trials were Morris et al.[250] using two USA cohorts and Moore et al.[251] using Australian cohorts. These observational studies showed a statistically significant association between a combination of low B_{12} and high folate status and an increased odds ratio of cognitive decline.

A safety report for FSANZ in 2006 concluded that there was no evidence that masking of the B_{12} deficiency at the level of mandatory folic acid fortification would be expected.[248] The SACN report described the evidence base of B_{12} masking as "poorly described case reports."[252] The P295 risk assessment concluded that there was no evidence of an increased risk of masking the diagnosis of vitamin B_{12} deficiency because this diagnosis relies on a combination of tests.[9]

Recovered literature

The recovered literature in this Report was mainly non-empirical in nature (Table 114). Four systematic reviews were identified, including one from the 'pearl' search (Wald et al.[253] published in 2010). Two reviews were removed from consideration (De-Regil et al.[254] and Rogovik et al.[255]) because neither took a systematic approach to adverse effects.

Table 114: Recovered literature for folic acid and B_{12} issues

Level of evidence	Number of citations in database search	Number of citations from other sources	Total
I or systematic review	3	1	**3**
II	3	0	**3**
III	2	0	**2**
IV	6	0	**6**
No empirical evidence	38	0	**38**
Total	**52**	**1**	**53**

A systematic review of folate and vitamin B_{12} status in Latin America and the Caribbean was conducted by Brito et al.[256] The results were divided into pre- and post-folic acid fortification periods and compared. The studies included in this review were limited and non-nationally representative.

The authors concluded that folate deficiency appeared to have decreased with fortification. However, low B_{12} concerns continued after folic acid fortification. The suggestion that B_{12} be added as a fortificant alongside folic acid was raised as a strategy in areas with vitamin B_{12} deficiency.[256]

Qi et al.[247] compared the presence of low B_{12} without anaemia prior to and after fortification in the United States.[247] They found no statistically significant difference in low B_{12} without the presence of anaemia. There is no consistent evidence of B_{12} masking post-mandatory folic acid fortification in the United States.[17]

One systematic review and meta-analysis investigated the relationship between folic acid and cognitive decline. Wald et al.[253] included placebo-controlled trials of folic acid (additional vitamins and minerals were not an exclusion criterium). Inclusion criteria included at least 20 participants, 45 years of age or older, no dementia at onset and reporting one or more cognitive function tests. The authors calculated the standardised mean difference between the intervention and the placebo groups because multiple cognitive function tests were used. A random-effects model was used, and the outcomes in each trial were assumed to be correlated.[253]

Nine RCTs were included, involving 2 835 participants, with a mean age of 60 years or over. The folic acid dose was from 0.2 mg to 15 mg. Four of the trials included B_{12} in the intervention group. The length of the trials was between 1 and 36 months.

The standardised mean difference for the entire trial population was 0.01 (95% CI -0.98-0.1 numbers above imply the folic acid arm was superior). This result included the potential impact of giving both B_{12} and folate. The result for folic acid without any other B vitamin was 0.1 (95% CI -0.06-0.25). Therefore, there was no evidence found that folic acid increased cognitive impairment on a population basis.

The indirect nature of the intervention (compared to folic acid fortification) is a limitation of these studies. The length of treatment is also an issue in terms of generalisability to the Australian population. The age of the participants, while being representative of the risk group, is not aligned with the population that receives the intervention of folic acid fortification.

The relationship between folic acid and cancer risk

The relationship between folic acid fortification and cancer risk has been debated in the literature. It has been argued that low dietary folate is a risk factor for cancer.[257] Some have argued that folic acid supplementation is a potential risk factor for cancer, especially colorectal cancer.[258] Others have argued that the relationship is more complex and non-linear.[259,260]

Folate is essential for DNA synthesis (and other essential physiological processes). Disordered DNA replication and mutation is a step in the development of cancer. Therefore, a potential role for folate in preventing carcinogenesis is postulated.

The FSANZ Final Assessment Report for the consideration of folic acid (Proposal P295)[9] concluded that there was no apparent increase in cancer risk with higher folic acid intakes for the population as a whole.

The AIHW report[7] reviewed selected cancer outcomes and all-cause mortality by way of the results of Mackerras et al.[13] This paper consisted of a meta-analysis of trials involving folic acid supplementation. The conclusion reached was there was no impact of folic acid supplementation on all-cause mortality.[13] There was an elevated point estimate risk for all cancers (1.04) but the confidence interval crossed unity. The AIHW report[7] concluded that no increase in cancer mortality could be directly associated with folic acid intakes in adults.

Cancer risk reduction is evident in cohort studies of diets high in folate-rich foods. The World Cancer Research Fund continuous update project attributed 16% of pancreatic cancer to low consumption of folate in 2009. However, since that project, evidence for cancer risk reduction with high folate foods has weakened. In the latest update, the evidence was considered less consistent and too limited to draw a conclusion.[261]

There has, however, been a concern expressed that increased folic acid intake may increase cancer risk or increase the rate of malignant transformation in pre-cancerous lesions. Anti-folate pharmaceuticals (such as methotrexate) are used in the treatment of several cancers. Additional folate can promote proliferation of existing cancers by providing substrate for DNA synthesis and rapid proliferation.[262]

Two articles were important in initiating this debate.[260] Mason et al.[258] suggested that the diagnosis rate of colorectal cancer increased temporarily after the introduction of folic acid fortification in Canada and the United States. They argued that the potential causation should be investigated but acknowledged that the observational data did not prove a causal link.[258] One mechanism that was postulated is that pre-cancerous lesions (adenomas) may be converted to cancers or, alternatively, smaller cancers to larger cancers that are more likely to be detected.

The other trial that contributed to the debate was by Cole et al.,[263] who published the results of an RCT that tested the use of folic acid (and aspirin) for the chemoprevention of future malignant events in a high-risk population.[263] The primary outcome of adenoma recurrence was statistically similar in each group. However, one of the secondary measures showed that the folic acid group was more likely to have more advanced lesions or multiple lesions.[263]

Another argument has been made that folic acid may play a role in the epigenetics of colorectal cancer development. DNA methylation is important in the development of colorectal cancer, and folic acid is involved in DNA methylation.[264] However, both high and low levels of activity of folate may be involved in changes of DNA methylation.[265]

Positions taken on the available evidence

In the United Kingdom, SACN assessed the impact of the papers published by Mason et al. [258] and Cole et al.[263] The Committee concluded that the relationship between cancer and folic acid was unclear.[266] It was suggested that because of a lack of data, as a precaution, there should not be a substantial increase in the average population's intake of folic acid.[266]

In Australia, the Cancer Council of Australia published a position paper on folic acid fortification. Their conclusion was that "based on the current evidence, the benefits of folic acid fortification for reducing the incidence of neural tube defects outweigh any potential increased risk of cancer".[257]

In 2016, the United States FDA concluded that the potential health outcomes such as the progression of established neoplasms the "evidence is not clear and suggests further study".[17]

A view shared by all the reviews of the evidence, however, is the importance of monitoring the population and research as the understanding of folate physiology and pathology grows.

Recovered literature

Most of the recovered literature was not empirical in nature and thus excluded. There were four meta-analyses of RCTs recovered. Two were identified in the database search,[254,267] one was required to be reviewed,[13] and one was recovered by 'pearl' searching.[264]

Table 115: Recovered literature for folic acid and cancer risk

Level of evidence	Number of citations in database search	Number of citations from other sources	Total
I or systematic review	2	2	**4**
II	3	0	**3**
III	5	0	**5**
IV	9	0	**9**
No empirical evidence	39	0	**39**
Total	**59**	**2**	**61**

Highest level of evidence: meta-analysis of folic acid supplementation

Four meta-analyses of RCTs were recovered. One was excluded as it did not contain a meta-analysis of safety although it commented on cancer risk.[254]

The inclusion criteria for Mackerras et al.[13] were RCTs conducted in humans for at least one year, and at least one trial arm that had used folic acid (which was required to be administered for a year). Co-administration of other vitamins was not an exclusion criterion. The use of pharmaceuticals (such as aspirin or statins) by both the intervention and placebo arms was not an exclusion criterion. The trials had to report at least one of: all-cause mortality, total cancer incidence, the incidence of specific cancer or recurrence of a colorectal adenoma. Trials were excluded if the recruited subjects had cancer or were cancer survivors. Other serious diseases such as end-stage renal failure or HIV were also exclusion criteria. Folic acid being administered as a component within a broad multivitamin was also an exclusion criterion. Recruitment of children (<18) was also an exclusion criterion.

There was no restriction on the dose of folic acid. The minimum dose in the trials was 0.4 mg.

There are limitations in the generalisability of this meta-analysis as the underlying study recruitment was mainly in men and older populations. The relative risk for the folic acid treatment was 1.04 (95% CI 0.97-1.11).[13] The trials included had a wider range of interventions than folic acid, for example, other vitamins could be included in the intervention arms. Pharmaceuticals could be included if they were included for both intervention and placebo arms. When only the trials involving lower doses of folic acid and no other B vitamins were included the confidence interval increased (relative risk 1.28 [95% CI 0.95-1.72]). Moreover, the interventions were not always continued in the trials, unlike the approach to fortification. The trials included in the meta-analysis ranged from one year to over six years.[13]

A similar result of no additional risk was found in a later meta-analysis by Qin et al.[264] of folic acid supplementation with regard to colorectal cancer. The relative risk of treatment with folic acid was 1.00 (95% CI 0.82-1.22).[264] Qin et al.[264] reported on a subgroup analysis on the basis of the level of folic acid supplementation and concluded that it did not alter the results. Qin et al.[264] assessed the RCTs as being of high quality.

A meta-analysis of folic acid supplementation for all cancers, by Vollset et al.[267] and published earlier than Mackerras et al.,[13] similarly found no increased risk (RR 1.06 [95% CI 0.99-1.13]).[267] The inclusion criteria were slightly different to Mackerras et al.[13] in that there needed to be 500 participants. Vollset et al.[267] used participant level data allowing increased subgroup analysis to be conducted. The average age of the participants included in the meta-analysis was 64 years, and 65% of the participants were male. The minimum dosage of folic acid in Vollset et al.[267] was 0.5 mg and the median dosage was 2.0 mg. There was a total of 1 904 cancers in the folic acid group and 1 809 in the placebo group. No site of cancer was found to be statistically significantly more likely with the supplementation of folic acid. Vollset et al. found no trend with a greater length of trial.[267]

The conclusions of the meta-analyses are described below in Table 116.

Table 116: Table of meta-analyses published post-2013 for cancer risk with folic acid

Source	Outcome of interest	Folic vs. Non-folic (95% CI)	Comment
Mackerras et al.[13]	Total cancer incidence (relative risk)	1.04 (0.97-1.11)	43 557 participants I^2 =0%
Mackerras	Total cancer incidence (relative	1.28 (0.95-1.72)	2 632[a]

Source	Outcome of interest	Folic vs. Non-folic (95% CI)	Comment
et al.[13]	risk)- restricted to folic acid 0.5-1 mg without other vitamins		I^2 =0%
Vollset et al.[267]	Total cancer incidence	1.06 (0.99-1.13)	24 799 participants with folic acid and 24 822 with placebo
Mackerras et al.[13]	Colorectal cancer incidence (relative risk)	1.00 (0.82-1.23)	33 922 participants I^2 =0%
Qin et al.[264]	Colorectal cancer incidence	1.00 (0.82-1.22)	17 317 participants with folic acid and 17 281 with placebo I^2 =0%
Mackerras et al.[13]	Breast cancer incidence (relative risk)	0.82 (0.63-1.07)	10 3611 participants I^2 =0%
Mackerras et al.[13]	Prostate cancer incidence (relative risk)	1.16 (0.65-1.60)	20 094 participants I^2 =53%
Mackerras et al.[13]	Lung cancer incidence (relative risk)	1.00 (0.84-1.21)	31 864 participants I^2 =0%
Mackerras et al.[13]	All-cause mortality (relative risk)	0.99 (0.92-1.05)	47 993 participants I^2 =11%
Mackerras et al.[13]	Colorectal adenoma recurrence (relative risk)	0.97 (0.83-1.14)	I^2 =26.8%

a Calculated from trial description in Table 2 of Mackerras[13]
Abbreviations: CI, confidence interval

Conclusions

Multiple meta-analytic studies do not reveal an overall statistically significant increase in cancer risk associated with folic acid supplementation (and other vitamins). This result is consistent across the meta-analyses.

This evidence is indirect because the intervention evaluated in the meta-analysis was supplementation rather than fortification. The dosage of folic acid was thus higher in the meta-analysis than expected for fortification. The interventions in the meta-analysis were not specific for folic acid, and other vitamins could be included in the meta-analysis. The interventions were also not always continuous, as fortification is intended to be. The population of the trials included in the meta-analysis may not be representative of the Australian population. The majority came from trials for which cardiovascular disease (including cerebrovascular disease) was required for the recruited population. Therefore, the meta-analysis population was more likely to be male and older than the general population.

There is an increased level of evidence compared to that available in 2006. Nonetheless, the indirect nature of the RCT evidence and the potential issues with differences in the meta-analysis population compared to the Australian population lower the quality of the evidence for assessing the safety of folic acid fortification (as opposed to supplementation) for the general population.

Folic acid and medication use

There were two systematic reviews included in the recovered literature (Table 117). These both investigated the implications for methotrexate (an anti-folate medication) of folic acid supplementation.

Table 117: Recovered literature for folic acid and changes in medication use

Level of evidence	Number of citations in database search	Number of citations from other sources	Total
I or systematic review	2	0	**2**
II	0	0	**0**
III	0	0	**0**
IV	3	0	**3**
No evidence	6	0	**6**
Total	**11**	**0**	**11**

Al-Dabagh et al.[268] reviewed the literature involving the use of folate/folic acid in patients (particularly with psoriasis) treated with methotrexate. They also analysed prescribing over time with the use of supplementation. Twenty-six studies were included, with seven focused on psoriasis. The seven trials of psoriasis included observational and RCTs including folonic acid and folic acid. The trials were small in size and showed inconsistent results. The authors concluded more examination was required of the effect of folic acid supplementation on psoriasis patients.

Prey et al.[269] conducted a systematic review and meta-analysis of RCTs involving rheumatoid arthritis and psoriasis with folic acid supplementation. Both folic acid and folonic acid were included. The use of folic acid or folonic acid reduced adverse effects of methotrexate. For three of the trials, the dosage was increased in the intervention arm compared to the placebo arm.

There was no evidence of harm in the meta-analysis of supplementation. However, increased doses of methotrexate may be required.

Folic acid and reproductive effects

Two level I or systematic reviews were recovered (Table 118).

Table 118: Recovered literature for folic acid and reproductive effects

Level of evidence	Number of citations in database search	Number of citations from other sources	Total
I or systematic review	2	0	**2**
II	0	0	**0**
III	0	0	**0**
IV	2	0	**2**
No empirical evidence	2	0	**2**
Total	**6**	**0**	**6**

Muggli and Halliday[270] conducted a systematic review of published studies from 1994 to 2006. The systematic review was designed to answer two separate questions.

- Does periconceptional supplementation with folic acid increase twinning?
- Has fortification of food with folic acid increased twinning?

Twelve studies were retrieved, six observational and six cohort studies. Confounders such as maternal age and the use of assistive reproductive therapy were considered in the review. Six observational studies investigated supplementation and six retrospective studies investigated fortification (five from the United States and one from Chile).

The quality assessment identified several issues in the studies associating mandatory folic acid fortification and twinning, including a lack of consideration of confounders and the period of voluntary folic acid fortification being considered as no exposure to folic acid fortification. Some studies found no change while other results estimated up to a 4.6% increase in the twinning rate.

The quality assessment concluded that the study by Vollset et al.[271] was well executed and contained the largest study population for supplementation (176 042 women). Vollset et al.[271] found a non-significant increase in the odds ratio for twinning (OR 1.02 [95% CI 0.85-1.24]) after adjustment for confounders. The odds ratio was higher for dizygotic twinning, but this was also not significant (OR 1.26 [95% CI 0.91-1.73]).

The authors concluded that there was possible evidence of a relationship between periconceptional folic acid intake and twinning.[270]

Das et al.[272] conducted a systematic review on the micronutrient fortification of food and its impact on the health of both women and children. The micronutrients included folic acid. For folic acid/folate, the outcomes analysed included twinning. Thirty-one pre-post cohort studies were included. The analysis showed a non-statistically significant impact on twinning (RR 1.06 [95% CI 0.92-1.22]) based on pre-post cohort studies.

There was no statistically significant increase in twinning demonstrated but the evidence base is low level, consisting of systematic reviews (and meta-analysis) of observational studies.

Maternal folic acid and impacts upon offspring

Four studies were recovered that were either meta-analyses or systematic reviews. One was not considered further because the systematic review did not evaluate impacts on offspring and there was a comment on the observational study associating high folate and low B_{12} status, with increased insulin resistance in babies in India.[254] The other three systematic reviews involved a consideration of autism spectrum disorder[273] and wheezing/asthma.[274,275] Pu et al.[273] found that periconceptional folic acid may reduce the risk of autism spectrum disorder and was not considered further (as folic acid was not associated with an adverse effect).

Table 119: Recovered literature for folic acid and impacts on offspring

Level of evidence	Number of citations in database search	Number of citations from other sources	Total
I or systematic review	2	2	**4**
II	0	0	**0**
III	0	0	**0**
IV	3	1	**4**
No empirical evidence	3	0	**3**
Total	**8**	**3**	**11**

Crider et al.[275] and Brown et al.[274] were systematic reviews of the relationship between maternal folic use periconceptionally and offspring asthma/wheezing. Crider et al.[275] included a meta-analysis.

Crider et al.[275] conducted a systematic review and meta-analysis of asthma, allergy, eczema and atopic dermatitis. Five trials were included, all observational in nature, three cohort studies and two case-control studies. Folic acid supplementation was used as the measure of exposure. A random-effects meta-analysis was used. For asthma, the relative risk was 1.01 (95% CI 0.78-1.3). For the combination of asthma and reports of wheezing in infants and toddlers, however, there was a small statistically significant increase in outcomes associated with folic acid supplementation. The relative risk was 1.05 (95% CI 1.02-1.09).

Limitations of this systematic review and meta-analysis, as acknowledged by the authors, included a lack of determination of other sources of folate/folic acid (including from fortification) and the potential for recall bias. The use of observational studies is a lesser level of evidence. However, the results did not support an association between folic acid supplements and asthma.

Brown et al.[274] conducted a systematic review of the association between maternal folate/folic acid and offspring wheeze/asthma. Ten studies were included, all observational. The populations of two studies were exposed to fortification. The studies had heterogeneous approaches to capturing the total folate/folic acid (DFE) in the diet of the mothers. Five studies considered folic acid supplements alone, four considered dietary folate and folic acid supplements and one considered dietary folic acid alone. The outcome measures were also heterogeneous with some studies having reported childhood asthma as an outcome and others having reported infant wheezing.

Six studies suggested there was no link and four a potential association. The authors concluded there was limited evidence of a consistent dose-response relationship and, among those that found a relationship, the risk was small and potentially transient. Additional follow-up into late childhood was recommended to elucidate potential long-term risks.[274]

Unmetabolised folic acid

One RCT was recovered from the literature on unmetabolised folic acid (Table 120).

Table 120: Recovered literature for folic acid and unmetabolised folic acid

Level of evidence	Number of citations in database search	Number of citations from other sources	Total
I or systematic review	0	0	**0**
II	1	0	**1**
III	2	0	**2**
IV	11	0	**11**
No empirical evidence	11	0	**11**
Total	**25**	**0**	**25**

Pentieva et al.[276] reported on the results of an RCT undertaken in pregnant women. Women with singleton pregnancies who had taken folic acid supplements for the first trimester of pregnancy were randomised to either continuing folic acid (n=96) or placebo (n=94).

Maternal blood at 36 weeks gestation and fetal cord blood were examined for unmetabolised folic acid (amongst other biomarkers of folate status). There were some dropouts from the study with 126 36-week samples and 53 cord blood samples being included in the results.

The intervention group had a statistically significant higher folate level in the 36-week blood and cord blood. However, there was no statistically significant difference in the concentrations of plasma folic acid between the groups. There was a difference in the proportion of mothers who had detectable folic acid in the plasma (42% versus 16%).

The authors concluded that a supplement of 400 µg/day of folic acid did not appear to have an impact on unmetabolised folic acid levels in pregnant women or neonates.[276]

Folic acid hypersensitivity

Only one article was recovered for hypersensitivity,[277] but it did not contain any empirical information.

Other adverse effects

Three articles were identified as reporting information about potential adverse effects associated with folic acid. Two were randomised controlled trials where folic acid was used as an intervention (Level II). The third was a letter expressing concern about the number of children who were exceeding the UL[278] but did not provide any empirical data.

Imasa et al. [279] was an RCT conducted in the Philippines. Patients with recent unstable angina or non-ST evaluation myocardial infarcts were recruited. Patients were randomised to receive folic acid, B_{12} and B_6 (n=116) or placebo (n=124). The composite outcome of death, non-fatal acute coronary syndrome and serious re-hospitalisation was significantly higher in the intervention group. The relative risk ratio was 1.2 (95% CI 1.00-1.44). The major difference was in re-hospitalisation which occurred in 11.3% of the intervention group and 2.2% of the control group (RR 5.11 [95% CI 1.14-23.00]). This is consistent with the literature that folic acid supplementation of cardiac disease is not beneficial for secondary prevention of cardiac disease.[280]

Taneja et al.[281] was an RCT on infants in India. The hypothesis was that respiratory disease and diarrhea might be responsive to B vitamin supplementation. A factorial design was used, and folate and B_{12} were the interventions. Two times the recommended daily allowance was given daily for six months to 1000 children aged between 6 and 30 months. The baseline B_{12} and folate levels were poor, and 70% of children were anaemic. There was an increased risk of diarrhea lasting more than 3 days (p=0.04) and more than 14 days in the folic acid group (p=0.03). This study was of limited generalisability to the Australian population.

Folic acid fortification safety conclusions

There is no conclusive evidence of toxicity associated with the use of folic acid fortification at the levels of intake that has occurred in Australia's mandatory folic acid fortification initiatives at a population level.

The issue of masking of B_{12} deficiency is likely to be restricted to the elderly or those with particularly poor diets.[14] There is no robust evidence to suggest this is a problem with levels of folic acid fortification without folic acid supplementation.

The meta-analysis of multiple RCTs for cancer risk is an addition to the literature since the 2006 review. It suggests, at a population level, that there is no additional risk of cancer from folic acid supplementation.

Multiple other risks have been hypothesised, such as unmetabolised folic acid interfering with folate metabolism, interference with medication and twinning. Associations between maternal folic acid supplement use and wheezing have also been published.[274] However, there is no consistent epidemiological evidence of safety risk. A systematic review conducted in 2014 concluded that there was limited evidence of any dose-response, and the majority of studies found no association.[274]

However, the evidence base is limited in a number of ways, and further research would be useful. The lack of information about high-risk subgroups is a weakness. The lack of information for children (who have been assessed as the most likely to exceed the UL) is also a weakness in the evidence base. The limitations include a preponderance of observational studies investigating fortification, a lack of consistency in the methods of estimating folate/folic acid exposure and the indirect evidence provided by higher level evidence meta-analysis of RCTs.

The use of indirect evidence from supplementation trials (a different intervention) provided the higher level of evidence (Level I and Level II evidence) for cancer risk and for B_{12} cognitive decline but suffer from concerns about transferability to the population of interest.

This Report's review of the literature has substantial limitations. The indirect nature of some of the evidence suggests that the literature search undertaken in relation to the safety of fortification might have only accessed a portion of the available literature. However, a full systematic literature search of folic acid (as opposed to a review of the safety of folic acid fortification) was beyond the scope of this Report.

The biochemical nature of folic acid and folate, especially the requirement of folate for DNA synthesis and methylation, suggests widespread hypothesis formation may occur. Associations of adverse effects occurring in the offspring of mothers with a higher intake of folic acid is an example of this form of hypothesis generation. Epigenetic changes are one mechanism by which this may occur.[282] Confirming or excluding causal relationships requires careful epidemiological and biomedical study. Continuing monitoring, additional meta-analyses (for outcomes other than cancer) and epidemiological studies for high-risk subgroups and children may be required in the future. Long-term epidemiological studies will be required for hypothesised adverse effects such as asthma and cognitive decline that may occur over a period of years.

There is a definite benefit to folic acid fortification in decreasing NTDs that needs to be weighed against the (thus far) hypothetical risks. An accurate and comparable assessment of population intake and status is required to combine the evidence produced in different studies.

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10 Alternative text for figures

This Section presents alternative text for each of the figures in the Report; it also presents the data in a tabular form where it could be informative. The tables in this Section are simple without any merged cells.

Figure 1: Proposed monitoring framework

This figure is a flow diagram that covers the appropriate areas that need to be monitored to assess the effects of the mandatory fortification requirements.[7] Three steps are identified: process, impact and outcome. Each step has a main question and a series of sub-questions for consideration in monitoring.

For process, the main question was: 'Has the program been implemented as intended?'

The sub-questions were:

- Are relevant industry groups complying with regulations?
- Have sufficient enforcement strategies been implemented?
- Are relevant industry groups informed of relevant regulations?
- Are relevant regulations in place and enforceable?
- Do consumers accept the need for mandatory fortification?

For impact, the main question was: 'Has nutrient availability and consumption increased?'

The sub-questions were:

- Has nutrient intake increased compared to baseline?
- Has the nutrient content of the food supply increased?

For outcome, the main question was: 'Is the program effective and safe?'

The sub-questions were:

- Has the desired health outcome been achieved?
- Are there any side effects resulting from increased nutrient status?
- Has nutrient status of the general population and of high-risk groups improved and is it adequate?

Figure 2: Folic acid fortification economic evaluation decision tree

This figure is a decision tree divided into two parts. The upper part of the decision tree shows the alternatives (Australia with mandatory folic acid fortification and Australia without mandatory folic acid fortification) and the division of the population into various subgroups. The lower part of the decision tree shows the outcomes associated with a pregnancy affects by a neural tube defect.

The top part of the decision tree divided the population into two main groups: women of childbearing age (16-44 years) and the remaining population. Women of childbearing age include women that are pregnant and non-pregnant. For those that are pregnant, the pregnancy can be impacted by a neural tube defect and the outcomes are traced through in the lower part of the decision tree or not impacted by a neural tube defect whereupon the pregnancy is assumed to progress normally. The remainder of the population was divided into an older and a younger group. The older group was used for considering adverse effects, such as the development of neurological abnormalities from a B_{12} deficiency that may be exacerbated by folic acid fortification

The lower part of the decision tree traced the impact of a pregnancy affected by a neural tube defect. A portion of pregnancies are terminated. If not terminated the birth could be a stillbirth or born alive, if alive, there is a chance of neonatal survival or neonatal death.

Figure 3: Tornado diagram for folic acid fortification economic evaluation base case

The figure is a tornado diagram estimating the sensitivity of the mandatory folic acid model to changes in the parameters. It takes the form of a horizontal bar graph. The horizontal axis is the incremental cost per quality-adjusted life year of the introduction of the alternative of Australia with mandatory folic acid fortification compared to the alternative of Australia without mandatory folic acid fortification (no mandatory folic acid fortification). The categories on the vertical axis are the parameters, each of which is varied over the range described.

The information in the tornado diagram is reproduced below in Table 121. Negative numbers imply that the alternative of mandatory folic acid fortification is less expensive and results in additional health. The results are most sensitive to the variation in the annual background reduction in the rate of neural tube defects.

Table 121: Tabular data for Figure 3

Parameter	Low Value	High Value	Low Value – cost per quality-adjusted life year	High Value – cost per quality-adjusted life year
annual background reduction in NTD rate	-0.000113667	-0.0000284	$AUD -43 266	$AUD 8 360
NTD 20-24 years post	0.000274	0.001645	$AUD -14 733	$AUD 10 275
NTD 35+ years post	0.000281	0.001936	$AUD -14 626	$AUD -3 380
NTD 25-29 years post	0.000252	0.001662	$AUD -13 786	$AUD -3 519
NTD 30-34 years post	0.000255	0.001727	$AUD -11 014	$AUD -3 651
cost of fortification (industry and government), post	0.01	0.05	$AUD -5 454	$AUD 1 746
NTD < 20 years post	0.00022	0.001365	$AUD -3 394	$AUD 1 623
cost of carer	96 402.14	385 608.55	$AUD -5 558	$AUD -1 190
NTD 30-34 years pre	0.000682	0.000792	$AUD -3 917	$AUD 31
cost of productivity loss for persons with NTD	77 451.71	309 806.83	$AUD -4 986	$AUD -1 476

Parameter	Low Value	High Value	Low Value – cost per quality-adjusted life year	High Value – cost per quality-adjusted life year
NTD 25-29 years pre	0.000747	0.000862	$AUD -3 760	$AUD -541
cost of spina bifida, health care, discounted	60 052.28	240 209.13	$AUD -4 129	$AUD -1 905
NTD 35+ years pre	0.000593	0.000695	$AUD -3 502	$AUD -1 352
NTD 20-24 years pre	0.000911	0.001037	$AUD -3 295	$AUD -1 775
probability of stillbirth, spina bifida	0.41195475	0.51110419	$AUD -3 216	$AUD -2 055
probability of spina bifida	0.45078914	0.5189775	$AUD -3 164	$AUD -2 265
probability of neonatal survivors, spina bifida	0.73687967	0.84627991	$AUD -3 098	$AUD -2 228
cost of non-NTD affected pregnancy, discounted	2 565.27	10 261.07	$AUD -2 925	$AUD -2 088
probability of encephalocoele	0.07116306	0.11011615	$AUD -2 967	$AUD -2 348
utility of spina bifida	0.09	1	$AUD -2 986	$AUD -2 370
cost of encephalocoele, health care, discounted	66575.07	266300.29	$AUD -3 013	$AUD -2 462
probability of termination of pregnancy	0.41530054	0.47690426	$AUD -2 906	$AUD -2 359
probability of stillbirth, encephalocoele	0.27098697	0.49605853	$AUD -2 899	$AUD -2 379
probability of neonatal survivors, encephalocoele	0.69143949	0.9170059	$AUD -2 815	$AUD -2 424
NTD < 20 years pre	0.00119	0.001333	$AUD -2 836	$AUD -2 448
cost of assistive technology	8124.33	32497.32	$AUD -2 891	$AUD -2 523
cost of termination of pregnancy, replacement child, discounted	2326.77	9307.09	$AUD -2 872	$AUD -2 533
cost of termination of	1086.74	4346.97	$AUD -2 751	$AUD -2 593

Parameter	Low Value	High Value	Low Value – cost per quality-adjusted life year	High Value – cost per quality-adjusted life year
pregnancy, discounted				
utility of encephalocoele	0.09	1	$AUD -2 729	$AUD -2 594
cost of spina bifida, discounted	1207.81	4831.25	$AUD -2 726	$AUD -2 606
utility of non-NTD affected pregnancy	0.86	0.87	$AUD -2 707	$AUD -2 646
cost of anencephaly, discounted	1980.04	7920.15	$AUD -2 679	$AUD -2 629
cost of anencephaly, NND, discounted	2609.33	10437.34	$AUD -2 663	$AUD -2 637
utility of termination of pregnancy, replacement child	0.86	0.87	$AUD -2 646	$AUD -2 622
survival of spina bifida neonatal deaths in life years	20.16	20.63	$AUD -2 649	$AUD -2 640
probability of stillbirth, anencephaly	0.5956498	0.75885026	$AUD -2 649	$AUD -2 643
cost of spina bifida, NND, discounted	2609.33	10437.34	$AUD -2 649	$AUD -2 644
survival of encephalocoele neonatal deaths in life years	19.82	20.37	$AUD -2 647	$AUD -2 645
survival of spina bifida neonatal deaths in life years	0.07173	0.07288	$AUD -2 646	$AUD -2 646
survival of encephalocoele neonatal deaths in life years	0.05738	0.06152	$AUD -2 646	$AUD -2 646
probability of anencephaly	0.39189763	0.45935423	$AUD -2 646	$AUD -2 646

Figure 4: Cost-effectiveness acceptability curve for folic acid alternatives

This figure is a line graph that estimates the probability of each alternative being the most cost-effective. The horizontal axis is the societal willingness to pay for an additional quality-adjusted life year. The vertical axis the probability of the stated alternative being superior for each value of willingness to pay. The blue squares represent the alternative of Australia with mandatory folic acid fortification. The red triangles represent the alternative of Australia without mandatory fortification (retaining the suite of policies that existed prior to mandatory fortification). The alternative of Australia with mandatory folic acid fortification is more likely to be superior over all values of willingness to pay for an additional quality-adjusted life year, including zero. At a willingness to pay of zero dollars per quality-adjusted life year, mandatory folic acid fortification has a probability of 70% of being acceptable. At a societal willingness to pay of $AUS 50 000, mandatory folic acid fortification has a probability of 99% of being acceptable.

The information contained in the figure is reproduced below in Table 122

Table 122: Tabular data for Figure 4: Cost-effectiveness acceptability curve for folic acid alternatives

Assumed willingness to pay	Probability mandatory fortification acceptable	Probability of no mandatory fortification being acceptable
$AUS 0	0.6977	0.3023
$AUS 5 000	0.8701	0.1299
$AUS 10 000	0.9346	0.0654
$AUS 15 000	0.9584	0.0416
$AUS 20 000	0.971	0.029
$AUS 25 000	0.9774	0.0226
$AUS 30 000	0.9824	0.0176
$AUS 35 000	0.9856	0.0144
$AUS 40 000	0.988	0.012
$AUS 45 000	0.9889	0.0111
$AUS 50 000	0.9901	0.0099
$AUS 55 000	0.9908	0.0092
$AUS 60 000	0.9912	0.0088
$AUS 65 000	0.9914	0.0086
$AUS 70 000	0.9915	0.0085
$AUS 75 000	0.9919	0.0081
$AUS 80 000	0.9921	0.0079
$AUS 85 000	0.9921	0.0079
$AUS 90 000	0.9923	0.0077
$AUS 95 000	0.9926	0.0074
$AUS 100 000	0.9929	0.0071

Figure 5: MUIC in Victoria Health Monitor data

This figure is a vertical bar graph illustrating the median urinary iodine concentration by calendar month in the Victoria Health Monitor data. The horizontal axis is the month and the year in which the sample was obtained. The vertical axis represents the median urinary iodine concentration. The median urinary iodine concentration in May 2009 was 77 µg/L, in April 2010 it was 101 µg/L

The data underlying the figure is replicated below in Table 123.

Table 123: Tabular data for Figure 5: MUIC in Victoria Health Monitor data

Month and Year	Median urinary iodine concentration (µg/L)
May 2009	77
June 2009	79
July 2009	80
August 2009	91
September 2009	82
October 2009	77
November 2009	81
December 2009	92
February 2010	111
March 2010	102
April 2010	101

Figure 6: Iodine fortification economic evaluation model structure

This figure is a diagrammatic representation of an idealised model for the economic evaluation of iodine fortification. The population is broken down into different subgroups, including newborn, children, males aged 16-44 years, females aged 16-44 years who are not pregnant, females aged 16-44 years who are pregnant and adults aged 45 years and over. The proportion of the population with different iodine statuses in each subgroup results in different health impacts. Included in the health impacts are hypothyroidism, cretinism, Hashimoto's, elevated (thyroid) autoantibodies and hyperthyroidism. Over time participants can transition from one age group to another, for example, the newborn can become children with cretinism.

The majority of this diagrammatic representation was not used in the economic evaluation of mandatory iodine fortification.

Figure 7: PRISMA flow chart for consumer understanding

This figure illustrates the number of inclusions and exclusions that occurred in the search strategy for consumer understanding in Australia and New Zealand. There were two Food Standards Australia New Zealand publications and an additional 598 included in the search strategy. When duplicates (n=273) and ineligible studies (n=291) were excluded, 36 studies were retrieved for detailed examination. Seventeen studies were included in the review.

Figure 8: Knowledge to make decisions involving iodine during pregnancy

This is a vertical bar chart which shows the percentage of pregnant women who received enough information to make a decision about iodine. The vertical axis is the percentage of women who received enough information. The studies, from both pre-mandatory fortification and post-mandatory fortification, are included on the horizontal axis.

The data underlying the figure are replicated below in Table 124.

Table 124: Tabular data for Figure 8

Study	Period	Percentage of women with enough information about iodine
Charlton 2010	Pre-mandatory fortification	17%
Axford	Post-mandatory fortification	25%
Charlton 2012	Post-mandatory fortification	34%
Charlton 2013	Post-mandatory fortification	32%

Figure 9: PRISMA flow chart for economic literature search

This figure illustrates the number of inclusions and exclusions that occurred in the search strategy for economic evaluations of folic acid fortification. Five hand-searched results and 52 results from the electronic search were included. When duplicates (n=10) and ineligible studies (n=34) were excluded, 17 studies were retrieved for detailed examination. Eleven studies were included in the review.

Figure 10: Relationship over time between iodine and human capital

This figure is an illustration of the relationship between iodine fortification and human capital. The illustration shows the temporal relationship between iodine fortification in the ante-natal period and the resulting increase in human capital 30 to 50 years later.

Figure 11: PRISMA flow chart for IQ and earnings

This figure illustrates the number of inclusions and exclusions that occurred in the search strategy for the association between IQ and earnings. One google result and 943 results from the electronic search were included. Ineligible studies (n=928) and duplicates (n=3) were excluded, 13 studies were retrieved for detailed examination and supplemented by nine studies from a manual search. Twenty-two studies were included in the review.

Figure 12: PRISMA flow chart for iodine fortification safety

This figure illustrates the number of inclusions and exclusions that occurred in the search strategy for economic evaluations of iodine fortification safety. Three hand-searched and 942 results from the electronic search were included. When duplicates (n=273) and ineligible studies were excluded, 30 studies were included.

Figure 13: PRISMA flow chart for folic acid safety review

This figure illustrates the number of inclusions and exclusions that occurred in the search strategy for economic evaluations of folic acid safety review. Thirty google searched and 1 073 results from the electronic search were included. When duplicates and ineligible studies were excluded, 131 studies were retrieved for detailed examination. Nine articles from hand-searching and the grey literature were also included.