Food Safety
AUTHORITY OF IRELAND

Report of the Scientific Committee
of the Food Safety Authority of Ireland

Update Report on Folic Acid and the Prevention of Birth Defects in Ireland

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Update Report on Folic Acid and the Prevention of Birth Defects in Ireland

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ABBREVIATIONS

µg	Microgram
DFEs	Dietary Folate Equivalents
EU	European Union
EUROCAT	European Network of Congenital Anomaly Registries
FSAI	Food Safety Authority of Ireland
g	Gram
HSE	Health Service Executive
ml	Millilitre
MSL	Maximum Safe Level
NANS	National Adult Nutrition Survey
NCFAFF	National Committee on Folic Acid Food Fortification
ng	Nanogram
nM	Nanomolar
NTDs	Neural Tube Defects
PAL	Public Analyst Laboratory
tHcy	Total Homocysteine
TUDA	Trinity-Ulster Department of Agriculture Project
UL	Tolerable Upper Intake Level
US	United States

FOREWORD

This report deals with folic acid, the synthetic form of the B vitamin known as folate. Folic acid is found in the human diet only in fortified foods and supplements; it is however readily converted to the natural forms of folate after ingestion. Folates found naturally in foods are inherently unstable and can have poor bioavailability; as a result their ability to influence blood folate levels (and thus health outcomes) is limited. Fortified foods can overcome these challenges because folic acid (the vitamin form used for fortification) is highly stable and bioavailable.

The achievement of optimal folate status is an important public health goal for Ireland as it is for populations worldwide. This is primarily because of conclusive scientific evidence linking low folate status with spina bifida and related birth defects, collectively known as neural tube defects (NTDs). These are major birth defects occurring as a result of a failure of the neural tube to close properly in the first few weeks of pregnancy, leading to death of the foetus or newborn, or to varying degrees of disability involving the spinal cord.

Nearly 25 years ago it was proven beyond doubt that maternal folic acid supplementation in early pregnancy protects against NTDs. Such evidence has led to very clear folic acid recommendations for women of reproductive age which are in place worldwide. For the prevention of NTDs, women are recommended to take 400 micrograms (µg) per day of folic acid from preconception until the end of the first trimester of pregnancy.

Folic acid supplementation is a highly effective means to optimise folate status in individual women who take their supplements as recommended. However, international evidence shows that in practice, very few women in Ireland or elsewhere, take folic acid supplements as recommended and there is particular concern that women from lower socioeconomic backgrounds are the least likely to follow current recommendations. Despite active health promotion campaigns over many years encouraging women to follow the recommendations, it is evident that promoting folic acid supplementation has had little impact in preventing NTDs. This is primarily because the neural tube closes in the first few weeks of pregnancy (by day 28 post-conception), and therefore the timing of folic acid usage by women is critical to preventing NTD-affected pregnancies. For many women, the period from preconception until the 28th day of the pregnancy (when folic acid is protective against NTDs) may have passed before folic acid supplements are even started. Thus, the benefit of folic acid supplementation is confined to those women (the minority) who follow the recommendations correctly.

Folate inadequacy remains a significant problem in European countries including Ireland, and this has resulted in an unacceptably high rate of NTDs. In fact, the evidence (as reported to international medical and scientific communities in 2005 and in 2015) shows that the prevalence of NTDs has not decreased in any European country over the 21 year period from 1990 to 2011 (a period during which folic acid supplementation was actively promoted). Of note, a total of 8,400 NTDs cases were documented in Europe in the 10-year period 2000-2010 (8.16 per 10,000 births); this is itself widely considered to be a gross underestimate of true rates of NTDs. The lifetime direct costs for spina bifida-affected live births for Germany in 2009 alone were estimated at €65.5 million. Of particular concern are reports that the incidence of NTDs in Ireland is increasing in recent years. In addition, rates of NTDs in Ireland are among the highest in the world. Addressing NTDs in Ireland should therefore be an urgent priority.

The average rate of NTDs in Europe was recently estimated to be 1.6 times higher than in regions of the world with mandatory folic acid-fortification policies in place. Such evidence makes a strong case for adopting a new food fortification policy in Ireland. Indeed, the World Health Organization (WHO) and the Food and Agricultural Organization of the United Nations (FAO) recognise that the purpose of food fortification, i.e. the process of adding essential micronutrients to foods, is *"to improve the nutritional quality of the food supply and to provide a public health benefit with minimal risk to health"*.

Folic acid, the form of folate used for food fortification, is cheap to produce, is very stable once added to foods and is highly bioavailable when ingested. Folic acid fortification, like folic acid supplementation, is therefore highly effective as a means of optimising folate status in people who choose to consume fortified foods. In countries such as Ireland

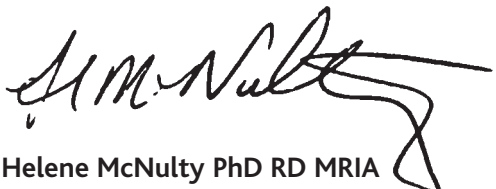
with voluntary fortification in place, folic acid fortified foods lead to improved folate status in regular consumers of these foods. Fortification has the advantage over supplementation that it can also be highly effective for populations.

When folic acid-fortification is undertaken on a mandatory basis, it has proven itself to be effective in increasing folate status in that population and in turn reducing rates of NTDs. Over 80 countries worldwide to date (including the United States, Canada and Australia) have passed regulations for the mandatory fortification of staple foods with folic acid. Those countries where mandatory folic acid fortification has been introduced have experienced significant increases in blood folate levels and marked reductions in NTDs. Reported rates of NTDs have declined by between 27% and 50% in the USA, Canada and Chile in response to mandatory folic acid fortification of food. In comparison to voluntary fortification (in place in Ireland and most European countries), a policy of mandatory fortification of foods with folic acid does not rely on individual food choices and thus reaches all sectors, ensuring a better and even distribution of folate status in the general population. Such policy has proven itself, wherever it has been introduced, in terms of lowering the risk of NTDs.

It is evident that folic acid fortified foods, since they were first introduced in Ireland in the early 1980s, have improved folate levels and in turn, have contributed to an important decline in NTDs which we experienced in the 10-15 year period starting in the early 1980s. The question therefore arises as to the impact of voluntary fortification and whether this would be adequate as a means to address NTDs in Ireland. The National Adult Nutrition Survey (NANS; funded by the Department of Agriculture Food and the Marine under its FIRM initiative) has recently provided the answer. The results of the NANS survey in relation to folate (published in 2015 in a leading international journal) show that under current fortification practice in Ireland, folic acid-fortified foods contribute very significantly to improving dietary and blood folate levels in Irish adults, with an overall 36% of women of reproductive age achieving a folate level required for optimal protection against NTDs. There is however, much individual variation and many women have inadequate status. Of particular concern, among young women who were non-consumers of fortified foods or supplements (one in five Irish women), only 16% had attained a blood folate concentration for optimal protection against NTDs.

What this latest population-based evidence shows is that voluntary fortification as it exists in Ireland, while undoubtedly having an important impact on folate status, is less effective than a mandatory fortification policy in terms of optimising folate status particularly in women in the target age group. Mandatory fortification with folic acid can be predicted to bring about a reduction in NTDs in Ireland. Of note, the experience of mandatory fortification of foods with folic acid in the USA since 1996 has shown that there is no evidence for the occurrence of adverse health effects in any population group since the introduction of this mandatory policy. Such a policy, were it to be introduced in Ireland, would therefore meet the WHO/FAO goal of food fortification *"to improve the nutritional quality of the food supply and to provide a public health benefit with minimal risk to health."*

Finally, although the preventative role of folic acid in NTDs is the major focus of public health efforts worldwide, it is worth bearing in mind that folate's role in human health extends throughout the lifecycle from conception to old age. Therefore, apart from preventing NTDs, there are anticipated health benefits of optimising folate status (arising through new fortification policy) for sub-groups in the population other than women of reproductive age.



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EXECUTIVE SUMMARY

Neural tube defects (NTDs), including spina bifida, anencephaly and related defects, are the most common major malformations of the central nervous system. There was a large decrease in incidence rate of NTDs in Ireland from the early 1980s (about 3.5 per 1,000 births) to the mid-1990s; however, the rate has remained relatively stable since then at about 1 per 1,000 births (about 80 cases per annum), similar to the UK. Recent studies suggest that the incidence of pregnancies in Ireland affected by NTDs may have increased between 2005-6 and 2010-11.

About 70% of NTDs are preventable with folic acid, a form of the B-vitamin folate, if taken from before conception until about the fourth week of pregnancy. Since 1993, the policy in Ireland has been to provide advice to all women of childbearing age who are capable of becoming pregnant, whether planning to do so or not, to take 400 µg of folic acid daily as a supplement. To date, this has had limited effectiveness and the rate of NTDs in Ireland remains significantly higher than in countries with mandatory fortification such as the United States (about 0.6 per 1,000 births). This is because compliance by women of childbearing age in Ireland with the recommendation to take a daily supplement of folic acid is generally poor, similar to experiences in other European countries. Voluntary fortification of food with folic acid by manufacturers makes a significant contribution to reduction in risk of NTD-affected pregnancies in Ireland (about 11-14%). It is estimated that about 36% of women of childbearing age in Ireland have blood folate levels that are adequate for optimal protection against NTDs.

Mandatory fortification of food staples, such as flour or cereals, has proved effective in decreasing the prevalence of pregnancies affected by NTDs in over 80 countries that have implemented this approach, e.g. by 35% in the USA. The experience of mandatory fortification of foods with folic acid in the USA since 1996 has shown that there is no evidence for the occurrence of adverse health effects in any population group following introduction of fortification. This report shows that in Ireland mandatory fortification of bread or flour to provide about 150 µg of folic acid per day in women of childbearing age could reduce the prevalence of NTDs by approximately 30%. Provided voluntary fortification of foods was continued, the benefit for reduction in the risk of occurrence of NTD-affected pregnancies by these foods could be retained. Mandatory fortification of flour or bread with folic acid would require legislation. An implementation programme would be needed to address legislation, consumer acceptability and consumer choice, technical issues, cost, and trade implications.

While voluntary food fortification with folic acid does make a significant contribution to reduction in risk of NTDs in Ireland, the lower level and uneven distribution of intake of folic acid among women of childbearing age makes it less effective than mandatory fortification. There is potential to improve the effectiveness of voluntary fortification by providing guidance on voluntary fortification of selected foods with folic acid by manufacturers, e.g. for levels of fortification and the range of foods fortified, in conjunction with a voluntary labelling scheme.

As mandatory or voluntary fortification of food with folic acid would only provide women with a proportion of the recommended amount to prevent occurrence of NTDs, the current policy of providing advice to all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid daily as a food supplement would need to be continued. Ongoing campaigns are required to promote folic acid supplement use to all women in the target group. Regular evaluation studies of these campaigns should be undertaken to develop strategies that are most effective.

It is difficult to obtain reliable estimates of the current incidence of NTDs in Ireland due to the absence of a comprehensive register of pregnancies affected by NTDs. Such a register is needed to evaluate the continuing effectiveness of national policy for prevention of NTDs. In addition, accurate data are needed on current levels of NTDs in Ireland prior to introduction of any new policy as recommended in the current report.

There is a need for ongoing monitoring of folic acid levels in foods and food supplements, and dietary intakes of folate (natural food folate and added folic acid) and blood folate levels in women of childbearing years as well as all other population groups. This is in order to provide the data required to assess the effectiveness and safety of the national policy for prevention of NTDs.

The policy for prevention of NTDs should be reviewed on a regular basis to assess its effectiveness and safety. This should be based on outcomes of monitoring of the rate of NTDs, compliance with advice on supplements, dietary intake and blood levels of folate for all population groups and updates on research related to safety.

This report presents two possible options to reduce risk of NTD-affected pregnancies in Ireland. For both options the available evidence shows that the levels of intake of folic acid that would occur would not increase the risk of adverse health effects in the population.

Recommendations

1. One of the following two options should be implemented to reduce risk of NTD-affected pregnancies in Ireland:

Option 1: Mandatory fortification together with voluntary fortification and advice on supplementation

Mandatory fortification of bread or flour with folic acid. This should be accompanied by advice to all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid daily as a food supplement. Voluntary fortification of foods with folic acid would continue. Mandatory fortification of flour or bread with folic acid would require legislation. Compared to the other option, this option has stronger evidence to support its effectiveness in further reducing the rate of NTD-affected pregnancies from the current rate

Option 2: Voluntary fortification together with advice on supplementation

Continuation of current policy to advise all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid daily as a food supplement. Voluntary fortification of foods with folic acid would continue. Compared to the other option, this option has weaker evidence to support its possible effectiveness in further reducing rates of NTD-affected pregnancies from the current rate

2. Guidance should be provided to food manufacturers for voluntary food fortification with folic acid to support the effectiveness of the chosen national policy.
3. Advice to women of childbearing age capable of becoming pregnant to take an additional 400 µg folic acid daily as a food supplement should be actively promoted and its effectiveness monitored.
4. A comprehensive nationwide register of pregnancies affected by congenital birth defects including NTDs, underpinned by specific legislation, needs to be introduced in Ireland. In addition, a national retrospective study on the incidence of NTDs in Ireland since 2012, should be undertaken.
5. There should be ongoing monitoring, informed by international best practice, of dietary intake and blood levels of folate, including:
    a) Folic acid in the food supply (folic acid in flour/bread products, other fortified foods and food supplements) and
    b) Total folate intake (natural food folate and added folic acid) and corresponding blood folate status for the target group (women of childbearing age) in addition to other population sub-groups
6. The policy should be reviewed on a regular basis to assess its effectiveness and safety.

GLOSSARY

Folate: A B vitamin found naturally occurring in foods such as green leafy vegetables, liver and beans

Folic acid: Synthetic form of the vitamin found in food supplements and fortified foods

Total folic acid: Used to describe folic acid from both fortified foods and supplements, excluding any folate from natural food sources, i.e. total folic acid = µg folic acid as fortified food + µg folic acid as supplements

Folate vs folic acid: Natural folate is usually found in the polyglutamyl form with varying numbers of glutamate residues. In contrast, folic acid is a monoglutamate containing just one glutamate moiety and is fully oxidised. As folic acid is the more stable form, this is the form of the vitamin which is used in food fortification and in supplements. Once ingested, folic acid is readily converted to the natural co-factor forms. Natural folates and folic acid also differ in terms of bioavailability as they are absorbed at different rates. Supplemental folic acid has been shown to have 100% bioavailability with folic acid fortified foods having 85% bioavailability and natural folate having the lowest bioavailability at just 50%

NTDs: Neural tube defects; caused by the failure of the neural tube to close properly during the first 21-28 days after conception

DFE: Dietary folate equivalents; only applies to food. Dietary folate equivalents have been devised based on differences in bioavailability between folates naturally occurring in foods and folic acid added to foods (DFE = µg natural food folate + 1.7 times µg folic acid from fortified foods)[1]

Voluntary folic acid food fortification: The voluntary addition of varying amounts of folic acid to various food types

Mandatory folic acid food fortification: The mandatory addition of a specific amount of folic acid to a certain food type

UL: Tolerable upper intake level; a UL is the highest level of long term daily intake of a nutrient, from all sources, judged to be unlikely to pose a risk of adverse health effects to humans.

Occurrence: Carrying or giving birth to a baby with an NTD

Recurrence: Carrying or giving birth to a baby with an NTD having previously carried or given birth to a baby with an NTD

[1] Institute of Medicine (1998) DRI Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. Washington, D.C.: National Academy Press

CHAPTER 1. INTRODUCTION

1.1 Folate and Folic Acid

Folate is a B vitamin which is essential to the normal development and functioning of the human body. The terms folate and folic acid are often used interchangeably, however there are important differences. Folate is the natural form found naturally occurring in foods such as green leafy vegetables, asparagus, liver and beans. Folic acid is the synthetic form of the vitamin. Folic acid is the form found in food supplements (either as folic acid alone or as part of a multi-nutrient complex) and the form added to fortified foods.

It is important to note that it is only folic acid, the synthetic form of the vitamin, which when taken prior to conception and for the first few weeks of pregnancy, can protect against an NTD-affected pregnancy. Folate, the natural form of the vitamin, while it can improve blood folate status, is not effective in protecting against NTD-affected pregnancies.

Folic acid, the synthetic form of the vitamin, is more stable and bioavailable than natural folate. This is as a result of the chemical differences between the two (see Glossary). No adverse effects have been associated with the consumption of excess folate from foods therefore there is no UL for naturally occurring food folates. The UL applies only to folic acid intakes, i.e. folic acid fortified food or supplemental folic acid, or a combination of both.

1.2 Prevention of Neural Tube Defects

NTDs are the most common major malformation of the central nervous system. They arise at a very early stage of pregnancy - between 21 to 28 days after conception - a time when most women do not yet know they are pregnant. At this stage in early pregnancy, the cells are developing, forming a tube-like structure known as the neural tube, from which the entire nervous system develops. The neural tube eventually becomes the brain and spinal cord. The development and closure of this neural tube is vital to the normal development of the baby. Failure of the proper closure of the neural tube results in an NTD which can involve the brain, spinal cord, meninges (covering membranes), skull and spine [1]. There are many different malformations involved and the terms used to describe them are based on clinical descriptions and the presumed embryological defect. These defects include spina bifida (accounting for approximately 51% of NTDs), anencephaly (40%), encephalocoele (8%) and iniencephaly (1%). different malformations involved and the terms used to describe them are based on clinical descriptions and the presumed embryological defect. These defects include spina bifida (accounting for approximately 51% of NTDs), anencephaly (40%), encephalocoele (8%) and iniencephaly (1%).

1.2.1 Form

The form of the vitamin is very important when it comes to protecting against the development of an NTD. The synthetic form, folic acid, is more bioavailable and stable than folate and is therefore, the only form which is effective in raising blood folate levels to the level required to protect against NTD-affected pregnancies. Folate is not as bioavailable or stable and cannot effectively raise blood folate levels to those required to protect against NTD-affected pregnancies.

It has been known since the early 1990s that folic acid intake taken prior to conception and during the very early stages of pregnancy can prevent up to 70% of NTDs. Two landmark randomised controlled trials provided the scientific evidence for the effectiveness of folic acid in preventing NTDs: the Medical Research Council (MRC) UK-based trial on NTDs recurrence [2] and the Hungarian trial on NTDs occurrence [3]. The MRC UK-based trial showed that a medicinal dose of 4 mg of folic acid (four times greater than the UL for food) protected against 70% recurrence of NTDs in women with a previously affected pregnancy. The causes of the 30% of NTDs that are not prevented by folic acid supplementation are unknown, but are likely to include genetic factors and environmental factors other than folic acid. Successful results from the Hungarian trial (which showed no NTDs births in women who received 800 µg of folic acid as part of a multivitamin supplement), and from an earlier study using 360 µg of folic acid, provided the scientific support for the recommended dose of 400 µg of folic acid for the prevention of NTDs occurrence. These findings have led to the establishment of worldwide public health campaigns aimed at increasing blood folate status of women of childbearing age. Throughout the world it has been recommended that **all women of childbearing age who are capable of becoming pregnant, take a 400 µg folic acid supplement every day** in order to reduce the risk of an NTD-affected pregnancy. Women who have had a previous NTD-affected pregnancy require higher doses of folic acid to prevent recurrence (see Section 1.2.3). However, the majority of these public health campaigns have been unsuccessful [4]. As a result, mandatory folic acid food fortification policies have been introduced by some countries including the United States (US) and Canada.

1.2.2 Timing

The short timeframe for the normal development of the neural tube means women need increased intakes of folic acid before conception. The most important aspect of the timeframe for the development and normal closure of the neural tube relates to the fact that it occurs at such an early stage in embryonic life - at a time when many women do not yet realise they are pregnant. In addition, most women do not present to their doctor at this very early stage in pregnancy and so there is no opportunity for medical intervention. As increased intakes of folic acid have been proven to reduce the risk of NTDs, the pre-conception period is the crucial time for strategies that increase women's intake of folic acid and so promote the normal closure of the neural tube. This is a significant challenge, because in spite of the major advances in contraception in developed countries, less than half of all pregnancies are planned in Ireland and elsewhere. Studies in Ireland have revealed that only between 40 and 45% of women have planned their pregnancy [5,6,7]. Therefore, to reduce the number of babies born with NTDs, all women of childbearing age who are sexually active and capable of becoming pregnant are advised to take a daily supplement of 400 µg folic acid.

1.2.3 Special cases

To prevent a recurrence of an NTD-affected pregnancy, and in some special circumstances, a medicinal level (4-5 mg) of folic acid is recommended. This is only appropriate for women under medical supervision. This level of folic acid is available under prescription only and is not available as a single-dose food supplement. Therefore, as this is a clinical issue, it will not be addressed in this report.

1.3 Food Fortification

1.3.1 Voluntary fortification

The voluntary fortification of foods for general consumption in Ireland allows folic acid to be added to food at any level (provided there is no unsafe food placed on the market (Regulation 178/2002) [8]. This means that there are different amounts of folic acid present in various categories of foods depending on whether the manufacturer decides to voluntarily add folic acid or not. For example, as outlined in Chapter 3, some breakfast cereals are fortified with folic acid and some have none added. Those that are fortified can contain various levels of folic acid. Whether women consume folic acid from fortified foods, and the amount they consume, depends entirely on their food choice (see Chapter 6).

1.3.2 Mandatory fortification

The difference with mandatory folic acid fortification of a staple food eaten by most, e.g. bread or flour, is that it would be fortified at a specific level and controlled by the Government. This would result in all foods in that category having the same specific amount of folic acid. The advantage of this is that it would ensure a fairly even distribution of intake of folic acid among all women of childbearing age. Since the late 1990s, over 80 countries, including the US and Canada, have implemented mandatory fortification of flour or cereals with folic acid in order to increase the amount of folic acid being consumed by women of childbearing age. Since the implementation of the mandatory folic acid food fortification policy, data from these countries have shown a significant reduction in the number of NTDs; ranging from 35% of births affected by NTDs in the US [9] and 50-78% in Canada [10,11,12,13]. The areas with the highest incidence rate have observed the greatest reduction of the numbers of pregnancies affected by NTDs. The number of people consuming fortified foods and the blood folate status of the population before the introduction of mandatory fortification also play a role in the high proportion of reduction of NTDs observed in these countries [14]. Data from Canada, South Africa, Costa Rica, Chile, Argentina, and Brazil have also suggested that an incidence rate of 5-6 cases per 10,000 pregnancies is the lowest rate achievable through folic acid fortification [14]. The experience of mandatory fortification of foods with folic acid in the US and other countries has shown that there is no evidence of adverse health effects in any population group following introduction of fortification.

1.4 Folic Acid Fortification and the Prevention of Birth Defects; the Irish Experience

Ireland is recognised as having one of the highest incidence rates of NTD-affected pregnancies in the world [15]. Studies have also shown that almost 50% of the indigenous Irish population has variations in the gene coding for an enzyme involved in folate metabolism, 5, 10 – methylenetetrahydrofolate reductase [16,17]. This genetic variation may account for up to one in four (26%) of NTD-affected pregnancies in Ireland [18]. As the Irish population is at particular risk of NTD-affected pregnancies due to this genetic make-up, it is vital that best practice for achieving adequate folic acid intake to ensure blood folate status is at protective levels for women of childbearing age is addressed.

In 2006, the National Committee on Folic Acid Food Fortification was established by the Minister for Health and Children to assess the introduction of a mandatory folic acid food fortification policy in Ireland in order to prevent the occurrence of NTD-affected pregnancies [19]. The National Committee on Folic Acid Food Fortification made the recommendation to introduce mandatory fortification of bread with folic acid at a level providing 120 µg per 100 g of bread. It was estimated that this would reduce the incidence of NTD-affected pregnancies by about 24% while ensuring that other population sub-groups do not consume excessive amounts of folic acid. Following on from this in 2008, an implementation group was convened [20], chaired by the Food Safety Authority of Ireland (FSAI), to put into effect the recommendations provided by the National Committee on Folic Acid Food Fortification in 2006. The implementation group undertook baseline monitoring work, recommended by the National Committee on Folic

Acid Food Fortification, which was carried out between November 2006 and June 2008. Following a new scientific assessment by the FSAI Implementation Group on Folic Acid Fortification which concluded that there would be no benefits to public health at that time to introduce mandatory folic acid fortification, it was recommended that mandatory fortification should be put 'on hold' and it was strongly recommended that all women of childbearing age would continue to be advised to take 400 µg folic acid in form of a food supplement. The reasons were threefold:

- A reduction in the incidence of NTDs in Ireland to 0.93 per 1,000 births, approaching the lowest achievable rate of 0.6-0.7 per 1,000 births, likely to be due to an increased amount of folic acid in the food supply. This was considered to be due to the increased voluntary fortification of foods on the Irish market
- The folate status of Irish women of childbearing age had improved
- Scientific studies, which were new at that time, suggested a possible relationship between high folic acid intakes and cancer risk, although this association was inconsistent and not conclusive

The implementation committee recommended that in order to ensure an even intake of folic acid across all population sub-groups, controls would have to be developed for voluntary fortification, both in terms of limits on the range of foods that could be fortified and on maximum amounts of folic acid that could be added to fortified foods. Controls on the amount of folic acid provided in supplements were also recommended. The implementation committee also recommended ongoing monitoring of the following:

1. Incidence of NTDs
2. Blood folate status of the various population sub-groups
3. Food supplements notified and tested to ascertain levels of overage
4. Fortified foods tested to ascertain levels of folic acid added
5. Health promotion campaigns to promote the use of folic acid supplements in women of childbearing age

1.5 Purpose of this Report

The purpose of this report is to provide:

- An update on the data relevant to the prevention of pregnancies affected by NTDs in Ireland and to provide recommendations on 'best practice' monitoring systems necessary to generate these data into the future
- An update on the latest scientific developments relevant to safe and effective dietary intakes of folic acid for the target group (women of childbearing age) in addition to other population groups
- Recommendations on suitable options for the prevention of NTDs in Ireland

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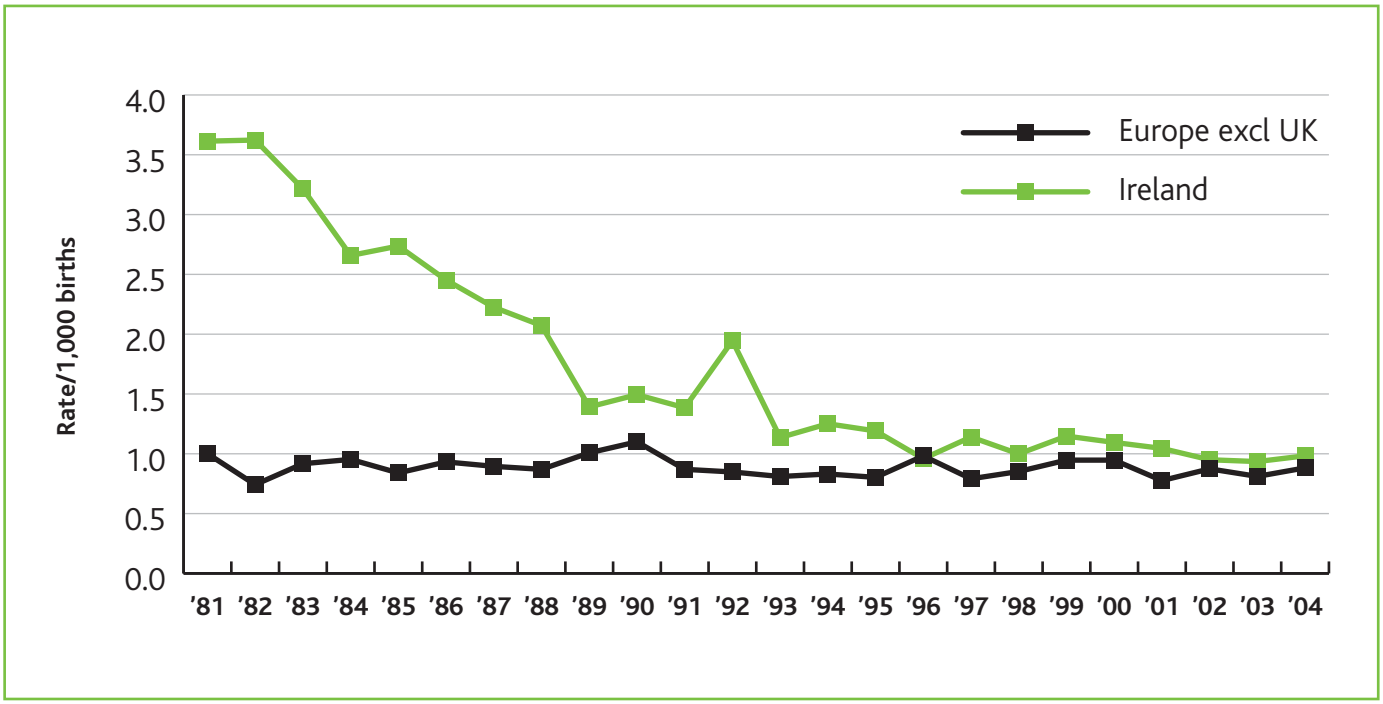
CHAPTER 2. INCIDENCE OF NTDS IN IRELAND

2.1 Background

Ireland had an extremely high incidence rate of NTDs in the 1980s, falling gradually during that decade and in the 1990s (Figure 2.1). The reasons for this decline are not known; however, it is likely that it was partly due to the introduction of foods voluntarily fortified with folic acid during the 1980s. While the rate stabilised in the mid-1990s, it continued to remain above that in the rest of Europe as a whole (excluding the United Kingdom); the NTD rate in all the regions of the UK is similar to that of Ireland. Overall, NTD rates in Ireland are significantly higher than in countries with mandatory fortification such as the United States and South America.

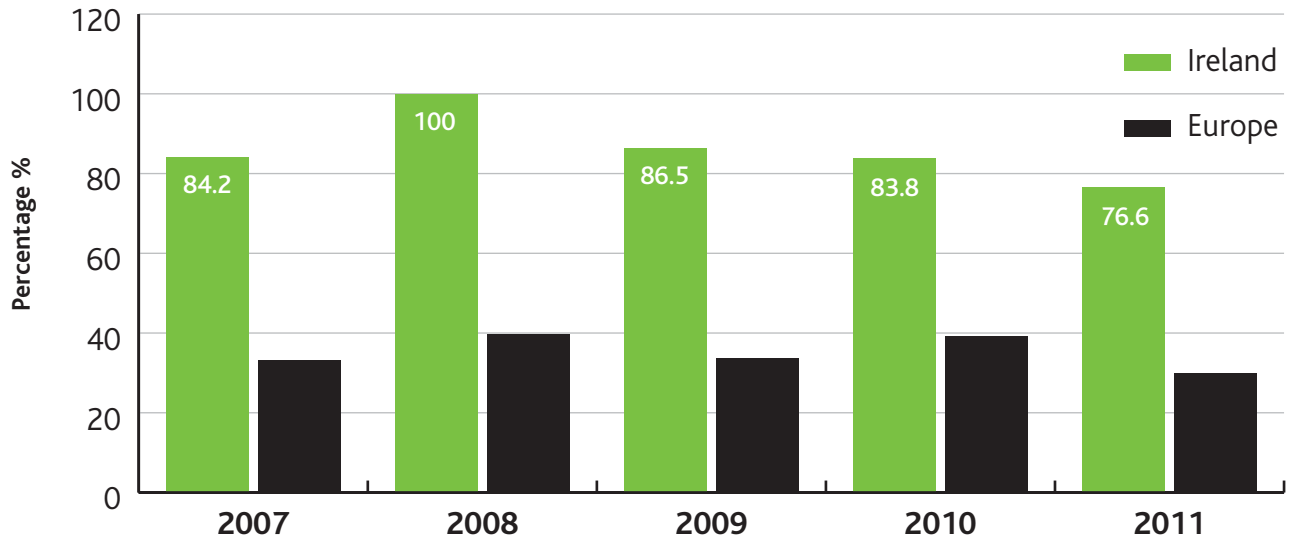
Figure 2.1 Trends in NTDs in Ireland and Europe, 1981-2004



Data Source: EUROCAT - EU Joint Research Centre

Ireland is in a unique situation within Europe with regard to NTDs. In addition to having a higher rate of NTD-affected pregnancies than in the rest of Europe, Ireland also has the highest proportion of children with spina bifida that are live-born (Figure 2.2), with an average of 86% live-born from 2007-2011. This contrasts with the UK, where the proportion of spina bifida live births is similar to that in the rest of Europe (approximately 37%). The fact that this high proportion of children affected with spina bifida are live-born in Ireland is of particular importance, not only because of the huge impact on the individual, the family, health, social and educational services, but it is also important because NTDs are largely preventable through adequate intake of folic acid peri-conceptionally by women of childbearing age.

Figure 2.2 Proportions of live births for spina bifida in Ireland and Europe



In 2011, the estimated total lifetime costs (including direct medical costs, special education and development services and indirect costs, i.e. increased morbidity and premature mortality) for each patient with spina bifida was more than half a million euro[1]. Apart from the impact on the individual with spina bifida, this highlights the huge impact of an NTDs-affected baby on the health, social and educational services within a country and on the patients' own family. It is imperative that (1) every effort is made to ensure that women of childbearing age are aware of the importance of peri-conceptual folic acid supplementation, (2) have an adequate daily intake of folic acid supplements, and (3) have adequate dietary folate intakes, particularly in the absence of mandatory folic acid fortification of food. However, virtually all studies in the past 20 years in Ireland have shown that supplement intake in women of childbearing age is very far below ideal (generally less than 50% of women take folic acid supplements).

Essential to the reduction of the number of pregnancies affected by NTDs annually is:

1. Documentation of the proportion of women of childbearing age who are complying with advice, compared with those who are not, in order to determine whether folic acid supplementation is being used by a sufficient amount of women to lower the rate of NTDs in Ireland
2. Accurate up-to-date data on the numbers of NTD-affected pregnancies must routinely be available for each year on an ongoing basis for the entire Republic of Ireland. This requires a registry that is adequately resourced and includes information on the number of new cases of NTDs each year. This is necessary in order to plan services for children who are born with an NTD
3. Data on whether current preventative strategies are reaching the target groups and working effectively

In the UK and many other European countries, information on the number of NTD cases is actively being gathered and made available.

2.1.1 Monitoring the incidence of NTDs in Ireland

Until recently, there were three active regional Health Service Executive (HSE) registries monitoring NTDs (and other major congenital anomalies) within Ireland. The three registries are located in the East, Southeast and South. Each is a member of the European Network of Congenital Anomaly Registries (EUROCAT). The Irish registries provide routine surveillance on 62% of births nationally. The largest registry is in the East (37% of births), followed by the South (14%) and the Southeast (11%).

However, there has been no routine surveillance of NTDs among births in the remaining 38% of the country (Midlands, Midwest, West, Northwest and Northeast) and the total annual number of cases of NTDs in Ireland as a whole is therefore, unknown.

The primary objective of the registries is to monitor the number and rate of congenital anomaly cases born each year in their regions, both live-born and still-born. However, as much as a quarter of cases are missed because some women, particularly those whose pregnancies are affected by NTDs which are incompatible with survival, i.e. anencephaly, go abroad for a termination and are lost to follow-up. Much of the information on these cases is currently not available to the registries, but it is an essential component that needs to be included so that accurate numbers are ascertained, thereby providing an accurate overall picture.

2.1.2 Difficulties in monitoring the numbers of NTDs

During the past decade, a tightening of the interpretation of data protection regulations by the Data Protection Commissioner's Office has meant that routine gathering of accurate information on the numbers of NTDs in the East is no longer possible and has also prevented expansion of NTDs surveillance into other regions. These data protection limitations are expected to be addressed in the long-awaited Health Information Bill. This should provide a mechanism through which the registries could obtain data on congenital anomalies that would be compliant with data protection legislation. The draft Health Information Bill was published in November 2015 as the Health Information and Patient Safety Bill (HIPS) but has yet to be enacted [(2)]. Prior to this, intermediate data-gathering measures that have been in place have proved ineffective.

The end result is that by 2015, surveillance of NTDs has been greatly limited in the East of the country, with a knock-on effect in the other two regional registries. Therefore, no reliable national data (or estimate) of NTDs incidence in Ireland, or reliable data from the largest registry in the East of the country are available.

With the publication of the draft 'Revised General Scheme' of the HIPS Bill, the current EUROCAT registries will now be in a position to plan for approval of their congenital anomaly surveillance operations under the terms of the Bill. However, it is not clear when the Bill will be enacted, and ascertainment of NTD cases until then will remain incomplete and inaccurate.

[2] Can be found online at http://health.gov.ie/wp-content/uploads/2015/11/Revised-General-Scheme-HIPS-Bill.pdf

2.1.3 National Registry for Congenital Anomaly surveillance

A national congenital anomaly registry would allow routine monitoring on an ongoing basis of NTDs and all other major congenital anomalies. A national registry would enable coordination of the data-gathering activities of the current regional registries as well as expansion of surveillance to the remainder of the country. A national registry would have to be underpinned by specific legislation that would allow unhindered data collection. In the UK, a new government body, underpinned by specific legislation, has been established by Public Health England to register all cases of congenital anomaly and rare diseases, the National Congenital Anomaly and Rare Diseases Registration Services (NCARDRS): https://www.gov.uk/guidance/the-national-congenital-anomaly-and-rare-disease-registration-service-ncardrs. NCARDRS could serve as a useful template for a centrally co-ordinated and regionally operated model for national congenital anomaly and rare diseases surveillance in Ireland.

2.2 Key Points for Update

2.2.1 National studies of NTDs total prevalence in Ireland

Although there is routine regional monitoring of NTDs in two of the three HSE registries (the South and Southeast; covering a quarter of the births nationally), there is no routine monitoring of NTDs in the remaining 75% of the country (including the East). The only national information on NTDs comes from two major studies during the past decade, the first of which was undertaken for the years 2005-2006 and the second for the years 2009-2011.

2.2.2 2005-2006 study

The 2005-2006 research was conducted by the FSAI. The aim of this study was to determine the rates of NTDs in Ireland prior to the introduction of mandatory folic acid food fortification (later postponed). In this study, obstetricians in all maternity units in the country were asked to complete an online form on every new case of NTDs they encountered between 2005 and 2006. The 2005-2006 study showed that there were 116 cases of NTDs during the two-year period. Of these, 45% were cases of anencephaly and 42% were spina bifida. The overall incident rate of NTDs during the two year period was 0.93/1,000 births. In almost 25% of cases, the outcome was a termination of pregnancy.

The NTDs rate of 0.93/1,000 was lower than the rates of NTDs from the regional HSE EUROCAT registries for the previous decade, though not as low as countries with mandatory fortification (0.5/1,000 births) [2].This was considered to be due to a variety of factors. These included much higher than expected blood levels of folate and high levels of voluntary folic acid food fortification. This information was one of a number of factors that led to the postponement of mandatory folic acid food fortification.

2.2.3 2009-2011 study

In 2010, paediatricians and obstetricians reported (anecdotally) that the numbers of new cases of NTDs being diagnosed and treated in maternity and paediatric hospitals were showing a noticeable increase compared with previous years, particularly among non-Irish born mothers. In response to this, and in order to inform further deliberations in a review of the mandatory folic acid fortification issue in Ireland, a more comprehensive national study on the birth prevalence of NTDs was undertaken by the HSE's Clinical Programme for Obstetrics and Gynaecology with the three EUROCAT registries.

In this study, obstetricians in all of the maternity units in the country were asked to complete a form for each new case of NTD they had become aware of during the three year study period. This was backed up by information from paediatricians, and the National Spina Bifida Centre in the Children's University Hospital in Temple St, Dublin. Results were collated for the three years and are summarised in the Table 2.1.

Table 2.1 Summary of results of NTD study for years 2009-2011

	Anencephaly			Spina Bifida			Encephalocoele			All NTDs	
	N	(%)	Rate*	N	(%)	Rate*	N	(%)	Rate*	N	Rate*
2009	30	(42.9)	0.39	37	(52.9)	0.49	3	(4.3)	0.04	70	0.92
2010	43	(54.4)	0.57	31	(39.2)	0.41	5	(6.3)	0.07	79	1.04
2011	33	(37.9)	0.44	47	(54.0)	0.63	7	(8.0)	0.09	87	1.17
2009-11	106	(44.9)	0.47	115	(48.7)	0.51	15	(6.4)	0.07	236	1.04

* Rate per 1,000 pregnancies

Results from this research showed that:

- The incident rate of NTDs increased from the 0.92 per 1,000 births in 2009, to 1.17 per 1,000 births in 2011
- Although there appeared to be a reversal of the lower rate in the 2005-2006 study, there were not enough data to determine if there was a now definite upward trend, i.e. further years of study from 2012 and beyond are needed to see if the rate is continuing to rise
- New cases were particularly apparent among non-Irish born mothers
- The overall rate was 1.04 per 1,000 births for the three year period. In almost 22% of cases, the outcome was a termination of pregnancy

2.3 Summary

It appears that the incidence of NTDs may be increasing again. However, at present, there is no reliable mechanism for gathering national data on NTDs incidence on an ongoing basis. National incidence data are only available in Ireland from two special studies (2005-6 and 2009-11).

It is essential that a national monitoring programme (national registry) for NTDs and other congenital anomalies, and rare diseases be introduced. Prior to this, appropriate legislation, e.g. the HIPS Bill, must be enacted to allow effective, unhindered and accurate ascertainment of the numbers of NTD-affected pregnancies and cases, including live-births, stillbirths and terminations of pregnancy.

National monitoring of the NTDs incidence will allow better planning of services for children born with an NTD and will also assist in the evaluation of NTDs prevention measures such as folic acid supplementation and fortification if introduced in Ireland.

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CHAPTER 3. FOLIC ACID FOOD ENVIRONMENT

3.1 Background

As outlined in Chapter 2, Ireland is recognised as having one of the highest rates of NTD-affected pregnancies in the world [1]. Since the early 1990s it has been well established that the consumption of 400 µg folic acid preconception and for the first three months of pregnancy can prevent the occurrence of NTD-affected pregnancies by up to 70% [2,3]. Some countries, such as the US and Canada, have introduced a mandatory folic acid food fortification policy which has resulted in a 20-70% reduction in pregnancies affected by NTDs [4,5]. In Ireland, folate can be obtained from the diet in three ways:

1. Natural sources of folate, e.g. leafy green vegetables, broccoli, asparagus, avocado, beans, seeds and nuts
2. Voluntarily fortified foods; there are various types and brands of food on the Irish market which are voluntarily fortified with folic acid
3. Food supplements; folic acid can be obtained from food supplements either as a multi-nutrient complex or as a supplement containing folic acid alone

3.1.1 Voluntary folic acid food fortification

As outlined in Chapter 1, folic acid may be added to foods in Ireland at the discretion of the manufacturer (provided there is no unsafe food placed on the market (Regulation 178/2002)) [6]. There is no regulatory requirement in Ireland to notify the authorities of fortified foods being placed on the market or levels of fortification.

The prevalence and level of fortification can affect the overall dietary intake of vitamins and minerals. The legislation on nutrition and health claims on foods (Regulation 1924/2006) [7] requires that foods must contain minimum levels to bear claims. For example, fortified foods claiming to be a 'source of' a particular vitamin or mineral must contain at least 15% of the Nutrient Reference Value (NRV) for that nutrient per 100 g (in the case of beverages it is 7.5% of the NRV per 100 ml). Similarly, fortified foods claiming to be 'high' in vitamins or minerals must contain 30% of the NRV per 100 g for that nutrient (in the case of beverages it is 15% of the NRV per 100ml). This legislation may encourage the fortification of foods in order to bear claims and could result in increased intakes of folic acid.

There has been an increase in the numbers of foods voluntarily fortified with folic acid on the Irish market. The numbers and types of foods fortified with folic acid, as well as the levels of folic acid being added to foods, have fluctuated in recent years, as outlined in the study (see Section 3.2.1b).

Currently, voluntary fortification of foods with folic acid makes a significant contribution to protection against NTDs. It is estimated that the risk of NTDs is approximately 11-14% lower as a result of consumption of voluntarily fortified foods, e.g. ready-to-eat breakfast cereals, resulting from an additional average daily intake of 50-63 µg folic acid in women of childbearing age (Appendix II). Some sectors of the food industry have reduced the amounts of folic acid in their products, e.g. fat spreads, over recent years in partial compliance with recommendations of the UK Scientific Advisory Committee on Nutrition in 2006 and 2009, and this may have reduced folic acid intakes and worsened the folate status of the Irish population as has occurred in the UK [8]. Ireland and UK are treated as a single market by some manufacturers of fortified foods, e.g. breakfast cereals, fat spreads.

In the past, the FSAI administered a 'Flash Labelling Scheme' for voluntary labelling of folic acid fortified foods. Manufacturers could use one of two logos on their products:

1. With extra folic acid – used where the amount of the foodstuff likely to be consumed in one day provides one sixth of the recommended daily amount (RDA) (RDA = 200 µg/day)
2. Contains folic acid – used on food labels where the amount of the foodstuff likely to be consumed in one day provides one half of the RDA

3.1.2 Mandatory folic acid food fortification

Many countries such as Canada, the US and Chile have introduced mandatory fortification of foods with folic acid. These countries have observed a significant reduction on the number of NTD-affected pregnancies, as outlined in Chapter 1. Although data from these countries found a significant reduction in NTD-affected pregnancies through mandatory fortification, western European countries have yet to implement mandatory fortification partly due to concerns about possible adverse health effects. However, the experience of mandatory fortification of foods with folic acid in the US and other countries has shown that there is no evidence for the occurrence of adverse health effects in any population group following introduction of fortification.

3.1.3 Food fortification legislation

Under EU legislation, in Ireland, food manufacturers are permitted to voluntarily fortify foods with vitamins and minerals at any level providing there are no unsafe foods placed on the market (Regulation 178/2002) [6]. Although Member States can request food manufacturers to notify the competent authority when placing a fortified food on the market or altering the level of fortification in an already fortified food (Regulation (EC) No 1925/2006 (Article 15)) [9], Ireland has no notification system in place. When newly fortified foods are placed on the market or if levels of fortification in an already existing fortified food are altered, there is no requirement of the food manufacturer to notify the FSAI.

3.1.2 Food supplement legislation

In Ireland, all food supplements must be notified to the competent authority, the FSAI. This comes from European rules on food supplements (Directive 2002/46/EC) which have been transposed into Irish law (S.I. No. 506 of 2007 as amended) [10,11]. A copy of the model label used for the product must be provided to the FSAI. This allows the FSAI to monitor compliance with the relevant legislation and enforce rules as necessary.

Food supplements are concentrated sources of micronutrients or other substances with a nutritional or physiological effect whose purpose is to supplement the normal diet (Directive 2002/46/EC).

3.1.3 Labelling and tolerances permitted around labelled amounts

In 2012, the European Commission Health and Consumers Directorate General published a guidance document on the setting of tolerances for nutrient values declared on a label in compliance with EU legislation [12]. Tolerances for nutrition labelling purposes refer to the acceptable differences between the nutrient values declared on a label and the measured values in the food or food supplement. The accepted tolerances are outlined in the EU guidance document for micronutrient values. For foods, the accepted tolerances permit measured levels of vitamins or minerals, in this case folic acid, to be up to a maximum of 50% greater than the labelled value and no more than 35% below the labelled value. For food supplements, the tolerances permit measured levels of vitamins or minerals, to be up to a maximum of 50% greater than the labelled value and no more than 20% below the labelled value. It is important to note that these acceptable tolerance levels are to provide guidance only and are not legislated

for. This guidance is very important for food businesses to consider when labelling nutrient values in a food or food supplement and authoritative bodies when measuring nutrient levels in a product.

The current EU regulations that govern vitamin and mineral addition to foods and use in the manufacture of food supplements allow for the setting of maximum amounts of these added micronutrients (Article 6 (1) of Regulation 1925/2006 and Art. 5 (1) of Directive 2002/46/EC) [9,10] however, no maximum amounts have been established to date.

The EU guidance document on the setting of tolerances for nutrient values declared on a label [12], states that (1) the accepted tolerances for the addition of vitamins or minerals to foods and food supplements is no more than 50% greater than the labelled value and no more than 35% or 20% below the labelled value, respectively and (2) the measured amount of the micronutrient cannot exceed the maximum amount, these maximum amounts have yet to be established by the EU.

In the absence of European maximum amounts, national rules apply; however, Ireland has no such national rules. Therefore, currently there is no maximum specified in EU legislation or Irish rules for vitamins and minerals added to food or food supplements. Vitamins and minerals can be added to foods and used in the manufacture of food supplements at the discretion of the manufacturer (provided there is no unsafe food placed on the market (Regulation 178).

Food supplements are regularly and randomly tested to determine how much of a given nutrient is in the product in comparison to the labelled value. This testing is carried out by a Public Analyst Laboratory (PAL). Currently, risk assessments are completed on food supplements notified to the FSAI with nutrient content per daily amount approaching the tolerable upper level (UL). As there are no maximum amounts currently specified in the food supplement regulations, the FSAI must consider internationally established ULs to support enforcement decisions. The ULs are considered in an Irish context taking into consideration Irish dietary intake of vitamins and minerals.

The FSAI is currently (2015) in the process of compiling a report to establish the safe upper levels for vitamins and minerals permitted to be used in food in Ireland. The safe upper levels correspond to the ULs which have been established by international scientific bodies; the European Food Safety Authority (EFSA) and the Institute of Medicine (IOM).

3.1.4 Nutrition and health claims legislation

The composition of foods and food supplements must meet strict criteria in order to bear a legally authorised claim. This includes the condition that a food must contain the beneficial nutrient for which the claim is made in the final product in a specific quantity. In order to bear a claim, the food must provide a minimum amount of the relevant micronutrient, usually equivalent to 15% or 30% of the NRV per 100 g/100 ml and 7.5% or 15% of the NRV per 100 ml for beverages. In addition, nutrition claims such as 'source' of (vitamin/mineral) and 'high' in (vitamin/mineral) can only be made on foods and food supplements containing a minimum of 15% and 30% of the of the NRV per 100 g/100 ml, respectively, for foods and 7.5% and 15% of the NRV, respectively, for beverages. Food supplements marketed in Ireland usually provide at least 100% of the NRV per daily amount. The minimum amounts outlined for foods also apply to the daily amount of a food supplement. This legislation may encourage the addition of vitamins and minerals to foods and food supplements in order to bear claims and could result in increased intakes of vitamins and minerals.

In the case of folic acid, there is an authorised health claim in the EU:

"Supplemental folic acid intake increases maternal folate status. Low maternal folate status is a risk factor in the development of neural tube defects in the developing foetus." The claim may be used only for food supplements which provide at least 400 µg of folic acid per daily portion. Information shall be provided to the consumer that the target population is women of childbearing age and the beneficial effect is obtained with a supplemental folic acid daily intake of 400 µg for at least one month before and up to three months after conception [13].

3.2 Key Points for Update

3.2.1 Voluntary folic acid food fortification

3.2.1 (a) 2007 study

In 2007, the FSAI carried out a food label survey of five major supermarkets to assess the extent of foods voluntarily fortified with folic acid on the Irish market [14]. The amounts of foods voluntarily fortified with folic acid as well as the levels of folic acid declared on the food labels (per 100 g or 100 ml) were recorded. A range of these fortified foods were used to develop daily meal plans in order to assess the feasibility of achieving the recommended 400 µg folic acid per day. The levels of folic acid were obtained from the portion size information on the product label or calculated using average food portion sizes [15] where only folic acid content per 100 g or 100 ml was provided. The majority of the fortified foods were found to be breakfast cereals followed by cereal bars, fat spreads, and juices. The daily meal plans created found that the recommended daily intake of 400 µg folic acid was easily achieved using a combination of the fortified foods. However, these meals plans are not typical of patterns of consumption of folic acid containing foods by women of childbearing age in Ireland and few women achieve 400 µg of folic acid from foods (Chapter 6).

3.2.1 (b) 2014 study

In 2014, the FSAI undertook a follow-up study to assess the changes in numbers of foods voluntarily fortified with folic acid and changes in the levels of folic acid added to fortified foods in 2007 compared with 2014 [16]. The same methods were used; the amounts of foods voluntarily fortified with folic acid as well as the level of folic acid in the product as declared on the label (per 100 g or 100 ml) were recorded in a scan of six major supermarkets. This research was also carried out online to give a national snapshot of all folic acid fortified foods on the market in Ireland. Foods were assigned to the same specific categories namely: breakfast cereals, cereal bars, milks and milky drinks, fat spreads, and miscellaneous. The numbers of foods fortified with folic acid in 2007 and in 2014 were comparable. However, it was found that there was an overall significant decrease in the amount of folic acid added to fortified foods in 2014 compared with 2007. When fortified foods which were available at both time points were assessed, it was found that there were much fewer fat spreads fortified and there was a significant decrease in the amount of folic acid added to the fat spreads.

Table 3.1 shows the differences in levels of folic acid in fortified foods which were on the market in both 2007 and 2014.

Table 3.1 Levels of folic acid in fortified foods which were on the Irish market at both time points (2007 and 2014)

	Anencephaly	2007	2014
	(*n*)	Median (Range) (µg/100g)	Median (Range) (µg/100g)
Cereals	61	200 (111-400)	212 (0-741)
Cereal Bars	13	135 (90-200)	135 (90-290)
Fat Spreads	6	1000 (500-1,000)	0 (0-500)*
Milks	2	70 (70-70)	70 (70-70)
Miscellaneous ‡	7	30 (18-200)	18 (0-200)

Wilcoxon Signed Rank Test: *p<0.05
‡ includes juices, breads and dried soups

3.2.2 Food supplements

In 2014, the FSAI carried out a study to assess folic acid-containing food supplements on the Irish market [16]. Folic acid food supplements were assessed in terms of daily amount, type of supplement and the target population. The FSAI food supplement database was used to identify all food supplements containing folic acid (*n*1,494). The target populations were grouped into six categories: infants, children, men, women of childbearing age, pregnant women and adults (target population was determined using product labels). The types of folic acid supplements were grouped into three different categories: folic acid alone, folic acid within a B-vitamin complex and folic acid within a multi-nutrient complex. As there is a national policy for women of childbearing age to take a daily 400 µg folic acid supplement, PAL Galway testing is regularly carried out on a random sample of food supplements containing folic acid. This is done in order to assess the amount of folic acid in the supplement compared with the labelled amount, allowing for the tolerance range of +50% and -20%. For this study, data on folic acid-containing food supplements tested between 2010 and 2014 were provided by the PAL for analysis.

Folic acid-containing supplements were found to represent 16% of annual food supplement notifications (*n*1,494 from a total of n9,483). Folic acid was found to be most common within a multi-nutrient complex (*n*1,347), with a small number found within a B-vitamin preparation (*n*105). The median daily amount of folic acid found for all supplements was 200 µg. Significantly higher median daily amounts of folic acid were found in the supplements containing folic acid alone in comparison with those containing folic acid within a multi-nutrient complex.

When the labelled amount of folic acid in food supplements was examined, it was found that 39% was labelled to provide the recommended daily dose of 400 µg folic acid.

The majority of supplements containing folic acid were found to be aimed at adults (*n*1,094), with just 7% targeted at women of childbearing age (*n*111). Of the supplements targeted at adults, most contained less than 400 µg folic acid (*n*647). Of all the supplements targeted at women of childbearing age (*n*111), 68 provided 400 µg folic acid, representing 5% of the total number of folic acid containing food supplements notified to the FSAI (*n*1,494). Three folic acid containing food supplements notified contained 400 µg folic acid alone.

Table 3.3 below shows the numbers of supplements aimed at the different population groups and whether they were labelled to contain < 400 µg, 400 µg or > 400 µg of folic acid.

Table 3.3 Number of supplements aimed at each population group labelled to contain < 400 µg, 400 µg or > 400 µg folic acid

Target population*	Labelled amount of folic acid provided daily in food supplements notified to the FSAI (*n*1,720)		
	< 400 µg	**400 µg**	**> 400 µg**
Infants (*n*8)	8	0	0
Children (*n*372)	304	61	7
Men (*n*73)	26	41	6
Women of childbearing age (*n*111)	38	68	5
Pregnant women (*n*62)	2	48	12
Adults (*n*1,094)	647	359	88
Total (*n*1,720)	**1,025**	**577**	**118**

* Deciphered using on pack labelling

3.3 Summary

These studies show that the numbers and types of foods fortified with folic acid, as well as the levels of folic acid being added to foods, have fluctuated in Ireland in recent years.

There were 68 supplements aimed at women of childbearing age and labelled to provide 400 µg of folic acid (in line with national policy), three of which contained folic acid alone.

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CHAPTER 4. HEALTH PROMOTION

4.1 Background

Ireland's current national policy recommends that all women of child bearing age who are capable of becoming pregnant, whether planning to do so or not, should consume 400 µg of a folic acid supplement every day. This is to reduce the occurrence of NTDs in Ireland. This policy has evolved since the early 1990s when it was previously recommended that:

- Women of childbearing age increase their intake of foods naturally rich in folate *and/or*
- Consume a higher number of foods fortified with folic acid *and/or*
- Women of childbearing age should take a folic acid supplement daily (400 µg) if there is any possibility of becoming pregnant

This recommendation was updated during the 1990s due to emerging research in the area;

1. It is now known that natural sources of folate do not provide enough folate to protect against NTDs
2. For women of childbearing age, daily intake of folic acid from voluntarily fortified foods is generally much less than 400 µg
3. The fact that NTDs develop at a very early stage in pregnancy, necessitated adoption of the national policy in its current format. The policy is now aimed at all women capable of becoming pregnant. This is because, similar to other developed countries, over half of all pregnancies in Ireland are unplanned

In spite of the existence of this policy, only a proportion of women in Ireland are regular consumers of folic acid supplements [1]. Research from the FSAI has found that there are 68 supplements on the Irish market which are aimed at women of childbearing age and labelled to provide 400 µg of folic acid (in line with national policy), three of which contained folic acid alone (see Chapter 3).

Ireland does not currently have a mandatory folic acid fortification policy. Voluntary fortification of foods with folic acid does occur; however, the numbers and types of foods fortified with folic acid, as well as the levels of folic acid being added to foods, have fluctuated in Ireland in recent years (see Chapter 3). Mandatory folic acid food fortification of a staple food (cereal-grain products such as bread) occurs in North America. This approach is an effective means of increasing women's folate status at the time of conception. The amount provided, on average, is about 160 µg daily. As the fortified food does not provide the full recommended amount of folic acid for women of childbearing age who are capable of becoming pregnant, daily folic acid supplementation is still required.

Current UK policy for the prevention of NTD-affected pregnancies is similar to that in the Republic of Ireland, i.e. to advise all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid as a supplement [2]. However, the UK Scientific Advisory Committee on Nutrition (SACN) has recommended to UK Health Ministers [2,3,4] options to improve the folate status of the UK population through the mandatory fortification of flour, accompanied by action to reduce folic acid intake from voluntarily fortified foods, e.g. fat spreads, and supplements. A decision on implementation of this proposed policy is still awaited.

Effectiveness of folic acid health promotion campaigns

Recently published data which looked at NTDs rates in 28 European countries from 1991 to 2011 found that the prevalence of NTDs in Europe is higher than in countries with mandatory folic acid food fortification in place. This was observed despite the existence of longstanding recommendations aimed at promoting peri-conceptional folic

acid supplementation, and voluntary fortification of food with folic acid. This highlights that public health campaigns are limited on their own and need to be supported through other public health initiatives [5,6].

4.2 Folic Acid Supplementation Promotion in Ireland

4.2.1 Promotion of folic acid policy before 2006

A national campaign was undertaken by the Department of Health in 2000-2001. The focus of this campaign was to increase public awareness about the importance of folic acid supplementation of 400 µg/day for women who could become pregnant. A number of leaflets were produced and women were advised on the necessity of consuming folate/folic acid. As science developed and more information became readily available about the necessity of taking folic acid supplements to prevent NTDs, the health promotion messages were updated [7].

4.2.2 Promotion of folic acid policy from 2006-2008

In 2006, the National Committee on Folic Acid Food Fortification highlighted that an integrated national health promotion programme was required in Ireland.

The recommendations of the report by the National Committee on Folic Acid Food Fortification (2006) [7] were:

1. To reduce the risk of NTDs, all women of childbearing age who are capable of becoming pregnant, are advised to take an additional 400 µg of folic acid daily in the form of a supplement
2. When a women discovers she is pregnant, she is advised to continue taking the folic acid supplement until the 12th week of pregnancy or until she attends her consultant or doctor who will advise her
3. In addition, women are advised to eat food fortified with folic acid and natural food sources of folate every day to meet their individual needs for the vitamin folate.
4. Women on long-term medication, e.g. those with diabetes or on anti-seizure medication, are advised to consult with their doctor, as they may have higher requirements for folic acid
5. To allay concerns among the general public about the fortification of foods with folic acid

In 2007, a Health Promotion Working Group was established as part of the implementation group to develop a plan and coordinate activities around the implementation of the recommendations set out in 2006 by the National Committee on Folic Acid Food Fortification.

The main areas of activity of the Health Promotion Working Group included:

1. Reviews of folic acid literature/resources, both hard copy and web-based, and an analysis of their compatibility with the current policy on folic acid
2. Evaluations of previous folic acid campaigns reviewed and difficulties encountered by organisations in promoting the 'folic acid policy message' collated. Identification of models of good practice from an education and social marketing perspective
3. Primary qualitative research, supported with low income groups, to identify barriers to folic acid supplementation. The research was funded by Safefood and supported by the HSE and University College, Cork [8]
4. Engagement with the pharmaceutical sector and key stakeholders on proposed folic acid education and communication proposals
5. Request to the Department of Health and Children to include key policy on folic acid supplementation and fortification in the forthcoming national nutrition policy, and to include the resourcing of a comprehensive folic acid public education programme in the 2009 estimates process

Based on the above information, the Health Promotion Working Group then made the following recommendations in 2008 [9]:

1. A comprehensive health promotion and social marketing campaign should be resourced and undertaken
2. The campaign will be fully integrated and will consider the use of a full spectrum of media channels available, i.e. TV, radio, outdoor, digital, online, information line, direct marketing, consumer publications, professional journals and PR. The use of texting services and popular online web pages should be considered in engaging with young people. In addition, key settings such as education, the workplace and the community should be targeted
3. The campaign will develop tailored messages and media to target the wide range of consumers, utilising the evidence arising from the primary qualitative research undertaken to identify barriers to the use of folic acid supplements by women from disadvantaged backgrounds
4. The resources identified are widely distributed and available to health care professionals who have a key role to play in promoting folic acid supplementation. Engagement with professional bodies to identify the most efficient education programmes, e.g. Continuing Medical Education, will be explored. Pre- and post-graduate programmes should include the issue of folic acid supplementation
5. Evidence-based social marketing methods should be used to target consumers, and in particular, those at risk of health inequalities, to ensure the uptake of folic acid supplementation. In particular, the use of new methods of marketing, such as digital, texting and online, should be fully exploited to ensure maximum uptake
6. The availability of folic acid free of charge on the General Medical Services scheme should be highlighted to health-care professionals and consumer groups
7. Particular consideration should be given to non-indigenous populations with distinct cultural and lifestyle practices

In 2008, when the decision was taken to put mandatory folic acid food fortification on hold, the health promotion working group led by the HSE and the FSAI expressed the view that health promotion campaigns were vital to increase awareness of the importance of:

- Taking folic acid supplements at 400 µg/day
- The timing of taking these supplements – preconception and during the first 12 weeks of pregnancy

Unfortunately however, between 2007 and 2014 there has been no national campaign promoting the use of folic acid. This may have been due to the financial crisis in Ireland which occurred around this time. Up until very recently (July 2015), the main activity undertaken to promote folic acid supplementation was the distribution by health care professionals who have a key role to play (Recommendation 4).

4.2.3 Health promotion campaigns since 2008

Since 2008, the following activities have taken place:

1. Promotion of folic acid supplementation was maintained by healthcare professionals at a local level
2. A section on folic acid was included in the *'Scientific Recommendations for Healthy Eating Guidelines in Ireland'* produced by the FSAI between 2011 and 2012. This highlighted the association with prevention of NTDs [10]
3. The importance of taking folic acid both preconception and during the first 12 weeks of pregnancy was highlighted within the *'The Scientific Recommendations for a National Infant Feeding Policy, 2nd Edition (2011)'*. This was outlined in the section which covers nutrition and lifestyle before and during pregnancy [11]

No national activity took place until July 2015 when Safefood ran a national campaign. This campaign is part of an all-island integrated multimedia campaign and this initial phase ran for a four week period with further phases planned for 2016 and beyond. The objective of the campaign was to:

- Raise awareness among women of the link between folic acid and NTDs and
- Promote increased consumption of folic acid prior to pregnancy

The first phase of this Safefood campaign was primarily carried out on digital and social channels and based on social marketing principles. It was informed by the evidence base on barriers to supplement use and formative research to test the campaign concept and creative material among the target audience. It addressed common barriers such as folic acid only being relevant if a woman is planning a pregnancy and the assumption that fortified foods and diet provide sufficient folic acid to support pregnancy.

The campaign incorporated three elements: digital and social media marketing, public relations and stakeholder engagement. An online hub was designed on the Safefood website (www.safefood.eu/Healthy-Eating/folic-acid) with key information for the target audience on:

a. Folic acid facts
b. Folic acid myths
c. A folic acid quiz
d. Real life stories from families who have been affected by NTDs
e. Useful links
f. Folic acid FAQs

The videos and information were disseminated throughout the phase through digital and social media channels. A public relations launch event was held and was supported by key advocates and foetal expert spokespersons. An extensive stakeholder engagement process took place involving:

- The HSE and the Irish College of General Practitioners – this allowed these organisations to disseminate details of the campaign to their health professional networks in engage with the target audience directly
- Charities for NTDs on the island of Ireland, SHINE and Spina Bifida and Hydrocephalus Ireland – to ensure campaign was sensitive to members and to support formative research
- Pharmacies and folic acid manufacturers - Safefood developed a suite of design materials for these stakeholders that they could tailor, co-brand and print for their own in-store promotions, signposting folic acid to their own customers. Pharmacies and retailers were also encouraged to share the Safefood campaign content through their own digital channels like Facebook or Twitter or alternatively offer discounts on folic acid products or promote them more prominently in store during the campaign

Evaluation of the first phase of this Safefood campaign was informed by digital and social media monitoring, press coverage, an online survey pre and posts the campaign, advertising and feedback for pharmacies and manufacturers. The key results are summarised in Figure 4.1.

Figure 4.1 Key findings from the evaluation of the Safefood folic acid campaign in 2015

Campaign Reach and engagement

- Website visits: **33,481 visits** to the folic acid pages
- YouTube: **3,366 views** of the animated videos on YouTube
- Facebook: posts seen over **830,000 times** with **20,000 engagement**
- Twitter: campaign posts seen **256,000 times** with **5,000 engagement**
- PR: **135** pieces of coverage on the island of Ireland (TV, radio, print, digital)

Changes to target audience knowledge, attitudes and behaviours

Positive changes were noted among women after the campaign. These reported changes include:

- The proportion of respondents (*n*=716) who believe all women who could become pregnant should take folic acid has risen from **26.4% to 74.8%**
- Individuals who say they routinely take folic acid even though they are not planning a pregnancy has increased from **7.3% to 14.2%** (*n*=155)
- **90%** of those who saw the campaign (*n*=333) said they were thinking about taking folic acid
- **38%** said they had started taking folic acid in the six weeks after the campaign (*n*=333)

Folic acid supplement sales

Folic acid supplements sales increased by **26% on average** from the same period in 2014. The following pharmacies, manufacturers and health stores reported the following sales figures:

- Lloyds pharmacies: sales increased by **30%**
- Confrey pharmacy: sales increased by **47%**
- Clonfolic (folic acid supplement manufacturers): sales increased by **24%** (for July 2015)
- Beeline Healthcare (folic acid supplement manufacturers): sales increased by **10.5%**
- Wholefoods Wholesale (Health Store): sales increased by **19%**

This is the first phase of the campaign and will be developed through subsequent phases and continued support from key stakeholders to reach the target audience. As this campaign was run predominantly online and through social media, it has the limitation that some of the target audience may have been overlooked. In particular, those who come from socio-economical disadvantaged backgrounds and who are of an older age. Therefore, they may remain uninformed about this area and may not have benefitted from such a campaign.

4.3 Evaluation of Effectiveness of Advising Women to take Folic Acid Supplements in Order to Protect Against NTD-affected Pregnancies

In order to evaluate the effectiveness of advising women to take a 400 µg folic acid supplement daily, two elements need to be evaluated:

1. Compliance with recommendations
2. Blood folate status of women of childbearing age

4.3.1 Prevalence of pre-conceptional folic acid supplementation in Ireland – observational evidence

Globally, pre-conceptional use of folic acid is estimated to be < 50% [12]. Although there has been a reported increase in the amount of women in Ireland aware of current folic acid recommendations, the proportion of women in Ireland who report consuming folic acid pre-conception remains low.

The studies presented in Table 4.2 (below) provide observational evidence of low to moderate compliance (ranging from 42.9%-64%) with current folic acid peri-conceptional supplementation guidelines within Ireland [13-17].

Although these findings provide useful information for current health promotion agendas, the lack of biomarker data makes it difficult to determine if women's reporting of folic acid use is reflected in their blood folate status.

4.3.2 Irish studies examining the effect of folic acid supplementation on blood folate status

A thorough estimation of compliance with recommendations in women of childbearing age within Ireland is necessary. This can be achieved through a comparison of blood folate status in pregnancy with self-reporting of folic acid supplementation use.

Data from the Rotunda Hospital in 2007 [17] comparing serum folate and red cell folate levels in pregnant women (2003-2004), with values found in a large case-control study based on over 56,000 women attending maternity hospitals in Dublin from 1986 to 1990 showed:

- Low peri-conceptional (13.9%) and post-conceptional (33.5%) folic acid supplementation rates among their obstetric population
- These low supplementation rates coincided with compromised blood folate levels
- 30% of women within this study displayed levels of red cell folate which would not protect their babies from an NTD (<400 µg/L)

Further research undertaken at the Northern Ireland Centre for food and health investigated compliance with current folic acid recommendations in relation to achieving a blood folate status associated with the lowest risk of NTDs [18]. This study examined 226 women who reported taking folic acid in the first trimester of pregnancy. Blood samples were taken at 14 weeks; dietary B vitamin intake and folic acid usage were also investigated.

Results showed that:

- 84% of the participants reported taking folic acid throughout the first trimester of pregnancy
- Only 19% of pregnant women reported taking folic acid pre-conception
- At 14 weeks gestation, red cell folate was correlated with the reported duration of folic acid usage
- The proportion of women failing to achieve optimal folate status (RCF concentration of 400 µg/L or greater) ranged from 27% in the preconception group to 38% and 53% in the 0-6 gestational week group and ≥6 gestational week group, respectively

These results verify that the use of folic acid as reported by pregnant women in Ireland was reflected in their folate biomarkers. These results are comparable with what was reported in the observational evidence Table 4.2.

Table 4.2 Recent observational evidence of folic acid use among women pre-conceptually and at different stages of pregnancy (% women taking folic acid)

Study	Size (*n*)	Subjects	Percentage of women who took folic acid			
			Pre-conception	**Peri-conceptional**	**Post – conception**	**No folic acid taken**
Mc Keating *et al*., 2015 [13]	42,042	Women who delivered a baby		43.9%[a]	49.4%[b]	6.6%
Cawley *et al*., 2015 [14]	587	Women from antenatal clinics	42.9%		96.1%[a]	3.9%
McNally *et al*., 2012 [15]	10,891	Women 9mnths postpartum from GUI*	64.0%		93.0%[c]	7.0%
Tarrant *et al*., 2011 [16]	450	Women from antenatal clinics		44.4%[a]	87.7%[d]	12.2%
Walsh *et al*., 2007 [17]	454	Women from 1st prenatal clinic		13.9%[a]	33.5%[b]	58.8%

* GUI; Growing Up in Ireland - the National Longitudinal Study of Children.
[a] Percentage of women taking folic acid supplements at both preconception and post-conception
[b] Percentage of women taking folic acid supplements post-conception only
[c] Percentage of women taking folic acid supplements during the 1st trimester only
[d] Total percentage of women taking folic acid supplements during pregnancy

The National Adult Nutrition Survey (NANS), which was carried out between 2008 and 2010, which did not include pregnant women, found that only 2% of women aged 18-35 years and 1% of women aged 36-50 years consumed the recommended 400 µg folic acid from food supplements[1]. Studies in maternity hospitals have shown a much greater proportion of women of childbearing age taking folic acid supplements periconceptionally, ranging from 25-36% [19,20]. This greater percentage may be due to the studies being carried out in maternity hospitals where women would be advised to take folic acid at this time. However, as stated previously, more than half of pregnancies in Ireland are unplanned.

4.4 Summary

- A national campaign to promote taking folic acid supplements for women of childbearing age who are capable of becoming pregnant whether planning to or not began in July/August 2015 and will be ongoing. It needs to be supported at a local level.
- Findings from the observational studies and strong biomarker evidence show that the proportion of women who take folic acid commencing before conception has remained very low since 2007. These findings strongly support the conclusion that past health-promotion strategies to increase folic acid use pre-conception, have not been effective.
- Compliance with current folic acid policy is low amongst women who are not planning on becoming pregnant [(1)]. Therefore, future campaigns need to increase awareness that all women should be taking folic acid supplements daily.
- Of particular concern for current health promotion guidelines is the need to raise awareness amongst women from lower socio-economic backgrounds and minority ethnic groups.
- Currently there are 68 supplements on the Irish market which are aimed at women of childbearing age and labelled to provide 400 µg of folic acid (in line with national policy), three of which contained folic acid alone (see Chapter 3).
- Any future campaigns will require clear direction from the Department of Health in terms of roles and responsibilities of all stakeholder agencies (FSAI, Safefood, HSE and non-governmental organisations).
- Women of childbearing age in Ireland remain at high risk of having a pregnancy affected by an NTD. Future campaigns promoting the use of folic acid supplements need to be continuous and well-funded in order to increase awareness and enhance compliance with this recommendation.
- Rigorous ongoing evaluation of any campaigns is necessary in order to determine effectiveness in terms of increasing compliance with the recommendations. Ongoing research needs to be conducted to measure compliance with the recommendations.

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CHAPTER 5. BLOOD FOLATE STATUS

5.1 Background

Prior to the proposed introduction of mandatory fortification of most bread with folic acid in 2005, the FSAI initiated a program to obtain background data on the blood folate status of certain sub-populations. This included women of childbearing age (16-50 years), children (2-15 years), a mixed population of males (16-65 years) and females (50-65 years), and older people (66 years and above). This would provide information on:

- Which groups would be most affected by mandatory fortification
- The impact of such a policy on the target population – women of childbearing age
- Whether or not voluntary folic acid fortification is providing women of childbearing age with enough folic acid to minimise the number of these women with folate status inadequate for optimal protection against NTDs

This work was undertaken in conjunction with Trinity College, Dublin.

5.1.1 Monitoring of blood folate status from 2005-2007

Between 2005 and 2007, both plasma folate and red cell folate were measured in >1,500 blood samples and the data used to estimate the folate status of the population (no red cell folate data were analysed in the cohort of older adults). The two measures were chosen because:

- Plasma folate provides information on the levels of folate circulating in the blood, and this level can be affected by recent food intake, especially folic acid in food or supplements
- In contrast, red cell folate levels represent the long-term intake of folate from the diet, including supplements

The results of this initial assessment of folate status confirmed that:

- Folate status of all surveyed categories had greatly improved since the previous decade [1,2]
- Overall, less than 5% of those included in the study had folate status that would have been classed as 'deficient' or 'possibly deficient'
- Some individuals (between 20 and 30%), particularly among young children and older adults, had unusually high blood levels of folate (measured both as plasma and red cell folate)

The reason behind this increase in folate status amongst the Irish population was the voluntary fortification of foods with folic acid by the food industry. This had notably increased in the few years prior to 2006. In addition, ascertainment of the numbers of pregnancies affected by NTDs found that the numbers of cases had dropped considerably compared with the previous decade.

5.2 Key Points for Update

5.2.1 Monitoring of blood folate status from 2009-2011

In 2009, a second phase of the previous study was commenced. The aims of this study were to:

1. Re-assess the blood status of the population sub-groups
2. Establish whether the blood folate status of the population had reached a new plateau or whether it was continuing to increase
3. Determine the presence of unmetabolised folic acid in blood

Methods

I. Participant recruitment

As in the 2005-2007 study, four sectors of the population were targeted in the 2009-2011 phase of the study:

- Non-pregnant women of childbearing age (16-50 years) – including generally healthy women attending the Coombe Women and Infants University Hospital, with further women recruited from general practitioners (*n*= 442 women). These were then split into four age categories (16-25, 26-40, 41-50, unknown)
- Children (2-15 years) – including children attending the outpatients department of the AMNCH Paediatric Unit (*n* = 238). Children were not divided by gender as no previous sex differences had been reported. They were split into four age categories (<3, 3-7, 8-15, unknown)
- General adult population of males (16-65 years) and females (50-65 years) – including those recruited from general practitioners surgeries in Dublin and hospital outpatient clinics and the Irish Blood Transfusion platelet donor clinic (*n* = 170). Men were split into four age categories (16-25, 26-40, 41-50, 50-65)
- Older people (66 years and above) – recruited from an on-going observational study the Trinity, University of Ulster and Department of Agriculture Study (TUDA) accessed with the permission of Dr Conal Cunningham and Dr Miriam Casey, Consultant Geriatricians in St James Hospital (*n* = 500)

All adult participants gave written consent. In the case of children, written consent was obtained from parents and verbal assent was obtained from the children.

II. Questionnaire information

Standard questionnaires were completed for all subjects which provided basic information on gender, age range, fortified food intake that might have a strong impact on folate status and supplement use. For the TUDA cohort participants, an extensive questionnaire was completed – data on age, gender and supplement use were extracted for this study.

III. Blood sampling [3-6]

Non-fasting blood samples were collected from:

(a) Colposcopy and minor surgery clinics in the Coombe Hospital

(b) The children's out-patients ward in AMNCH, where children who were scheduled for venepuncture for other purposes were asked to provide an additional 2.5 mL blood in a separate tube during the phlebotomy procedure

(c) General practitioners surgeries in the north, south and west Dublin regions

(d) The memory and bone clinics in the geriatric unit of St James Hospital, where samples and data from persons over 60 years old who were attending these out-patient clinics with mild cognitive dysfunction or bone disease were recruited for the TUDA cohort

Full details of specific analysis of unmetabolised folic acid, serum folate and red cell folate analysis can be found in Appendix I.

IV. Collation of data and reporting

All blood and questionnaire data were collated into electronic format for the final analysis. Data analysis was carried out using SPSS Version 16 for Windows. In general, data for blood metabolites were not normally distributed and are presented as medians and interquartile ranges. Full details of statistical analysis are available in the Appendix I.

The following tables outline the results of blood sampling analysis for all the different population sub-groups. Data are shown in terms of plasma folate and red cell folate. Proportions (%) of individuals whose blood folate levels range from deficient to high are provided in five separate categories. The low-adequate and adequate-high categories contain those individuals who surpass the threshold for adequate blood folate levels which will protect against an NTD-affected pregnancy. It is important to note that women of childbearing age need to have their blood folate status falling within these upper two categories in order to protect them against an NTD-affected pregnancy.

Results – plasma folate and red cell folate

I. Women of childbearing age (16-50 years)

Table 5.1 Distribution of plasma folate and red cell folate in women of childbearing age (16-50 years)

Plasma Folate (A)			Red Cell Folate (B)		
Status	**2007** All Women N=501	**2011** All Women N=442	**Status**	**2007** All Women N=500	**2011** All Women N=432
Deficient ≤2 µg/L (4.5nM)	1.2%	2.0%	**Deficient** ≤150 µg/L (340nM)	1.2%	2.3%
Possible Deficiency 2-3 µg/L	6.2%	3.6%	**Possible Deficiency** 151-200 µg/L	4.2%	3.7%
Low-Adequate 3-10 µg/L	49.7%	50.7%	**Low-Adequate** 201-400 µg/L	40.6%	41.4%
Adequate-High* 10-20 µg/L	33.5%	29.1%	**Adequate-High*** 401-1,000 µg/L	50.8%	50.5%
High* >20 µg/L (45nM)	9.4%	14.5%	**High*** >1,000 µg/L (2,265nM)	3.2%	2.1%

* Protective against NTD-affected pregnancies

Table 5.1 presents the 2007 data summarised alongside the 2011 data for the distribution of **plasma folate (A)** and **red cell folate (B)** in women of childbearing age (16-50 years).

Both plasma folate and red cell folate were strongly correlated at both time points (2007 and 2011) (data not shown).

Plasma Folate (A)

- Median values for plasma folate remained the same between 2007 and 2011 (data not shown).
- However, a significant proportion of this group (>50%) have levels below the adequate to high range.
- Although there was a difference in the frequency distributions for all women between 2007 and 2011, this is likely due to chance, as there is no apparent evidence of a trend in the data between 2007 and 2011.

Red Cell Folate (B)

- The percentage of women with a red cell folate status which would offer substantial protection against an NTD was the same in 2007 and 2011 (>400 µg/L).
- No significant trend is apparent between 2007 and 2011.
- This supports the suggestion that the slight difference between 2007 and 2011 observed for the distribution of plasma folate was due to chance.

These results support the conclusion that folate status has remained stable between the two time-points for women of childbearing age.

II. Children (aged 2-15 years)

Table 5.2 Distribution of plasma total folate and folic acid in children (2-15 years)

Plasma Folate (A)			Red Cell Folate(B)		
Status	**2007** All Children N=220	**2011** All Children N=238	**Status**	**2007** All Children N=218	**2011** All Children N=238
Deficient ≤2 µg/L (4.5nM)	0.9%	0%	**Deficient** ≤150 µg/L (340nM)	0.5%	1.3%
Possible Deficiency 2-3 µg/L	1.4%	1.3%	**Possible Deficiency** 151-200 µg/L	1.8%	0.4%
Low-Adequate 3-10 µg/L	34.1%	37.4%	**Low-Adequate** 201-400 µg/L	27.5%	31.9%
Adequate-High* 10-20 µg/L	39.1%	39.1%	**Adequate-High*** 401-1,000 µg/L	66.5%	66.0%
High* >20 µg/L (45nM)	24.5%	22.3%	**High*** >1,000 µg/L (2,265nM)	3.7%	0.4%

* Protective against NTD-affected pregnancies

Table 5.2 presents the 2007 data summarised alongside the 2011 data for the distribution of plasma folate and red cell folate in children aged 2-15 years.

Plasma Folate (A)

- Plasma folate status declined significantly with increasing age (data not shown) - this is consistent with other published data.
- There are no significant differences in the distributions for all children between 2007 and 2011.

Red Cell Folate (B)

- Red cell folate status declined significantly with increasing age (data not shown) - this is consistent with other published data.
- There were no significant differences between the frequency distribution of individuals for red cell folate at the two time points (2007 and 2011).
- This is consistent with the plasma folate data.

These results support the conclusion that folate status has remained static over the five-year period for children aged between 2-15 years.

III. General adult population

45.9% of this group was women aged between 50-65 years. The remainder was men aged between 16-65 years.

Table 5.3 (a) Distribution of plasma folate and red cell folate in the general male adult population (16-65 years)

Plasma Folate (A)			Red Cell Folate (B)		
Status	**2007** Men N=265	**2011** Men N=88	**Status**	**2007** Men N=265	**2011** Men N=87
Age (years)	**16-65**	**16-65**	**Age (years)**	**16-65**	**16-65**
Deficient ≤2 µg/L (4.5nM)	1.5%	1.1%	**Deficient** ≤150 µg/L (340nM)	0 %	2.2%
Possible Deficiency 2-3 µg/L	11.3%	3.4%	**Possible Deficiency** 151-200 µg/L	0.8%	5.4%
Low-Adequate 3-10 µg/L	64.2%	59.1%	**Low-Adequate** 201-400 µg/L	31.7%	40.2%
Adequate-High* 10-20 µg/L	20.4%	29.5%	**Adequate-High*** 401-1,000 µg/L	66.8%	45.7%
High* >20 µg/L (45nM)	2.6%	6.8%	**High*** >1,000 µg/L (2,265nM)	0.8%	1.1%

* Protective against NTD-affected pregnancies

Table 5.3 (b) Distribution of plasma total folate and folic acid in the general female adult population (50-65 years)

Plasma Folate			Red Cell folate		
Status	**2007** Women N=62	**2011** Women N=78	**Status**	**2007** Women N=62	**2011** Women N=74
Age (years)	**50-65**	**50-65**	**Age (years)**	**50-65**	**50-65**
Deficient ≤2 µg/L (4.5nM)	4.8%	0%	**Deficient** ≤150 µg/L (340nM)	1.6%	1.4%
Possible Deficiency 2-3 µg/L	3.2%	5.2%	**Possible Deficiency** 151-200 µg/L	1.6%	1.4%
Low-Adequate 3-10 µg/L	67.7%	50.6%	**Low-Adequate** 201-400 µg/L	48.4%	37.0%
Adequate-High* 10-20 µg/L	22.6%	28.6%	**Adequate-High*** 401-1,000 µg/L	50.0%	57.5%
High* >20 µg/L (45nM)	1.6%	15.6%	**High*** >1,000 µg/L (2,265nM)	0%	2.7%

* Protective against NTD-affected pregnancies

Table 5.3 (a) presents the 2007 data summarised alongside the 2011 data for the distribution of **total plasma folate** and **red cell folate** in the general male adult population. **Table 5.3 (b)** presents the 2007 data summarised alongside the 2011 data for the distribution of **total plasma folate** and **red cell folate** in the general female adult population.

No significant differences in folate status were found between groups.

Plasma Folate (A)

- Women tended to have a higher plasma folate status than men – consistent with published data.
- Median folate for the total group was higher in 2011 than in 2007 (data not shown).
- It appears that there was an increase in the proportion of women with a 'high' folate status in 2011.
- There was a reduction in the proportion of the total group with a 'low-adequate' folate status in 2011 compared with 2007.

Red Cell Folate (B)

- 86% of men and 95% of women had RCF within the normal range (between 200 µg/L and 1000 µg/L).
- Corresponding with plasma folate there was an increase in the percentage of women within the 'adequate to high category'.
- There was a reduction in the proportion of the total group in the 'low-adequate' category.

IV. Older adults (over 66 years)

Table 5.4 (a) Distribution of plasma total folate in elderly subjects in 2007 and 2011

Plasma folate				
Status	**2007** Total N=442	**2011** Total N=540	**2011** Women N=369	**2007** Men N=146
Deficient ≤2 µg/L (4.5nM)	0.7%	0.2%	0.3%	0%
Possible Deficiency 2-3 µg/L	1.8%	2.0%	1.1%	4.1%
Low-Adequate 3-10 µg/L	31.4%	36.9%	36.6%	40.4%
Adequate-High* 10-20 µg/L	31.7%	28.0%	27.6%	28.1%
High* >20 µg/L (45nM)	34.4%	33.0%	34.4%	27.4%

* Protective against NTD-affected pregnancies

Table 5.4 presents the distribution of plasma folate for elderly participants as a total group between 2007 and 2011 and by gender in 2011.

Plasma Folate (A)

- There was no significant difference between the distributions in 2007 and 2011 for the total group.
- There were no significant gender differences between folate status groups in 2011.
- This indicates that the folate status of older persons was stable over the five year period.

Red Cell Folate (B)

- No red cell folate data were collected for 2007 so a comparison between time points is not possible.
- In 2011, only 43% of participants were analysed for red cell folate concentration.
- No gender differences were found.

Results for plasma folate and red cell folate were strongly correlated for all elderly adults (r=0.82).

Table 5.4 (b) Distribution of red cell folate in elderly subjects in 2011

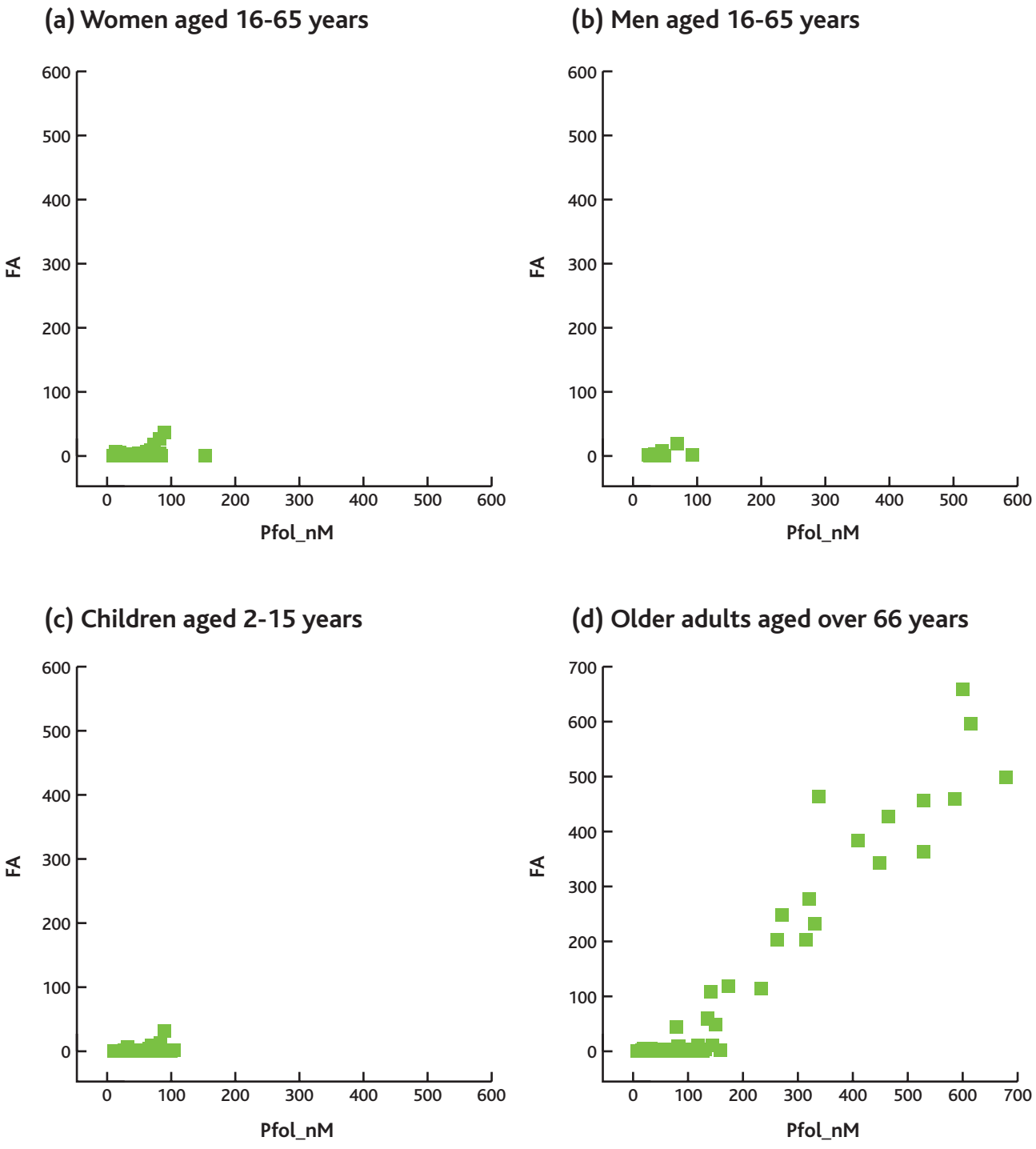
Red Cell folate			
Status	**2011** Total N=234	**2011** Women N=158	**2011** Men N=75
Deficient ≤150 µg/L (340nM)	1.3%	1.9%	0%
Possible Deficiency 151-200 µg/L	3.8%	3.2%	5.3%
Low-Adequate 201-400 µg/L	42.7%	40.5%	46.7%
Adequate-High* 401-1,000 µg/L	45.7%	48.1%	41.3%
High* >1,000 µg/L (2,265nM)	6.4%	6.3%	6.7%

* Protective against NTD-affected pregnancies

Results - Free Plasma Folic Acid (FFA; see Figure 5.1)

- Free plasma folic acid was measured in a representative sub-set of 800 individuals across all four sectors (57% of the population) in 2011, using a block randomisation strategy and oversampling in those with the highest total folate status in all sectors.
- Unmetabolised folic acid was above the detection limit in 30.2% of samples,
  - 15% of males; 20% in women of childbearing age; 24% of children; 46% of elderly.
- In subjects with measurable folic acid, the median folic acid content as a percentage of total plasma folate was 3.1%.
- Forty seven individuals had > 10% of their total plasma folate as free folic acid.
- The results indicate that 6% of the population (predominantly older adults taking vitamin supplements) have substantial amounts of free folic acid in their circulation.

Figure 5.1 Scatterplots of free folic acid *vs.* total folate for different cohorts with scales adjusted



5.3 Summary

Several important conclusions can be made to date:

- There has been no significant change in folate status among the studied sectors of the Irish population over the five year interval between 2005 and 2010
- Less than 5% of the total population surveyed had red cell folate levels (an indicator of long-term status) below 200 µg/L (453 nmol/L) which is generally accepted to include 'possibly deficient' and 'deficient' status
- The percentage of women of childbearing age with a red cell folate status which would offer substantial protection against NTDs (>400 µg/L; >907 nmol/L) was the same (about 53%) in 2007 and 2011
- In this non-fasting study group, 12% of the population had blood concentrations of unmetabolised folic acid that were above the upper limit as seen in a recent smaller study of fasting Irish elderly persons [7]
- The majority of these high folic acid samples from the current survey (69%), were from elderly persons of whom 55.1% of participants reported the use of multivitamin or folic acid supplements

5.4 References

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CHAPTER 6. DIETARY FOLATE INTAKES IN RELATION TO BIOMARKER STATUS IN IRISH ADULTS

6.1 Background

Folate is available in the diet either in natural forms occurring in a variety of foodstuffs, e.g. green leafy vegetables, asparagus, beans, legumes, liver and yeast, or in the synthetic form known as folic acid occurring in the diet only as fortified foods or dietary supplements, which is readily converted to the natural vitamin forms after ingestion. Compared with natural food folates at equivalent intakes, folic acid provides a more stable and more bioavailable form of the vitamin. Therefore, food fortification with folic acid is potentially an effective means of increasing the folate status of a population.

The Irish National Adult Nutrition Survey (NANS) 2008-2010 is one of the few national dietary surveys in Europe to have collected comprehensive brand level dietary intake data on both fortified foods and dietary supplements in addition to blood folate data. NANS, which was supported by DAFM and HRB (FHRI initiative), therefore provides an excellent resource to assess the impact of voluntary fortification and supplement use in a nationally representative population currently exposed to food fortification on a voluntary basis.

6.2 Key Points for Update

A recent analysis was conducted to evaluate dietary intakes and blood folate levels in the Irish adult population, and to examine the relative contribution of voluntary fortification and supplement use to these intakes and corresponding biomarker status.

6.2.1 Methods

The survey

NANS was a cross sectional food consumption survey carried out between May 2008 and April 2010 in the Republic of Ireland in a national sample of 1,500 adults aged 18-90 years (men: n = 760; women: n = 740). Ethical approval was obtained from the Ethics Research Committees at University College, Cork and University College, Dublin and written informed consent obtained from all participants. Outlined below is a concise overview of subject sampling procedures and the analysis relating to folate intake and biomarker status. A more detailed description of the methodologies used has been reported elsewhere [1,2].

Sampling procedure

Individuals were selected for participation from the Data Ireland (An Post) database of free-living adults in Ireland in twenty geographical clusters across the country, selected to provide proportional representation across the urban–rural continuum. There were few exclusion criteria, other than pregnancy/lactation and inability to complete the survey due to disability. The sample was representative of the Irish adult population with respect to age, gender, social class and urban/rural location when compared with the 2006 Irish census [3]. In addition to the collection of food and beverage intake data and blood samples, data on lifestyle, health indicators and attitudes to food and health were investigated. The overall response rate was 60%. After the exclusion of participants being prescribed high dose folic acid or B_{12} injections, the present analysis included only those participants who had provided full dietary intake and blood data for folate (n=1,126).

Assessment of dietary intakes and blood folate levels

Food and beverage intake data were collected using a four consecutive day semi-weighed food diary which included at least one weekend day. Participants were asked to record the type and amount of all food, beverages and supplements consumed, at brand level where possible, and where applicable to record recipes, cooking method and details of leftovers. Participants were asked to retain the packaging of foods and beverages they consumed which was later used to develop the Irish Food and Ingredients Database version 3.0 (INFID)[4]. INFID is a multifaceted database which records detailed information printed on food packaging as consumed in NANS and in previous food consumption surveys in Ireland (including nutritional content and ingredients list). Following quantification [5], food intake data were analysed using the food composition database WISP© version 3.0 (Tinuviel Software, Anglesey, UK) which uses data from McCance and Widdowson's 'The Composition of Foods' sixth and fifth editions plus all nine supplemental volumes to generate nutrient intake as described elsewhere [1]. Adjustments were made to the food composition database to take account of recipes, nutritional supplements, commonly consumed generic Irish foods and new foods on the market. All food and beverages consumed in NANS were grouped into one of 21 food groups.

Folate intakes from natural food sources and from fortified foods were estimated using a customised version of WISP© v3 (Tinuviel Software, Anglesey, UK). However, as WISP© does not distinguish between the natural folates and folic acid, this database needed to be customised before using it for the current study. Additional analysis was completed to identify fortified foods and supplements as consumed in NANS using INFID, manufacturers' websites or supermarket audits. In addition, manufacturers of fortified foods were contacted for information regarding their stated folate content and existing fortified foods in the database were updated to reflect current levels of fortification. Newly identified fortified foods were allocated a new food code. Apart from these modifications, WISP was also customised for the purpose of this study to include the contribution of supplements. The vitamin content of supplements was obtained from INFID or directly from product labels. In this manner, it was possible to distinguish and separately quantify natural food folates and the synthetic folic acid added during manufacturing. Dietary Folate Equivalents (DFE) were calculated as natural folate (µg) + (folic acid from fortified food (µg) x 1.7) [6].

Blood samples were collected and blood folate was measured at Trinity College, Dublin by microbiological assay [7] as described in Chapter 5. Samples were analysed blind and quality control was carried out by repeated analysis of stored batches of pooled samples covering a wide range of values.

To examine the relative impact of voluntary fortification and supplement use, participants were categorised into six mutually exclusive consumption groups formed according to their source of folic acid intake from the four day food diary. Non consumers consumed no folic acid during the food diary recording period (Group 1). Fortified food consumers consumed a folic acid fortified food at least once during the recording period and were further stratified into low, medium and high consumers based on tertiles of folic acid intake (Groups 2-4). Supplement users were defined as participants who consumed folic acid from a supplement at least once during the recording period, but no folic acid from fortified food (Group 5). Supplement users and fortified food consumers consumed folic acid from both sources (Group 6). Dietary folate intakes and biomarker status were subsequently compared across the consumption groups.

6.2.2 The findings

As shown in Table 6.1, median intakes of total folate, i.e. from natural folate and folic acid from supplements and fortified foods in the total population were 312 µg/day, with the majority derived from natural folate forms (223 µg/day) and with intakes of 64 µg/day from folic acid, predominately from folic acid-fortified foods (50 µg/day). Overall, 74% of total folate intake was obtained from natural sources, with 20% from fortified foods and 6% from supplements. The comparable dietary intake value when expressed as DFE (which accounts for differing bioavailability of folate and folic acid in foods) in the total population was 323 µg/day. A distribution of intakes was clearly evident with the lowest intakes of all forms for females aged 18-50 years (who had total folate intakes of 260 µg/day (DFE: 267 µg/day) while the highest were in males aged 51-64 years (total folate: 351 µg/day, DFE: 409 µg/day). The majority of the population were consumers of folic acid-fortified foods (79%), whereas the use of a supplement containing folic acid ranged from 8% in older men to 20% in women aged 51-64 years. Chief dietary sources of natural folate were potatoes, vegetables and brown bread (40% of natural folate intakes), while ready-to-eat breakfast cereals, spreads and milks accounted for 68% of total folic acid intakes. Median concentrations of RBC folate and serum folate were 872nmol/L and 25.5nmol/L respectively in the total population. However, biomarker status was generally reflective of intake data, with the lowest red blood cell folate status observed for women aged 18-50 years (799nmol/L) (Table 6.1) which is lower than the optimal red blood cell folate status for NTD protection (>907nmol/L).

Since NANS was completed in 2010 there has been a reduction in the number of fat spreads and breads fortified with folic acid. Updating intake estimates of folic acid for 2015 to take account of these changes shows median (mean) daily intakes of folic acid in women aged 18-50 years to be 43 (92) µg. The mean daily intake of folic acid from foods voluntarily fortified is estimated as 50 µg but could be up to 63 µg if it is assumed that the folic acid content exceeds the declared value on the label by an average of 25%, in keeping with usual practice of manufacturers to allow for losses during processing and storage (L Kehoe, J Walton, A Flynn, personal communication).

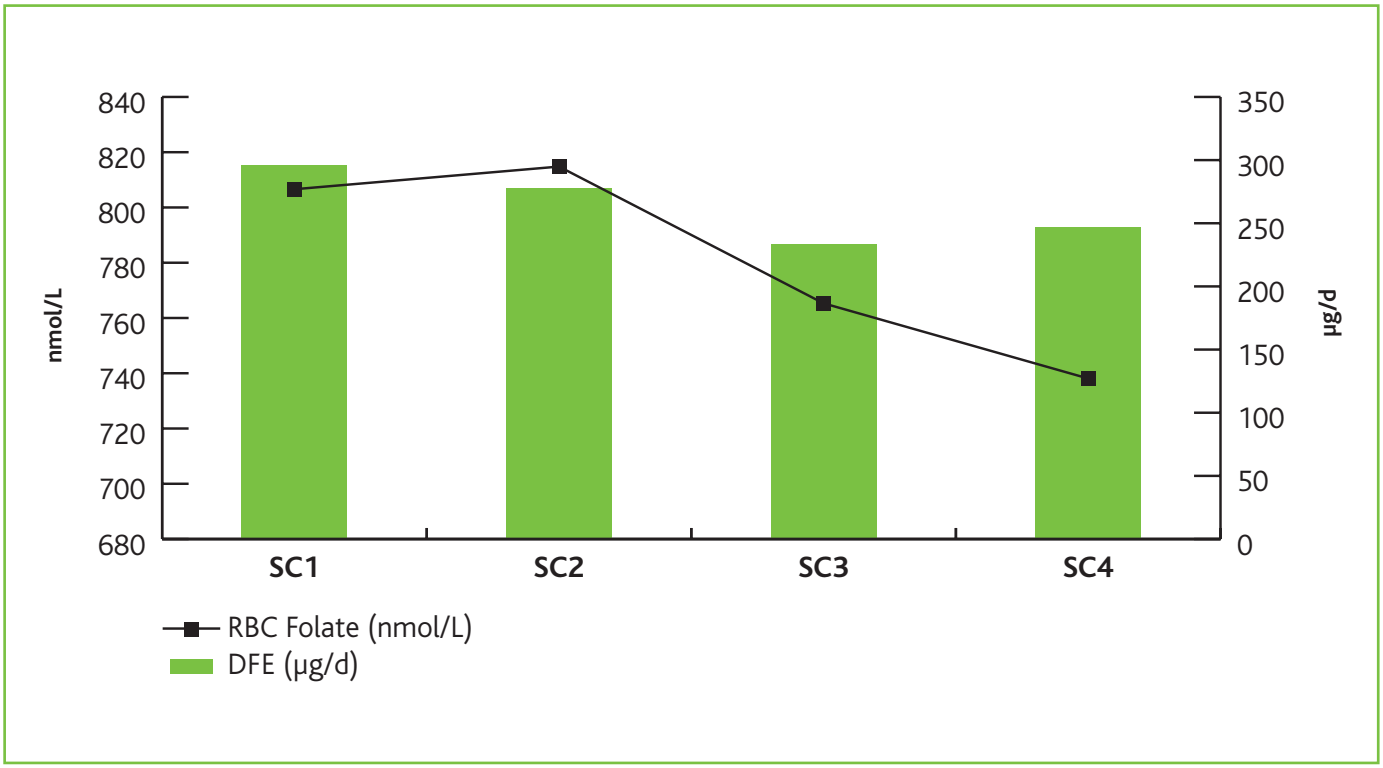
Dietary folate and blood folate according to intakes of folic acid-fortified foods and supplements

Almost one fifth (18%) of the population reported consuming no folic acid from either fortified foods or supplements (Group 1) while the majority (68%) consumed folic acid from fortified foods only (Groups 2-4) (Table 6.2). Among supplement users, 3% did not consume fortified foods (Group 5) while 11% also consumed folic acid from fortified foods (Group 6). There was a significant stepwise increase in total folate and folic acid intakes with increasing intake of fortified foods and with supplement use The dietary intake pattern was typically reflected in serum folate and RBC folate, but concentrations of both reached a plateau among high fortified food consumers with no further significant increases in supplement users. Only three participants had an intake of folic acid exceeding the tolerable upper level (1,000 µg/d); of whom one participant was a high fortified-food consumer and two were supplement users only.

Folate status in women of reproductive age

Within NANS, women of reproductive age were classed as aged 18-50 years. Women in this age category had median daily intakes of total folate of 260 µg/day, natural folate of 189 µg/day and folic acid from fortified foods and supplements of 52 µg/day. However, while 78% of women in this category consumed fortified foods, only 16% consumed folic acid supplements (Table 6.1). These low intakes were reflected in serum RBC and folate concentrations whereby the lowest RBC folate status was observed for women aged 18-50 years (799nmol/L). Analysis by social class revealed a downward trend in both dietary intakes and biomarker status from the professional/managerial/technical social class (SC1) to the semi-skilled/unskilled (including students) social class (SC4) (Figure 1).

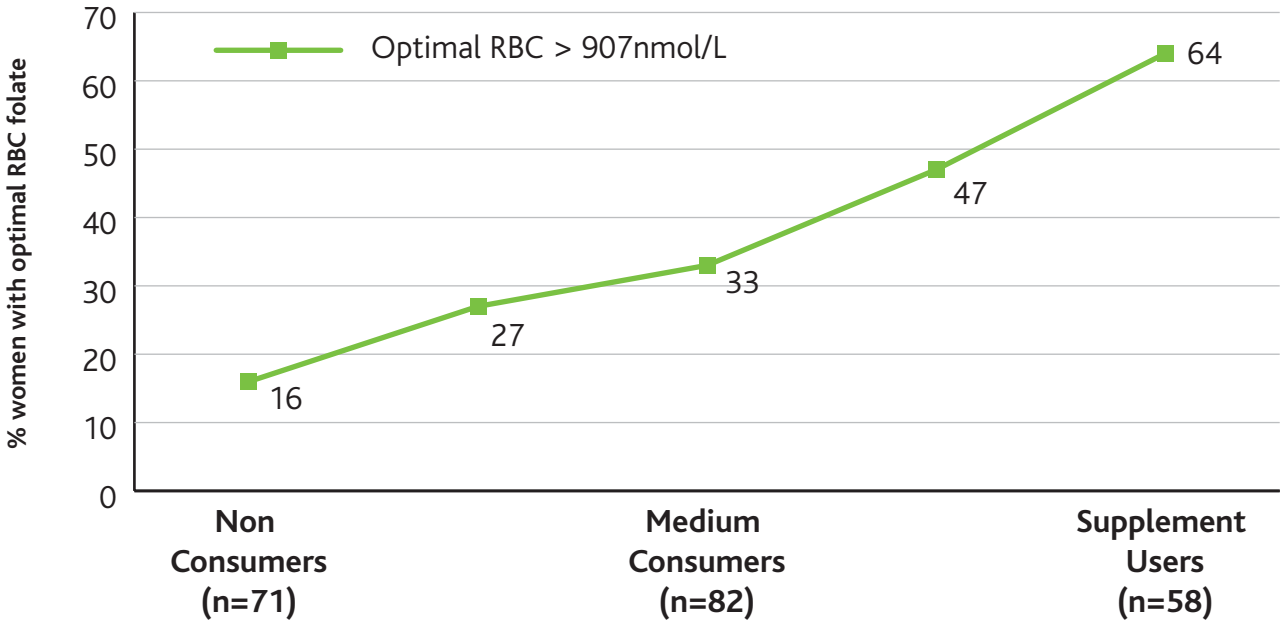
Figure 1. Comparison of intakes of folate (expressed as dietary folate equivalents) and serum red blood cell folate status by social class in women of childbearing age (age 18-50 years)



SC1: Professional/managerial/technical; SC2: Non-manual/skilled; SC3: Manual skilled; SC4: Semi-skilled/unskilled (including students)

Overall, only 36% of women of reproductive age (134 out of 371) achieved an optimal folate status for NTD protection (>907nmol/L), of whom a significantly higher proportion were in the high fortified food consumer group (47%) and supplement user group (64%) compared with the other three groups (16-33%) (Figure 2).

Figure 2. Proportion of Irish women aged 18-50 years with optimal red blood cell (RBC) folate status for protection against NTDs according to folic acid intake from fortified foods and supplements



Data modified from Hopkins *et al* 2015

NANS did not include pregnant women. McGowan and McAuliffe [8] have however described dietary patterns and associated folate intakes during pregnancy in a cohort of 398 healthy pregnant women attending the National Maternity Hospital, Dublin during 2007 – 2011. Mean daily intakes of total folate, i.e. combining natural forms and folic acid in fortified foods, were 272 µg/day in pregnancy with only marginally higher intakes in those women who could be classified as being 'health conscious' (*n*161; 287 µg/d) compared to those women classed as 'unhealthy' (*n*124; 252 µg/d). Furthermore, intakes of folate did not vary greatly across trimesters. Overall, only 2.1% were compliant with RDA for folate from dietary sources alone.

There is generally a lack of comprehensive intake-status data in relation to folate during pregnancy, although well-established evidence shows that blood folate concentrations decline markedly between the first and third trimesters of pregnancy – irrespective of dietary folate intakes – unless folic acid supplementation is continued beyond the period covered by current folic acid recommendations, i.e. until the end of the 12th gestational week. In any case, for the purposes of the current report focussing on NTDs, this is not considered to be an issue given that the relevant public health concern for preventing NTDs relates to folate status before conception and during the very early stages of pregnancy before most women will have come into contact with maternity services. For the purposes of this report, the folate status of non-pregnant women of reproductive age as reported above is key.

6.2.3 Conclusion

In conclusion, the above results from NANS showed that consumption of voluntarily fortified foods and supplements were each associated with significantly higher blood levels of folate in a nationally representative sample of Irish adults. Nevertheless, the population impact of these measures was unevenly distributed and their impact was found to be generally inadequate in providing the majority of women of reproductive age with an optimal RBC folate level to protect against NTDs. These folate intake-status data will serve as an important population-based baseline against which any future changes in fortification practices and supplement use in Ireland can be monitored.

6.3 Summary

Ireland has traditionally operated a liberal policy of voluntary fortification but little is known about how this practice, along with supplement use, affects population intakes and status of folate. Using data from the Irish National Adult Nutrition Survey (NANS) (2008-2010), the relative impact of voluntary fortification and supplement use on dietary intakes and biomarker status of folate was examined. Folic acid intakes from fortified foods and supplements were estimated using brand information. Dietary and biomarker values for folate were then compared across six mutually exclusive consumption groups formed on the basis of folic acid intake.

The results showed that consumption of folic acid through fortified foods at low, medium and high levels of exposure [median intakes of 22, 69 and 180 µg/d respectively], supplements [203 µg/d] or both [287 µg/d] was associated with significantly higher folate intakes and status compared to non-consumption of folic acid (18% of the Irish population). Median values for red blood cell (RBC) folate increased significantly from 699 nmol/L in non-consumers to 1,040 nmol/L in consumers with a high intake of fortified foods, with further non-significant increases in supplement users. Overall, only 36% of women of reproductive age achieved an optimal folate status for NTD protection (>907nmol/L). Of note, two thirds of young women had suboptimal RBC folate for protection against NTDs; among non-consumers of folic acid only 16% attained optimal RBC folate. Consumption of voluntarily fortified foods and/or supplement use was associated with significantly higher dietary intakes and biomarker status of folate in Irish adults. Of concern, the majority of young women remain sub-optimally protected against NTDs.

This research described above has been reported in full elsewhere [2] was funded by the DAFM, the HRB under their joint Food for Health Research Initiative (2007-12) (grant number FHRIUCC2).

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Table 6.1 Median intakes of folate and Vitamin B-12 according to dietary source in the total population and percentage consumers of fortified foods and supplements and biomarker status by sex and age group

	All Ages	Males			Females		
	18-91y	**18-50y**	**51-64y**	**≥ 65y**	**18-50y**	**51-64y**	**≥ 65y**
	(n=1115-1126)	*(n=388-392)*	*(n=112)*	*(n=63)*	*(n=368-371)*	*(n=109-110)*	*(n=76-78)*
Folate intakes (µg/d)							
DFE	323 (234, 474)[1]	389 (294, 554)	409 (292, 580)	356 (233, 581)	267 (197, 363)	303 (230, 464)	269 (210, 451)
Total[2]	312 (228, 448)	372 (280, 506)	351 (265, 497)	314 (214, 470)	260 (192, 349)	297 (225, 423)	277 (198, 391)
Natural	223 (173, 286)	274 (204, 344)	271 (213, 325)	223 (184, 274)	189 (151, 231)	207 (171, 268)	210 (158, 248)
Total folic acid[3]	64 (14, 167)	74 (20, 175)	68 (9, 205)	71 (12, 183)	52 (13, 135)	66 (24, 196)	63 (12, 177)
Fortified foods[4]	50 (9, 118)	58 (12, 125)	60 (8, 169)	64 (11, 180)	35 (6, 87)	40 (9, 109)	47 (0, 138)
Consumers of folic acid (%)							
Fortified foods	79	80	80	81	78	80	74
Supplements	14	14	9	8	16	20	14
Folate status							
Red blood cell folate (nmol/L)	872 (672, 1196)	905 (700, 1154)	924 (713, 1228)	964 (740, 1414)	799 (626, 1110)	936 (969, 1334)	926 (747, 1296)
Serum folate (nmol/L)	25.5 (16.7, 38.8)	24.4 (17.0, 35.5)	24.8 (16.9, 38.5)	30.2 (19.2, 38.6)	25.2 (16.1, 37.2)	32.0 (18.9, 47.8)	27.0 (14.1, 54.9)

[1] Interquartile range in parentheses (all such values), smaller 'n' values relate to sample sizes available for biomarker analysis.

[2] Refers to total folate intakes from natural food sources, fortified foods and supplements.

[3] Refers to total folic acid intakes from both fortified foods and supplements.

DFE, dietary folate equivalents calculated as follows: natural folate (µg) + (folic acid from fortified foods (µg) x 1.7) (IOM,1998)

Table 6.2 Dietary intakes and biomarker status of folate and Vitamin B-12 grouped by participants' intake of folic acid fortified foods and supplements[1]

	Non-consumers (1)	Low Consumers (2)	Medium Consumers (3)	High Consumers (4)	Supplement Users (5)	Supplement Users & FF consumers (6)	P-value[2]
	18-91y	**18-50y**	**51-64y**	**≥ 65y**	**18-50y**	**51-64y**	**≥ 65y**
Folic acid intake	**0 µg/d**	**1-45 µg/d**	**46-108 µg/d**	**109-1,044 µg/d**	**10-2,000 µg/d**	**33-958 µg/d**	
n	*200*	*254*	*252*	*261*	*36*	*123*	
General Characteristics							
Male: female (%)	48:52:00	43:57:00	52:48:00	62:38:00	42:58:00	43:57:00	<0.001
Age (y)	45 (31, 56)[3]	43 (28, 55)	39 (27, 52)	45 (28.5, 58)	38 (27, 52)	38 (26, 57)	0.056
BMI (kg/m^2)	27.1 (23.7, 30.1)	26.6 (23.8, 29.9)	26.6 (23.8, 30.1)	26.3 (23.7, 29.1)	25.6 (22.9, 28.3)	25.3 (22.8, 28.2)	0.037
Energy (MJ/d)	7.9 (6.5, 9.7)^{a}	7.9 (6.2, 9.7)^{a}	8.2 (6.4, 10.6)^{ab}	9.0 (7.2, 11.3)^{b}	8.7 (6.8, 10.5)^{ab}	8.6 (7.2, 11.2)^{ab}	<0.001
Smoker (%)	30	23	20	12	19	13	<0.001
Dietary Intakes Folate (µg)							
Total	206 (160, 293)^{a}	233 (186, 291)^{b}	288 (242, 349)^{c}	445 (363, 535)^{d}	558 (267, 636)^{de}	582 (431, 746)^{e}	<0.001
Natural	206 (160, 293)	211 (161, 272)	214 (170, 278)	248 (195, 309)	237 (179, 306)	246 (185, 309)	0.366
Folic acid	0	22 (13, 32)^{a}	69 (56, 84)^{b}	180 (137, 248)^{c}	203 (150, 400)^{cd}	287 (220, 438)^{d}	<0.001
DFE	206 (160, 293)^{a}	249 (199, 310)^{b}	338 (291, 406)^{c}	572 (472, 709)^{d}	237 (179, 306)^{ab}	373 (252, 546)^{e}	<0.001
Biomarkers							
Serum folate (nmol/L)	17.0 (12.3, 24.8)^{a}	21.7 (14.2, 30.3)^{b}	23.2 (16.8, 33.1)^{b}	36.9 (26.3, 53.6)^{c}	32.9 (22.6, 48.1)^{c}	44.9 (29.2, 68.6)^{c}	<0.001
RBC folate (nmol/L)	699 (538, 934)^{a}	784 (623, 1018)^{b}	825 (695, 1083)^{b}	1040 (83, 1390)^{c}	1013 (812, 1487)^{c}	1156 (831, 1501)^{c}	<0.001

[1] Non-consumers (1) consumed no folic acid from fortified foods or supplements during the food diary. Those who consumed folic acid from fortified foods at least once during the food diary were categorised as low (2) medium (3) or high (4) consumers based on tertiles of folic acid intake from fortified foods. Supplement users (5) consumed folic acid from supplements at least once during the food diary and no fortified foods. Supplement users and fortified consumers (6) consumed folic acid from both supplements and fortified foods.

[2] General characteristics were compared across the groups using Chi square analysis and one-way ANOVA (scheffe post hoc tests). B vitamin dietary intakes and biomarkers were compared using one-way ANCOVA controlling for gender, BMI, energy intakes and smoking status. [abc] Values across a row with unlike superscript letters were significantly different (bonferroni post hoc tests). P <0.05. [3]Median and interquartile range in parentheses (all such values).

CHAPTER 7. SCIENTIFIC DEVELOPMENTS

7.1 Background

Established and emerging evidence indicates that the achievement of optimal folate status should be an important public health goal for populations worldwide. In practice however this is challenging. Folic acid, the form of folate used for fortification, is cheap to produce, is very stable once added to foods and is highly bioavailable when ingested. Thus, depending on local fortification policy, the folate status of populations can vary greatly from one country to the next and this is reflected in differences in health outcomes, most notably in the case of NTDs which are causatively linked with low maternal folate. Apart from preventing NTDs, there are other potential benefits of optimal folate status throughout the lifecycle.

7.2 Key Points for Update

7.2.1 Roles of folate in human health

Biologically, folate is required for one-carbon metabolism. This involves the transfer of one-carbon units in essential pathways incorporating DNA and RNA synthesis, amino acid metabolism and numerous methylation reactions [1]. Folate plays a particularly important role in pregnancy and foetal development as it is essential for cell division and tissue growth. Conclusive evidence has existed for nearly 25 years that folic acid supplementation in early pregnancy protects against NTDs.

Although the preventative role of folate in NTDs is the major focus of public health efforts worldwide, the evidence-base at this time also supports other potential benefits of optimal folate status throughout the lifecycle from pregnancy, through childhood, to preventing chronic disease in ageing, including cardiovascular diseases, certain cancers, osteoporosis, and cognitive dysfunction (Figure 1). Folate in early life is considered fundamental however; indeed recent scientific interest is focused on the effects of maternal folate status during pregnancy on health outcomes in later life.

Figure 1. Folate throughout the lifecycle

Known and emerging roles of optimal folate in human health

Early life	**Strength of evidence**
• Maternal health in pregnancy	conclusive
• Fetal development	conclusive
• Offspring health and folate in pregnancy	new
Later life	
• Prevention of heart disease/stroke	conclusive
• Cancer prevention	promising
• Bone health	possible role
• Cognitive function in ageing	possible role

In recent years, it is becoming more evident that optimal folate functioning and the health effects of folate involve important metabolic interrelationships with other B vitamins, namely vitamins B_{12}, B_6 and B_2, i.e. riboflavin, and indeed highly relevant gene-nutrient interactions [1].

7.2.2 Folate insufficiency

Clinical folate deficiency leads to megaloblastic anaemia, a condition which is characterised by immature, enlarged blood cells and which is reversible with folic acid treatment. Folate deficiency of pregnancy is a well-recognised heath concern and dates back to the first discovery of this vitamin in the 1930s. Pregnancy is a time when folate requirement is greatly increased in order to sustain the demand for rapid cell replication and growth of foetal, placental and maternal tissue [1]. Certain gastrointestinal conditions, most notably coeliac disease, can cause folate deficiency through chronic malabsorption. In addition, some commonly used drugs can lead to folate depletion through various mechanisms, e.g. phenytoin and primidone (anticonvulsants), pyrimethamine (an antimalarial), and sulfasalazine (used in the treatment of inflammatory bowel disease).

It is important to appreciate that the absence of folate deficiency does not necessarily mean that folate status is optimal in terms of maintaining health and preventing folate-related disease including NTDs. Thus, in Ireland and many other developed countries, folate deficiency may be relatively rare, but sub-optimal folate status for prevention of NTDs is commonly encountered in women of childbearing age (Chapter 6).

Establishing the extent of low or sub-optimal folate status within or between different populations requires dietary intake data to be linked with folate biomarkers. Dietary data only, without corresponding biomarkers, will provide an incomplete picture of folate status in a given population because no account can be taken of the amount of folate absorbed and available for metabolic processes, i.e. bioavailability, in the assessment of folate status.

7.2.3 Folate bioavailability from natural food sources and fortified foods

Bioavailability can be defined as the proportion of an ingested nutrient that is absorbed and becomes available for metabolic processes or storage. It is very well established that the bioavailability of folate from naturally occurring food sources is poor, for reasons related to the chemical structure of folate in its natural form which make it inherently unstable, and because other dietary constituents may contribute to the instability of labile folates during digestion [1]. As a result, naturally occurring folates show incomplete bioavailability compared with folic acid at equivalent levels of intake [2]. Apart from their limited bioavailability once in the body, natural folates in foods can undergo significant losses before they are eaten. Food folates (particularly green vegetables) can be unstable under certain conditions of cooking, and this can substantially reduce the folate content of these foods before they are even ingested [3].

In contrast, folic acid (as used in fortified food and supplements) provides a highly stable and bioavailable vitamin form. The bioavailability of folic acid is assumed to be 100% when ingested as a supplement, while folic acid in fortified food is estimated to have about 85% the bioavailability of supplemental folic acid. Folate intakes and recommendations in the United States and certain other countries are expressed as DFEs, a calculation which was devised to take into account the greater bioavailability of folic acid from fortified foods compared with naturally occurring food folates. DFEs are defined as the micrograms of natural food folate plus 1.7 times the micrograms of folic acid from fortified food [2].

7.2.4 Achieving optimal biomarker status of folate

There are potentially three options to achieve optimal folate status in individuals and in populations: increased intake of naturally-occurring food folates, folic acid supplementation, folic acid fortification.

Owing to the instability and poor bioavailability of the natural vitamin discussed above, optimising folate biomarkers by means of increasing natural food sources has proven to be largely ineffective even when significantly higher dietary folate intakes are achieved experimentally [4].

Folic acid supplementation is a highly effective means to optimise folate status in individual women who take supplements as recommended [4]. However, it has limited effectiveness as a public health strategy for populations. International evidence shows that in practice only about 20-30% of women globally take folic acid supplements as recommended, i.e. 400 µg/day folic acid from preconception until the end of the first trimester of pregnancy [5], and there is particular concern that women from lower socioeconomic backgrounds are the least likely to follow the current recommendations. Available evidence shows that patterns of folic acid usage in Irish women appear similar to women in most other developed counties worldwide (Chapter 4).

Folic acid fortification, like folic acid supplementation, is highly effective as a means of optimising folate status in individual women [4]. Furthermore, this option has the advantage over folic acid supplementation that it can also be highly effective for populations. In countries with voluntary fortification in place, folic acid fortified foods have been shown to have a significant impact on folate intakes and biomarker status of consumers of these foods.

7.2.5 Preventing NTDs – evidence of the effectiveness of different policies

For almost 25 years, conclusive evidence has existed that folic acid in early pregnancy can prevent the occurrence of NTDs. This evidence has led to very clear folic acid recommendations for women of reproductive age which are in place worldwide. For the prevention of NTDs, women worldwide are recommended to take 400 µg/day folic acid from preconception until the end of the first trimester of pregnancy. In the absence of mandatory fortification, folic acid supplementation has been the focus of health promotion for the prevention of NTDs in Ireland and elsewhere in Europe for more than 20 years.

Over the years, health promotion campaigns have been introduced to encourage women to follow the recommendations correctly. Despite these efforts however, it is evident that promoting folic acid supplementation has had limited impact as a strategy to achieve further reductions in the rate of NTDs. This is primarily because the neural tube closes in the first few weeks of pregnancy (between the 3rd and 4th week post-conception) and therefore, the timing of folic acid usage by women is critical to preventing NTD-affected pregnancies. In many cases the malformations of NTDs may have occurred before a woman even knows that she is pregnant. Although this is a particular concern for women with unplanned pregnancies (estimated to account for up to 50% of all pregnancies in Ireland and elsewhere), the problem of poor compliance with current recommendations is not confined to this group. Thus for the majority of women the period from preconception until the 28th day of the pregnancy (during which folic acid is protective against NTDs) may have passed before folic acid supplementation is started.

While there was a large decrease in incidence rate of NTDs in Ireland from the early 1980s (about 3.5 per 1,000 births) to the mid-1990s[c], the rate has remained relatively stable since then at about 1 per 1,000 births. The current rate of 1 per 1,000 births means that there are about 80 cases per annum (see Fig 2.1) similar to the UK, despite the introduction in both countries of a policy of advice on peri-conceptional supplementation with folic acid in 1993. This rate remains significantly higher than in countries with mandatory fortification such as the United States (about 0.6 per 1,000 births). Compliance by women of childbearing age with this recommendation in Ireland (and elsewhere) is generally poor and therefore, it has had limited effectiveness. This has been similar to experiences in other European countries that have a similar policy.

Evidence from a large multicentre study examining 13 million birth records from nine European countries, showed that there was no detectable impact on incidence of NTDs in any country over the ten year period from 1988 to 1998, covering the time before and after current folic acid recommendations were introduced and actively promoted [6]. In general, agreement with these findings, evidence just published estimated that there had been 7,484 cases of spina bifida and anencephaly (of 8,400 documented NTDs cases) in Europe in the period 2000-2010 (0.8 per 1,000 births), and this equated with a 1.6 times higher prevalence of NTDs in Europe compared to regions of the world with mandatory fortification policies in place [7]. The latter paper estimated the lifetime direct costs for spina bifida-affected live births for Germany in 2009 alone at €65.5 million. Both of these papers show the limited effectiveness of current public health strategies - based on folic acid supplementation - for preventing NTDs in Europe.

Voluntary fortification

The question often arises as to the impact of voluntary fortification on NTDs. Foods voluntarily fortified with folic acid currently make a significant contribution to folic acid intakes in women of childbearing age and reduction in risk of NTD-affected pregnancies in Ireland (estimated as 11-14%, see Chapter 8). There is potential to improve the effectiveness of voluntary fortification. In New Zealand, encouragement of voluntary fortification of selected foods with folic acid by manufacturers led to a significant increase in folic acid intake by women of childbearing age, but much less than could be achieved if mandatory fortification had been implemented [8].

The measurement of red blood cell (RBC) folate in women of reproductive age is a useful way to assess NTD risk within populations on the basis of the known continuous dose-response inverse relationship between maternal RBC folate concentrations and NTDs [9]. Of note, the New Zealand Adult Nutrition Survey (NZANS)[10] identified that while mean folate concentrations appeared satisfactory in women aged 16 to 44 years under conditions of voluntary fortification, only 27% had RBC folate concentrations considered optimal in terms of reaching the level associated with lowest risk of an NTD-affected pregnancy, i.e. 907 nmol/L or higher. Likewise, the recent National Adult Nutrition Survey (NANS) in Ireland[11] (Chapter 6) showed that mean folate intakes and status were generally high in the Irish population, but non-consumers of folic acid from fortified food or supplements (18% of the population) were at high risk of suboptimal folate status. Overall, only 36% of women of reproductive age achieved an optimal folate status for NTD protection (>907nmol/L). Of concern, among young women who were non-consumers of folic acid, only 16% had attained a folate biomarker level for optimal protection against NTDs (11) (Chapter 6). What these studies show is that it is not enough to rely on mean dietary intake (and/or biomarker) data when assessing folate status within populations. At-risk groups (especially women of childbearing age) need to be more thoroughly investigated with a focus on those with lower folate intakes and status, i.e. non-consumers of folic acid from fortified foods or supplements.

The recent population-based evidence from Ireland and New Zealand shows that, while voluntary fortification can make a significant contribution to reduction in risk of NTD-affected pregnancies, the lower level and uneven distribution of intake of folic acid among women of childbearing age makes it less effective than mandatory fortification.

Mandatory fortification

Over 80 countries to date have passed regulations for the mandatory fortification of staple foods with folic acid (Figure 2). Compared with voluntary fortification, the policy of mandatory fortification of foods with folic acid, by ensuring a higher level of intake and more even distribution of folate status in women of childbearing age, has been shown to be more effective for lowering the risk of NTDs. Those countries worldwide where mandatory folic

[c] Although voluntary fortification of food with folic acid started in Ireland around the mid-1980s it is not entirely clear what drove the reduction in the incidence rates of NTDs up to the mid-1990s. Other factors cannot be ruled out.

acid-fortification has been introduced have experienced marked reductions in NTDs. Reported rates of NTDs have declined by between 27% and 50% in the USA, Canada and Chile in response to mandatory folic acid fortification of food [12,13,14]. Such evidence makes a strong case for adopting mandatory fortification in European countries, particularly given recent reports that the incidence of NTDs in Ireland and UK may be increasing in recent years [15].

Figure 2. Wheat flour fortification legislation

October 2012: 75 countries require iron and/or folic acid in wheat flour

All countries in green fortify flour with iron and folic acid
except **Australia** *which does not include iron* and **Venezuela**, the **United Kingdom**, the **Philippines**, and **Trinidad and Tobago** *which fortify with iron only and do not include folic acid*

7.3 Safety Issues

Folic acid, the synthetic form of folate, is used widely for food fortification and supplementation purposes. Traditionally the main safety concern related to the potential risk that long-term exposure to high dose folic acid might mask the anaemia of vitamin B_{12} deficiency in older people, while allowing the associated irreversible neurological symptoms to progress. This is no longer considered to be a public health concern given the experience of mandatory fortification of foods with folic acid in the US where there is no evidence of a higher prevalence of vitamin B_{12} deficiency in the absence of anaemia or macrocytosis among nationally representative U.S. adults aged >50 years. This indicates that exposure to higher levels of folic acid in fortified foods and supplements has not resulted in masking of undiagnosed vitamin B_{12} deficiency in the population or delayed its diagnosis [16]. A risk assessment carried out during the preparation of this report has shown that the effect of mandatory fortification of

bread or flour on the risk of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults in Ireland would be negligible (Chapter 8; Appendix II).

It has been suggested that in older adults the combination of high folic acid intakes and low vitamin B_{12} status might impair cognitive performance. A recent review by the US National Toxicology Program [17] concluded that while there is some evidence from observational studies, the available data are limited and there are no available randomised controlled trials that were designed to address this question. The available evidence shows that cognitively intact individuals consuming high levels of folic acid are not at increased risk of cognitive impairment [17].

Once ingested, folic acid is reduced by dihydrofolate reductase (DHFR) and after subsequent methylation, it is released in the systemic circulation as 5-methyltetrahydrofolate. However, the capacity of DHFR in humans to efficiently metabolise folic acid is limited and thus exposure to high oral doses of folic acid can result in the appearance of unmetabolised folic acid in the circulation [1]. The latter is not a normal constituent of plasma or other tissues. On this basis, concerns have been raised regarding potential (though not established) adverse health effects of unmetabolised folic acid in the circulation arising through high folic acid intakes from supplements and fortified foods. A number of observational studies conducted in countries with either mandatory or voluntary folic acid food fortification have reported detectable amounts of unmetabolised folic acid in the circulation in considerable proportions of adults and children (albeit at low concentrations). However, there are no definitive studies that have found adverse health effects from exposure to unmetabolised folic acid [18]. An expert international panel recently provided an in-depth review of folate in health and disease including safety issues and concluded that it was 'not aware of any toxic or abnormal effects of circulating folic acid' even from much higher exposures than those typically obtained through food fortification [1]. At the generally low concentrations arising through food fortification, the balance of evidence shows that it is unlikely that there are any adverse health effects associated with the presence of unmetabolised folic acid in the circulation.

Other evidence suggested that folic acid doses in excess of 1 mg/d may potentially promote the growth of undiagnosed colorectal adenomas in those with pre-existing lesions [19]. An extensive review by SACN in 2009 [20] concluded that there were insufficient data to support the concerns that mandatory folic acid fortification would promote cancer. A recent review by an expert panel for the US National Toxicology Program [17] concluded that although there are numerous studies of high folic acid intake across multiple cancer types in a wide variety of populations the results were inconsistent in relation to folic acid exposure and cancer risk. Nevertheless, the panel found that there is a consistent enough suggestion in human studies of an adverse effect on cancer growth from folic acid from supplements to justify further research. One recent meta-analysis of randomised controlled trials (involving 50,000 individuals in 13 trials of folic acid supplements with a median dose of 2mg/d) concluded that folic acid supplementation neither increased nor decreased site-specific cancer within the first five years of treatment [21]. This finding is supported by two other meta-analyses [22,23] of trials with supplements providing total folic acid intakes from supplements and diet (about 2.1-2.3 mg/d) equivalent to two to three times higher than those experienced by high consumers in the USA mandatory fortification programme or than would be expected in high consumers with the introduction of mandatory fortification in Ireland (about 0.6-0.8mg/d). Since mandatory folic acid food fortification was introduced in the United States in 1996, rates of all cancer, colorectal cancer, and prostate cancer have not significantly increased [24].

The evidence for possible effects of folic acid on diabetes-related disorders was reviewed recently by the US National Toxicology Program [17] which concluded that, based on the limited data available, there is no consistent evidence for any effects of high folic acid intakes or high folate status on diabetes risk or glucose/insulin metabolism.

Other possible adverse health effects of folic acid fortification related to epilepsy, multiple births and embryo selection have been reviewed by the UK Scientific Committee on Nutrition [25] which concluded that there is no basis for public health concern regarding these. Neither high folic acid intake nor high levels of biomarkers of folate in blood have been shown to induce asthma in either adults or children [17].

Regarding possible adverse effects in children, a review by the UK Scientific Committee on Nutrition concluded that there are no data to suggest that high intakes of folic acid have any adverse effects on children [25]. This conclusion was based in part on a review by the UK Expert Group on Vitamins and Minerals [26] which found no data reporting adverse effects in children.

The experience of mandatory fortification of foods with folic acid in the US since 1996 has shown that there is no evidence for the occurrence of adverse health effects in any population group following introduction of fortification[18].

The available evidence shows that programmes of mandatory fortification of foods with folic acid at levels sufficient to provide significant protection to women of childbearing age against NTD-affected pregnancies do not increase the risk of adverse health effects in the population. Nevertheless, it is prudent to avoid population-wide long-term intakes of folic acid at levels higher than are necessary for beneficial effects.

7.4 Summary

- The evidence linking low, but not necessarily deficient, folate status in women of childbearing age with pregnancies affected by NTDs is conclusive and beyond debate. Folate levels inadequate to minimise risk of NTDs is a significant problem in European countries including Ireland, and this has resulted in an unacceptably and unnecessarily high rate of NTDs.
- Despite the known benefit in preventing NTDs, achieving optimal folate status in women of childbearing age presents significant challenges. This is partly because natural food folates are inherently unstable and have limited bioavailability; thus their ability to influence folate biomarker status is limited. Folic acid is a more stable and bioavailable form of folate which may be obtained from food supplements or from fortified foods.
- Advice on folic acid supplementation as a sole health promotion measure to prevent NTDs in Ireland and most European countries, has had limited effectiveness in achieving further reductions in the occurrence of NTDs owing to generally poor compliance with advice to take daily supplements. Recent evidence shows that there has been no change in the rate of NTDs in Ireland or other European countries over the 20 year period that this strategy has been in place.
- Folic acid fortification of food can overcome the challenges of optimising folate status in women of childbearing age by providing a highly stable and bioavailable form of the vitamin. When this is undertaken on a population-wide basis, i.e. mandatory fortification, it has proven effective in increasing folate status in women of childbearing age and in turn reducing rates of NTDs. While voluntary fortification of foods with folic acid can make a significant contribution to reduction in risk of NTD-affected pregnancies, it is less effective than mandatory fortification.
- Folate status in women of childbearing age in Ireland, like other European countries, is insufficient for protecting against the occurrence of NTDs, and rates of NTDs are higher than in countries where mandatory fortification is implemented.

- Ireland, the UK and other European countries have delayed decisions to introduce mandatory fortification with folic acid on the basis of concerns relating to possible risk. In 20 years of widespread international use of mandatory folic acid fortification, the putative health risks have not materialised. The balance of evidence at this time, including the experience of the USA and other countries that have introduced mandatory fortification, shows a very strong case for fortification and indicates that there are proven benefits in terms of reducing NTDs without increasing risk of adverse health effects in the population.

7.5 References

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CHAPTER 8. OPTIONS FOR THE PREVENTION OF NTDS IN IRELAND

8.1 Introduction

Two options to reduce risk of NTD-affected pregnancies in Ireland are presented:

Option 1. Mandatory Fortification Together with Voluntary Fortification and Advice on Supplementation

Mandatory fortification of bread or flour with folic acid. This should be accompanied by advice to all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid daily as a food supplement. Voluntary fortification of foods with folic acid would continue. Mandatory fortification of flour or bread with folic acid would require legislation.

Option 2: Voluntary Fortification Together with Advice on Supplementation

Continuation of current policy to advise all women of childbearing age who are capable of becoming pregnant, to take an additional 400 µg folic acid daily as a food supplement. Voluntary fortification of foods with folic acid would continue.

As advice on folic acid supplementation for women of childbearing age is an important element of both options, there will be a need for an ongoing programme for promotion and monitoring of awareness and compliance with this advice regardless of the policy adopted (Chapter 4). In addition, both options would require comprehensive, national monitoring of rates of NTD-affected pregnancies, and monitoring of folic acid intake and blood folate status of women of childbearing age and other population groups (Chapter 2).

8.2 Option 1. Mandatory Fortification Together with Voluntary Fortification and Advice on Supplementation

One option to reduce the risk of NTD-affected pregnancies is to introduce mandatory fortification of bread or flour with folic acid together with advice to all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid as a supplement, and continuing voluntary fortification of foods with folic acid.

In several countries, mandatory folic acid fortification of staple foods has been shown to be effective in further reducing the occurrence of NTD-affected pregnancies in a sustained manner with no adverse effects on health of other population groups, e.g. USA, Canada and Chile: see Chapter 1.

An analysis of the health benefits and possible health risks of mandatory fortification of bread and flour with folic acid was performed (see Text Box and Appendix II). This was based on levels of fortification with folic acid previously recommended for bread (120 µg/100 g, as consumed) by the Irish National Committee on Folic Acid Food Fortification [1] and for flour (225 µg/100 g, as consumed) by the UK Scientific Advisory Committee on Nutrition [2].

Estimates were made of the reduction in risk of occurrence of NTD-affected pregnancies based on the increase in average daily folic acid intake from fortified bread or flour in women aged 18-50 years. The possible risk of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults was assessed from the probability of exceeding the UL of 1,000 µg for folic acid, together with the magnitude of any possible excess, based on the total intake of folic acid from fortified bread or flour (as well as other fortified foods and food supplements) in men and women aged over 50 years.

Addition of folic acid to (most) breads at a level of 120 µg or 225 µg/100 g bread would reduce the risk of NTD-affected pregnancies by approximately 17-31%, while addition of folic acid to all wheat flour at a level of 225 µg/100 g would reduce the risk of NTD-affected pregnancies by approximately 32%. For all three scenarios, the effect on the risk of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults would be negligible.

The benefit for reduction in the risk of occurrence of NTD-affected pregnancies by foods voluntarily fortified with folic acid (about 11-14%) could be retained. There is potential to improve the contribution of voluntary fortification by providing guidance to manufacturers, e.g. for levels of fortification and the range of foods fortified, in conjunction with a voluntary labelling scheme. Intakes of folic acid from food supplements and foods voluntarily fortified with folic acid should be monitored as maximum levels of folic acid in these sources are not currently regulated.

Mandatory addition of folic acid to flour or bread would require legislation and an implementation programme would be needed to address:

- Legislation
- Consumer acceptability and consumer choice
- Technical issues, in consultation with the food industry, e.g. optimal level of addition of folic acid to bread or flour, most appropriate point of addition of folic acid, labelling, cost, trade
- Monitoring dietary intake and blood folate levels of all population sub-groups in addition to folic acid levels in food (flour, bread, other fortified foods and food supplements)

Compared with Option 2 - folic acid supplementation (in association with voluntary fortification), this option:

- Has stronger evidence to support its effectiveness in further reducing rates of NTD-affected pregnancies below the present rate
- Would require legislation and an implementation plan for management of mandatory fortification of bread or flour

Impact of mandatory fortification of bread and flour with folic acid in the Republic of Ireland

The effects of fortification of bread and flour with folic acid on reduction in risk of occurrence of NTD-affected pregnancies and on possible risks of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults were estimated by simulation of dietary intake data for adults in the Republic of Ireland from the Irish National Adult Nutrition Survey (2008-10).

Estimates were made of the reduction in risk of occurrence of NTD-affected pregnancies based on the increase in average daily folic acid intake from fortified bread or flour in women aged 18-50 years. Two studies carried out in Ireland in 1995 and 1997 were used to relate the change in risk of NTDs to the additional intake of folic acid.

Addition of folic acid to breads (all commercial white, brown and whole meal breads, but excluding soda breads) at a level of 120 µg or 225 µg/100g bread, as consumed, would reduce the risk of NTD-affected pregnancies by approximately 17% and 31%, corresponding to an increase of 77 µg and 148 µg, respectively, in the average daily folic acid intake of women of childbearing age.

Addition of folic acid to all wheat flour at a level of 225 µg/100 g as consumed, would reduce the risk of NTD-affected pregnancies by approximately 32%, corresponding to an increase of 151 µg in the average daily folic acid intake of women of childbearing age.

The possible risk of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults was assessed from the probability of exceeding the UL of 1,000 µg for folic acid, together with the magnitude of any possible excess, based on the total intake of folic acid from fortified bread or flour (as well as other fortified foods and food supplements) in men and women aged over 50 years.

For these levels of addition of folic acid to bread and flour, the risk of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults would be negligible. This is because the probability of exceeding the UL for folic acid, even by a small amount, is very low (0.1-0.2%), with 95% of adults aged over 50 years having usual daily folic acid intake less than 623 µg, and 99% having usual daily folic acid intake less than 822 µg.

These levels of addition of folic acid to bread and flour would allow safe consumption of folic acid at current levels from other foods fortified with folic acid and supplements. Foods that are voluntarily fortified with folic acid at current levels reduce the risk of occurrence of NTD-affected pregnancies by about 11-14%.

8.3 Option 2. Voluntary Fortification Together with Advice on Supplementation

An alternative option to reduce the risk of NTD-affected pregnancies in Ireland is to continue current policy, i.e. to advise all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid as a supplement, while continuing voluntary fortification of foods with folic acid. Evidence indicates that this has limited effectiveness at present, as there is low compliance with this advice (see Chapters 3 and 6). This is similar to experience in many other countries. In order to improve the effectiveness of this policy in Ireland, there would need to be an ongoing programme to increase awareness and improve compliance. In addition, effectiveness would need to be evaluated by monitoring awareness and compliance.

Promotion of the use of folic acid supplements may be supported by a health claim related to reducing risk of neural tube defects in the developing foetus which has been authorised recently by the EU which may be made on supplements with at least 400 µg folic acid (see Chapter 3).

Because foods voluntarily fortified with folic acid currently make a significant contribution to folic acid intakes and reduction in risk of NTD-affected pregnancies (estimated as 11-14%, see Chapter 3) in women of childbearing age, the policy of advising on use of folic acid supplements could be complemented by measures to increase intake of folic acid from this source. For example, manufacturers could be guided to fortify certain foods with folic acid in conjunction with a voluntary labelling scheme similar to the 'Flash Labelling Scheme' administered by the FSAI in the past where the label could be used on condition that the food contained a minimum amount of folic acid, e.g. 'source or 'high' as defined in the Regulation on Nutrition and Health Claims made on Foods (see Chapter 3). Foods which would be most suitable could be identified and consultation with industry would be required to establish potential level of interest in such a scheme.

Compared with the option for mandatory fortification of bread or flour with folic acid, together with folic acid supplementation, this option:

- Has weaker evidence to support its effectiveness in further reducing rates of NTD-affected pregnancies below the present rate
- Would not require legislation or an implementation programme for mandatory fortification of bread or flour

8.4 References

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CHAPTER 9. CONCLUSIONS AND RECOMMENDATIONS

This report provides a comprehensive update on folic acid nutrition and the prevention of NTDs in Ireland since the last national reports of 2006 and 2008. The aspects covered include the possible increase in the incidence of pregnancies affected by NTDs in 2009-11 compared with incidence in 2005-6 (see Chapter 2), how the food environment has changed in relation to folic acid (food supplements and fortified foods) (see Chapter 3), national folic acid health promotion campaigns (Chapter 4), dietary folate (natural folate and folic acid) intakes and blood folate status of all population sub-groups (see Chapters 5 and 6). All of this information was compiled having considered international scientific developments in this area (Chapter 7). In Chapter 8, two options to reduce risk of NTD-affected pregnancies in Ireland are presented.

9.1 Conclusions

1. Recommended options to reduce risk of NTD-affected pregnancies in Ireland

Two possible options are recommended. For both options, the available evidence shows that the levels of intake of folic acid that would occur would not increase the risk of adverse health effects in the population.

Option 1) Mandatory fortification together with voluntary fortification and advice on supplementation

Mandatory fortification of food staples, such as flour or cereals, has proved effective in decreasing the prevalence of pregnancies affected by NTDs in countries that have implemented this approach, e.g. by 35% in the USA. This report shows that in Ireland mandatory fortification of bread or flour to provide about 150 µg of folic acid per day in women of childbearing age could reduce the prevalence of NTDs by approximately 30%. The benefit for reduction in the risk of occurrence of NTD-affected pregnancies by foods that are now voluntarily fortified with folic acid (about 11-14%) could be retained. There is potential to improve the contribution of voluntary fortification by providing guidance to manufacturers, e.g. for levels of fortification and the range of foods fortified, in conjunction with a voluntary labelling scheme. Intakes of folic acid from food supplements and foods voluntarily fortified with folic acid should be monitored as maximum levels of folic acid in these sources are not currently regulated.

Mandatory fortification of flour or bread with folic acid would require legislation. An implementation programme would be needed to address legislation, consumer acceptability and consumer choice, technical issues, cost, and trade implications.

Mandatory fortification of food with folic acid would only provide women with a proportion of the recommended amount to prevent occurrence of NTDs. Therefore, promotion of the current recommendation for all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid daily as a food supplement, needs to be continued, as in other countries worldwide in which mandatory folic acid fortification is practiced.

Option 2) Voluntary fortification together with advice on supplementation

While there was a large decrease in incidence rate of NTDs in Ireland from the early 1980s (about 3.5 per 1,000 births) to the mid-1990s, the rate has remained relatively stable since then at about 1 per 1,000 births (about 80 cases per annum), similar to the UK, despite introduction of a policy of advice on peri-conceptional supplementation with folic acid in 1993. This rate remains significantly higher than in countries with mandatory fortification such as the United States (about 0.6 per 1,000 births). Compliance by women of childbearing age with this recommendation in Ireland (and elsewhere) is generally poor and therefore, it has had limited effectiveness. This has been similar to experiences in other European countries that have a similar policy. While voluntary food fortification with folic

acid does make a significant contribution to reduction in the risk of NTD-affected pregnancies, the lower level and uneven distribution of intake of folic acid among women of childbearing age makes it less effective than mandatory fortification. There is potential to improve the effectiveness of voluntary fortification by providing guidance on voluntary fortification of selected foods with folic acid by manufacturers, e.g. for levels of fortification and the range of foods fortified, in conjunction with a voluntary labelling scheme. Intakes of folic acid from food supplements and foods voluntarily fortified with folic acid should be monitored as maximum levels of folic acid in these sources are not currently regulated.

2. Health promotion campaigns on folic acid for the prevention of NTDs

Ongoing campaigns to promote folic acid supplement use by women of childbearing age are essential to guide the young women continuously entering this target group. These should be implemented through an ongoing multifaceted national campaign, sustained local health promotion activities and by health professionals. From 2006 until 2015, health promotion activities were undertaken at a local level. An ongoing national health promotion campaign that reaches all women in the target group regardless of socio-economic status, age, cultural background or education level achieved, are required. Such a campaign was initiated in 2015 and plans are in place to continue this campaign. Regular evaluation studies of these campaigns should be undertaken to develop innovative and captivating strategies that are effective.

3. Monitoring the incidence of pregnancies affected by NTDs in Ireland

It is difficult to obtain reliable estimates of the current incidence of NTDs in Ireland due to the absence of a comprehensive register of pregnancies affected by NTDs. Special national studies undertaken in 2005-2006 and 2009-2011 show the incidence of pregnancies in Ireland affected by NTDs may have increased from the earlier time period to the later (from 0.92/1000 pregnancies to 1.04/1,000 pregnancies). A similar national study should be undertaken in order to establish baseline data on levels of NTDs in Ireland prior to introduction of a new policy as recommended in the current report. To assess the continuing impact of policy and health promotion campaigns, ongoing comprehensive information on all pregnancies affected by NTDs is essential.

4. Monitoring of dietary intake and blood levels of folate

There should be continuous monitoring of folic acid in flour/bread products, other fortified foods and food supplements. Foods marketed in Ireland that are voluntarily fortified with folic acid are randomly assessed in food inspection surveys. This includes laboratory testing to ensure that the amounts present are accurate in relation to the amounts declared in labelling.

Representative national surveys are required on a regular basis, e.g. approximately every five years, to assess a) intakes of total folate (natural food folate and added folic acid) of women of childbearing years as well as all other population sub-groups and b) blood folate status in women of childbearing age and other population sub-groups, to include several blood folate variables to provide comprehensive data on the effectiveness and safety of the policy.

5. Regular review

The policy should be reviewed on a regular basis to assess its effectiveness and safety. This should be based on outcomes of monitoring of the rate of NTDs, compliance with advice on supplements, dietary intake and blood levels of folate for all population groups and updates on research related to safety.

9.2 Recommendations

1. **One of the following two options should be implemented to reduce risk of NTD-affected pregnancies in Ireland:**

   Option 1: Mandatory fortification together with voluntary fortification and advice on supplementation

   Mandatory fortification of bread or flour with folic acid. This should be accompanied by advice to all women of childbearing age who are capable of becoming pregnant to take an additional 400 µg folic acid daily as a food supplement. Voluntary fortification of foods with folic acid would continue. Mandatory fortification of flour or bread with folic acid would require legislation. Compared to the other option, this option has stronger evidence to support its effectiveness in further reducing the rate of NTD-affected pregnancies from the current rate.

   Option 2: Voluntary fortification together with advice on supplementation

   Continuation of current policy to advise all women of childbearing age who are capable of becoming pregnant, to take an additional 400 µg folic acid daily as a food supplement. Voluntary fortification of foods with folic acid would continue. Compared to Option 1, this has weaker evidence to support its possible effectiveness in further reducing rates of NTD-affected pregnancies from the current rate.

2. **Guidance should be provided to food manufacturers for voluntary food fortification with folic acid to support the effectiveness of the chosen national policy.**

3. **Advice to women of childbearing age capable of becoming pregnant to take an additional 400 µg folic acid daily as a food supplement should be actively promoted and its effectiveness monitored.**

4. **A comprehensive nationwide register of pregnancies affected by congenital birth defects including NTDs, underpinned by specific legislation, needs to be introduced in Ireland. In addition, a national retrospective study on the incidence of NTDs in Ireland since 2012 should be undertaken.**

5. **There should be ongoing monitoring, informed by international best practice, of dietary intake and blood levels of folate, including:**

   a) Folic acid in the food supply (folic acid in flour/bread products, other fortified foods and food supplements) and;

   b) Total folate intake (natural food folate and added folic acid) and corresponding blood folate status for the target group (women of childbearing age) in addition to other population sub-groups

6. **The policy should be reviewed on a regular basis to assess its effectiveness and safety.**

APPENDIX I: BLOOD FOLATE STATUS MODELLING METHOD

A. Recruitment of participants

As in the first program carried out between 2005 and 2007, four sectors of the population were targeted in the 2009-2011 phase of the study. These included non-pregnant women of childbearing age (between the ages of 16 and 50), children (aged 2-15), a population of older people (aged 66 years and above) and a mixed population of males (aged 16-65) and females (aged 50-65). Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee, Trinity College, Dublin, the Coombe University Hospital Research Ethics Committee and the Federated Hospitals Research Ethics Committee. All adult participants gave written consent. In the case of children, written consent was obtained from parents and verbal assent was obtained from the children.

I. Non-pregnant women of childbearing age

As noted earlier, this cohort was sampled from generally healthy women attending the Coombe Women and Infants University Hospital for routine non-pregnancy related tests such as colposcopy, with a target of 500 subjects. Although over 500 women were recruited from this source, some were over 50 years old and were re-categorised. Additional women were recruited from GP practices.

II. Children (2-15years)

This cohort was sampled from children attending the outpatients department of the AMNCH Pediatric Unit who were scheduled for phlebotomy. The recruitment was planned to start in the first few months of 2010, in order to tie in with the previous phase when children were sampled during the winter months. Recruitment was carried out by 4th year medical students who were on rotation in AMNCH. The target of 200 samples was exceeded with a total of 251 bloods and questionnaires collected. However, some of these were 16 year old girls and these were re-categorised into cohort 1 (women of childbearing age). One limitation of this collection was the low amount of blood obtained per sample, because only an additional 2.5 mL of EDTA blood was requested in addition to the phlebotomy that was scheduled for the children. The volume of plasma was always a limiting factor, especially since the full 2.5 mL was not always available. We were aware that children would be an important group for monitoring the prevalence of very high folate status and the occurrence of free folic acid in plasma, therefore a priority list of variables to be measured was set up, with the order of assay to be (i) total folate, (ii) free folic acid, (iii) vitamin B_{12}, (iv) tHcy. In the end we were able to report plasma and red cell folate data on all samples, Vitamin B_{12} on 95% and tHcy on 86% as well as carrying out folic acid analysis on a random subset of 55% of the children. Data analysis was carried out on all children within each age range, with no separate analysis by gender since we had observed no differences by gender in the previous study. The final group of 238 children between the ages of 2 and 15 consisted of 108 girls (45.3%) and 130 boys (54.7%)

III. General adult population

This cohort was sampled from several sources including general practitioners surgeries in the Dublin area and hospital out-patients clinics. The group includes adult males between 16 and 65 years and women between 50 and 65 years old. The recruitment setting differed from the previous study in which participants were recruited from the Irish Blood Transfusion platelet donor clinic. The target of 200 samples was difficult to reach and recruitment had to be closed at 170 because of time constraints with the medical students who were the recruiting researchers. Data analysis was carried out on men within four age ranges, and women as one additional separate group. In total, the group consisted of 45.9% women and 54.1% men with an even distribution of men across all the age ranges considered.

IV. Older people (66+ years)

The population of older people was accessed with the permission of Dr Conal Cunningham and Dr Miriam Casey, Geriatric Consultants in St. James Hospital, and forms part of an ongoing observational cohort study of over 5,000 participants (the TUDA cohort), designed to collect environmental, medical, metabolic and genotype data on older persons with mild cognitive dysfunction, bone disease or hypertension. The TUDA cohort is funded by the Irish Department of Agriculture through the Food Institutional Research Measure (FIRM) and additional support was received from the Northern Ireland Government. The cohort is the product of a collaborative project between the University of Ulster at Coleraine and Trinity College Dublin.

B. Blood sampling:

Non-fasting blood samples were collected from (a) colposcopy and minor surgery clinics in the Coombe Hospital; (b) the children's out-patients ward in AMNCH, where children who were scheduled for venepuncture for other purposes were asked for an additional 2.5 mL blood in a separate tube during the phlebotomy procedure, (c) general practitioners' surgeries in the north, south and west Dublin regions, (d) the memory and bone clinics in the geriatric unit of St James Hospital, where samples and data from persons over 60 years old, who were attending these out-patient clinics with mild cognitive dysfunction or bone disease were recruited for the TUDA cohort.

Bloods were collected into a 7 – 10 ml EDTA tube and all were processed within 2-3 hours after collection. On receipt into the laboratory, samples were mixed well on a blood roller and the packed cell volume was determined. 100 µl of whole-blood was aliquotted into a tube containing 900 µl of freshly prepared 1% ascorbic acid solution and mixed well. The whole-blood/ascorbic acid mixture was left at room temperature for 30 minutes to allow folate polyglutamates released from the lysed red cells to be converted to the assayable monoglutamate forms by endogenous serum folate conjugase. These ascorbic acid lysates were then be stored at -80°C until assayed. The remainder of the blood was centrifuged to separate the plasma (2,500rpm for 12 min). The plasma was aspirated carefully from the packed cells and aliquotted into duplicate labelled micro-tubes for storage at -80°C prior to assay.

I. Development of methodology to measure unmetabolised folic acid in serum

As noted in our first report, a new HPLC instrument was purchased in October 2008 and a postdoctoral fellow (Dr Rosalia Poo-Prieto) was recruited in January 2009 for six months, to develop the new method. The basic development was successfully conducted and a senior research technician in the laboratory completed the assay validation. Progress was slow because the initial solid-phase extraction step left the recovery of folic acid too low to quantitate with acceptable precision. Nevertheless, most of the recovery problems were solved but after exhaustive concentration and validation experiments, it became clear that sample extracts were reading close to the limit of detection of the microbiological assay and, with recoveries less than 50% after the initial solid-phase extraction step, the final calculated amount of folic acid present in spiked samples used for recovery studies was too imprecise. While this work was on-going, colleagues in Bergen, Norway published the development and validation of a new HPLC/MS/MS method for free folic acid that required ten-fold less serum for analysis. In order to ensure that our obligations to the FSAI with regard to providing information on free folic acid in blood were met, we decided to use the remaining funds to have as many samples as possible assayed in Bergen. The cost negotiated allowed analysis of 800 samples (57% of the population).

In order to optimise the value of this sub-set, a block randomisation scheme was used to select samples for free folic acid analysis. In total, 1,392 blood samples were collected and available for analysis in this study. For free folic acid analysis, a subset of 800 samples was selected using the following strategy:

1. All samples in the upper 90th Percentile for plasma folate were selected for analysis. This included 141 samples with total plasma folate ≥ 30 µg/L
2. All samples with total plasma folate < 3 µg/L were excluded (N=50) because these were in the clinically deficient/marginal range and would have had concentrations close to free folic acid limit of detection (this approximates the lower 2.5th percentile)
3. All other samples (1,392-191=1,201) with free folic acid between 3 and 30 µg/L were randomly selected to generate a further 659 samples for free folic acid analysis (using a random number generator)

II. Analysis of total folate and related metabolites in serum

Plasma and red cell folate were measured using a microtitre plate, high-throughput microbiological assay based on growth of chloramphenicol resistant *Lactobacillus casei (L. rhamnosus)*. Vitamin B_{12} was also measured by a microbiological method using a microtitre plate adaptation of the colistin resistant microorganism *Lactobacillus leichmannii* after carrying out an initial extraction step. Plasma total homocysteine (tHcy) was measured on an Abbott AxSym analyser using a fluorescent polarisation immunoassay technique.

III. Analysis of folic acid levels in serum

Free folic acid analysis was carried out using a high throughput LC/MS/MS method recently developed in Bergen, Norway. The method measures 5-methyltetrahydrofolate (5mTHF), 4-alpha-hydroxy-5-methyltetrahydrofolate (hmTHF), folic acid, 5-formyltrahydrofolate (5fTHF), p-aminobenzoylglutamate (pABG), and p-acetamidobenzoylglutamate (apABG) simultaneously. The authors reported a detection limit of 0.07-0.52 nmol/L for all folate vitamer species. Using the method, the authors found in a Norwegian reference group that on average, 2.1% of serum folate was present as free folic acid but there was a wide range. The HPLC method correlated well with the microbiologic assay (r = 0.92)

IV. Collation of data and reporting

All blood and questionnaire data were collated into electronic format for the final analysis. Data analysis was carried out using SPSS Version 16 for Windows. In general, data for blood metabolites were not normally distributed and are presented as medians and interquartile ranges. Where comparative analysis was performed, this was carried out on data transformed to base10 logarithm (log). One-way analysis of variance (ANOVA) was used to compare quantitative data across groups. Chi Square tests were used for comparison of categorical data. Because of non-normal distributions, Spearman correlation coefficients were used to determine associations between blood nutrient variables.

APPENDIX II. IMPACT OF MANDATORY FORTIFICATION OF BREAD AND FLOUR WITH FOLIC ACID IN THE REPUBLIC OF IRELAND

Summary

- The effects of fortification of bread and flour with folic acid on reduction in risk of occurrence of NTD-affected pregnancies and on possible risks of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults were estimated by simulation of dietary intake data for adults in the Republic of Ireland from the Irish National Adult Nutrition Survey [1].
- Estimates were made of the reduction in risk of occurrence of NTD-affected pregnancies based on the increase in average daily folic acid intake from fortified bread or flour in women aged 18-50 years. The studies of Daly *et al* (2) and Daly *et al* (3) were used to relate the change in risk of NTDs to the additional intake of folic acid.
- Addition of folic acid to breads (all commercial white, brown and whole meal breads, but excluding soda breads) at a level of 120 µg and 225 µg/100 g bread, as consumed, would reduce the risk of NTD-affected pregnancies by approximately 17% and 31%, corresponding to an increase of 77 µg and 148 µg, respectively, in the average daily folic acid intake of women of childbearing age.
- Addition of folic acid to all wheat flour at a level of 225 µg/100 g, as consumed, would reduce the risk of NTD-affected pregnancies by approximately 32%, corresponding to an increase of 151 µg in the average daily folic acid intake of women of childbearing age.
- The possible risk of masking of anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults was assessed from the probability of exceeding the UL of 1,000 µg for folic acid, together with the magnitude of any possible excess, based on the total intake of folic acid from fortified bread or flour (as well as other fortified foods and food supplements) in men and women aged over 50 years.
- For these levels of addition of folic acid to bread and flour, the risk of masking anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults would be negligible. This is because the probability of exceeding the UL for folic acid, even by a small amount, is very low (0.1-0.2%), with 95% of adults aged over 50 years having usual daily folic acid intake less than 623 µg, and 99% having usual daily folic acid intake less than 822 µg.
- These levels of addition of folic acid to bread and flour would allow safe consumption of folic acid at current levels from other foods fortified with folic acid and supplements. Foods that are voluntarily fortified with folic acid at current levels reduce the risk of occurrence of NTD-affected pregnancies by about 11-14%.

Introduction

There is strong evidence that folic acid, when taken before conception and during the early months of pregnancy, can reduce the risk of occurrence of neural tube defects in the foetus (see Chapter 1). In several countries, mandatory folic acid fortification of staple foods has been shown to be effective in reducing the risk of occurrence of NTD-affected pregnancies, e.g. USA, Canada and Chile: see Chapter 1.

The effects of increasing folic acid intake on reduction in risk of occurrence of NTD-affected pregnancies may be estimated from the studies of Daly *et al* [2] which describes the relationship between maternal folate status (as determined by red cell folate measurement) and the risk of NTDs, and Daly *et al* [3] which describes the relationship between additional intake of folic acid (100 µg, 200 µg and 400 µg as supplements) and median red cell folate in women.

The possible health risk associated with increasing folic acid intakes of the population concerns the potential for high intakes of folic acid to mask the anaemia that is an early symptom of vitamin B_{12} deficiency (megaloblastic anaemia) in older people and delay its diagnosis, facilitating progression of the neurological symptoms of the deficiency (see Chapter 7). Prolonged deficiency of vitamin B_{12} can cause irreversible damage to the nerves and the spinal cord (neuropathy) (there is no evidence for risk associated with high intakes of the natural folates present in food) (see Chapter 7). A UL of 1,000 µg for folic acid per day in adults has been established by the EU Scientific Committee on Food [4] and the US Food and Nutrition Board [5] from a Lowest Observed Adverse Effect Level (LOAEL) of 5,000 µg per day for masking of the haematological signs and possible progression of the neurological symptoms in vitamin B_{12}-deficient individuals, using a five-fold safety margin in order to protect those individuals most sensitive to this adverse effect. The UL is an estimate of the highest (usual) level of intake which carries no appreciable risk of adverse health effects in a population, including the most sensitive individuals.

The effects of increasing folic acid intake on possible risk of masking of undiagnosed vitamin B_{12} deficiency in older adults may be assessed from the probability of exceeding the UL of 1,000 µg for folic acid, together with the magnitude of any possible excess.

The objectives of this study were to estimate the effects of fortification of bread and flour with folic acid on reduction in risk of occurrence of NTD-affected pregnancies and on possible risks of masking of undiagnosed vitamin B_{12} deficiency in older adults. The scenarios examined were the addition of folic acid to:

1) Breads (all commercial white, brown and whole meal breads, but excluding soda breads) at a level of 120 µg/100 g bread, as consumed, as recommended by the Irish National Committee on Folic Acid Food Fortification [6]
2) Breads (all commercial white, brown and whole meal breads, but excluding soda breads) at a level of 225 µg/100 g bread, as consumed, equivalent to the level of addition to flour recommended by the UK Scientific Advisory Committee on Nutrition [7] and
3) All wheat flour at a level of 225 µg/100 g, as consumed, as recommended by the UK Scientific Advisory Committee on Nutrition [7]

Methods

The effects of fortification of bread and flour with folic acid on reduction in risk of occurrence of NTD-affected pregnancies and on possible risks of masking of undiagnosed vitamin B_{12} deficiency in older adults were estimated by simulation of dietary intake data for adults in the Republic of Ireland studied in the Irish National Adult Nutrition Survey [1] in 2008-10.

Subjects and Methods

Study population

Data for this analysis were derived from the NANS, a nationally representative cross sectional food consumption survey carried out between 2008 and 2010 in the Republic of Ireland. The survey collected data on habitual food and beverage consumption in a nationally representative sample of 1,500 adults aged 18 - 90 years (men: n=760; women: n=740). A more detailed description of the study population, recruitment methods and sampling procedures are outlined in the main survey report [1].

Assessment of dietary intakes of folic acid

Food and beverage intake data were collected using a four day semi-weighed food diary which included at least one weekend day. Participants were asked to record the type and amount of all food, beverages and supplements consumed, at brand level where possible, over four consecutive days and where applicable, record recipes, cooking method and details of leftovers. Participants were asked to retain the packaging of foods and beverages they consumed which was later used to develop the Irish Food and Ingredients Database version 3.0 (INFID)[8]. INFID is a multifaceted database which records detailed information printed on food packaging as consumed in NANS and in previous food consumption surveys in Ireland (including nutritional content and ingredients list). Food intakes were quantified using the protocol developed by the Irish Universities Nutrition Alliance[9], updated for NANS and is described in the main survey report [1].

Fortified foods and supplements containing folic were identified using the ingredients list on the label as recorded in INFID. Folic acid intakes from fortified foods and supplements were estimated using a customised version of WISP© v3 (Tinuviel Software, Anglesey, UK), which includes data from McCance and Widdowson's 'The Composition of Foods' sixth and fifth editions plus all nine supplemental volumes. The database was amended to include folic acid content of foods and supplements. Folic acid content of fortified foods was estimated as the difference between total folate content as declared on the label and the natural folate content obtained from published food composition data[1] (as described in Chapter 6). The folic acid content of supplements was obtained from INFID or directly from product labels. The food composition database was further updated in 2015 to take account of the reduction in the number of fat spreads and breads fortified with folic acid. Seven individuals consuming supplements which contained levels of folic acid (5,000 µg) deemed to be medicinal were removed from the analyses.

Simulation scenarios for bread and flour fortification

The scenarios examined were the addition of folic acid to:

1) Breads (all commercial white, brown and whole meal breads, but excluding soda breads) at a level of 120 µg/100 g bread, as consumed, as recommended by the Irish National Committee on Folic Acid Food Fortification [6]
2) Breads (all commercial white, brown and whole meal breads, but excluding soda breads) at a level of 225 µg/100 g bread, as consumed, equivalent to the level of addition to flour recommended by the UK Scientific Advisory Committee on Nutrition [7] and
3) All wheat flour at a level of 225 µg/100 g, as consumed, as recommended by the UK Scientific Advisory Committee on Nutrition [7]

The simulation scenarios examined are based on intakes of folic acid at current levels in voluntarily fortified foods and supplements. As it is usual for manufacturers to include additional folic acid ('overage') in fortified foods and supplements to allow for losses during processing and shelf-life, estimates of intakes of folic acid were made assuming the folic acid content of voluntarily fortified foods and supplements exceeded the declared value on the label by an average of 25%.

In order to assess the possible effect of restriction of voluntarily fortified foods (as considered by SACN [7]), additional scenarios were examined for flour fortification: 1) effect of exclusion of folic acid from voluntarily fortified foods, 2) effect of exclusion of folic acid from supplements, 3) effect of exclusion of folic acid from voluntarily fortified foods and supplements.

For bread, all food codes relating to white, whole meal and brown breads and rolls and recipes containing white or brown bread in which the weight of bread contributed >10% of the total weight were identified. White and brown soda breads, gluten free breads, pitta breads, scones, bagels, croissants, paninis, tortillas, bracks, currant breads, muffins, malt and rye breads, naan breads were excluded. Folic acid in breads that are currently fortified with folic acid voluntarily was excluded from the analysis. The amount of folic acid from mandatory fortification was calculated for each bread as follows:

Folic acid intake (µg) = weight of bread consumed (g) x 1.2

For recipes, the proportion of the total weight made up by bread was estimated and the folic acid content for that proportion was calculated as *per* the above formula.

For flour, food groups which were contributors to wheat flour in the diet were identified and included breads, biscuits, savouries, cakes, pastries, buns, sponge and other cereal-based puddings. The amount of wheat flour per 100 g of each food was estimated from the starch content of the food based on the assumption that all the starch content came from flour and that 1 g of flour contains 0.762 g of starch [10]. The amount of flour was calculated for each food as follows:

Flour content (g) = starch content (g)/0.762

The amount of folic acid from mandatory fortification was calculated for each food as follows:

Folic acid intake (µg) = weight of food flour consumed (g) x 2.25

Folic acid in flour-containing foods that are currently fortified with folic acid voluntarily was excluded from the analysis.

Statistical analysis

Analysis was conducted using SAS Enterprise Guide© for Windows™ Version 6.1 (SAS Institute Inc., Cary, NC, USA). Usual intake distributions of folic acid were estimated using the validated National Cancer Institute (NCI)-Method [11]. The NCI-Method calculates estimates of usual intake based on non-linear mixed regression models. The model separates usual intake into two parts: the probability to consume a food or nutrient on a particular day, and given that the food/nutrient was consumed, the amount eaten on the consumption day. The NCI-Method was implemented in SAS macros (v2.1), which were downloaded from the website http://appliedresearch.cancer.gov/diet/usualintakes/macros.html (date of download: 27th July 2015).

Mean daily folic acid intakes were estimated for women aged 18-50 years and P_{95}, P_{99} of folic acid intake and %> UL were estimated for adults aged over 50 years.

Estimation of risk reduction for NTDs

Estimates were made of the reduction in risk of occurrence of NTD-affected pregnancies based on the increase in average daily folic acid intake from fortified bread or flour in women aged 18-50 years. The studies of Daly *et al* [2] and Daly *et al* [3] were used to relate the reduction in risk of NTDs to the additional intake of folic acid. The effect of additional folic acid intake on risk of NTDs was estimated by linear interpolation between the observations provided by Daly *et al* [3] for 100 µg and 200 µg supplements of folic acid.

Assessment of possible risk of masking undiagnosed vitamin B_{12} deficiency

The possible risk of masking of megalobalstic anaemia associated with (undiagnosed) vitamin B_{12} deficiency in older adults was assessed from the probability of exceeding the Tolerable Upper Intake Level (UL) of 1,000 µg for folic acid[4,5] based on the total intake of folic acid from fortified bread or flour (as well as other fortified foods and food supplements) in men and women aged over 50 years, together with the magnitude of any possible excess above the UL.

For each fortification scenario the increase in the %> UL and the 95th and 99th percentile of folic acid intake were calculated for adults aged >50 years. In addition, intakes of folic acid in the highest consumers were examined to estimate the magnitude of any possible excess above the UL.

Effect of energy underreporting

Preliminary analyses excluding potential energy under-reporters had little effect on the change in risk of NTDs in women of childbearing age or on the upper percentiles of intake or the proportion exceeding the UL among of older adults with each fortification scenario, and it was decided therefore, not to exclude under-reporters from further analyses.

Results and discussion

The mean daily intake of folic acid in women aged 18-50 years in the Republic of Ireland in 2015 is estimated as 92 µg (median= 43 µg), but could be as high as 114 µg if it assumed that the folic acid content of fortified foods and supplements exceeds the declared value on the label by an average of 25% in keeping with usual practice of manufacturers to allow for losses during processing and storage. This is equivalent to a reduction in risk of NTD-affected pregnancies of 20-25%. For foods voluntarily fortified, the mean daily intake of folic acid is estimated as 50 µg but could be up to 63 µg, equivalent to a reduction in risk of NTD-affected pregnancies of 11-14%.

For the bread and flour fortification scenarios examined, the mean daily intake of folic acid of women aged 18-50 years would increase by 77 – 151 µg/day, equivalent to a reduction in risk of NTD-affected pregnancies of 17-32% (Table 1). For the flour fortification scenario, exclusion of folic acid in fortified foods, supplements or both would result in smaller reductions in risk of NTD-affected pregnancies (20%, 22% and 8%, respectively).

The estimates of reductions in NTDs risk resulting from fortification should be considered as broad indicators rather than precise estimates. This is because of uncertainties in the relationship between change in folic acid intake and risk of NTDs, as estimated by Daly *et al* [2,3], and because this relationship depends on the folate status of the mother in early pregnancy, e.g. lower folate status results in a greater reduction in NTD risk.

Table 1. Effect of mandatory fortification of breads (all commercial white, brown and wholemeal breads, but excluding soda breads), or all wheat flour, on folic acid intakes and risk of NTDs in women 18-50 years (*n*= 485)

Fortification scenario	Folic acid intake µg/d	Folic acid intake µg/d	% reduction in NTDs
Baseline*	114	0	0
Bread 120 µg/100 g	191	77	17
Bread 225 µg/100 g	262	148	31
Flour 225 µg/100 g	265	151	32
Flour 225 µg/100 g and excluding fortified foods	204	90	20
Flour 225 µg/100 g and excluding supplements	215	101	22
Flour 225 µg/100 g and excluding fortified foods and supplements	152	38	8

* Baseline represents current intakes of folic acid from voluntarily fortified foods and supplements, including an additional 25% as overage.

The probability of exceeding the UL for folic acid in older adults (>50 year olds) is very low (0.1%) at present levels of intake from fortified foods and supplements and would remain very low (0.1-0.2%) with the fortification scenarios from bread and flour which also include folic acid from voluntarily fortified foods and supplements (Table 2). The magnitude of any possible excess intake of folic acid above the UL would be small, given the patterns of folic acid intake observed in highest consumers. P_{95} and P_{99} intakes of folic acid did not exceed 623 µg/d or 822 µg/d, respectively, for any fortification scenario examined. Highest consumption of folic acid in these fortification scenarios was mainly associated with use of multiple supplements and supplements containing 400 µg folic acid per daily amount.

For the flour fortification scenario, exclusion of folic acid in fortified foods, supplements or both would result in zero probability of exceeding the UL for folic acid in older adults and P_{95} and P_{99} intakes of folic acid would not exceed 477 µg/d or 604 µg/d, respectively (Table 2).

Table 2. Effect of mandatory fortification breads (all commercial white, brown and whole meal breads, but excluding soda breads), or all wheat flour, on folic acid intake in adults aged ≥50 years (*n*=527)

Fortification scenario	P_{95} folic acid intake µg/d	P_{99} folic acid intake µg/d	%>UL
Baseline	409	682	0.1
Bread 120 µg/100 g	489	695	0.1
Bread 225 µg/100 g	623	822	0.2
Flour 225 µg/100 g	592	774	0.1
Flour 225 µg/100 g and excluding fortified foods	455	594	0
Flour 225 µg/100 g and excluding supplements	477	604	0
Flour 225 µg/100 g and excluding fortified foods and supplements	328	408	0

The risk of masking of megaloblastic anaemia associated with (undiagnosed) vitamin B_{12} deficiency, with possible progression of neurological symptoms, from excessive intake of folic acid in older people may be considered to be negligible with the fortification scenarios examined when the following are considered:

- 5-10% of older adults may have (undiagnosed) vitamin B_{12} deficiency [7], a small fraction of whom will have megaloblastic anaemia [12]
- 0.1-0.2% of older adults with megaloblastic anaemia may also have usual daily folic acid exceeding UL (Table 2), only by a small magnitude
- At this level of intake, only a small fraction of these, i.e. the most sensitive, would be susceptible to masking (undiagnosed) vitamin B_{12} deficiency anaemia because this level is about five times lower than lowest intake at which masking has been observed, i.e. the LOAEL of 5,000 µg [4,5]

This conclusion is supported by the experience of mandatory fortification of foods with folic acid in the US where there is no evidence of a higher prevalence of vitamin B_{12} deficiency in the absence of anaemia or macrocytosis among nationally representative U.S. adults aged >50 years. This indicates that exposure to higher levels of folic acid in fortified foods and supplements have not resulted in masking of undiagnosed vitamin B_{12} deficiency in the population or delayed its diagnosis [13].

Soda bread was excluded from the scenarios for bread fortification because it may not be amenable to fortification as readily as other breads and considerable losses of folic acid occur. However, inclusion of soda bread in the simulation scenarios for bread fortification had little effect on risk of NTDs in women aged 18-50 years or on P_{95} or P_{99} of folic acid intake in older adults (data not shown).

The simulation scenarios examined for bread and flour include intakes of folic acid at current levels in voluntarily fortified foods and supplements, assuming the folic acid content of voluntarily fortified foods and supplements exceeded the declared value on the label by an average of 25%.

Conclusions

The three scenarios reduce the risk of NTD-affected pregnancies by approximately 17-32%, corresponding to an increase in the average daily folic acid intake of women of childbearing age of 77-151 µg. For these levels of addition of folic acid to bread and flour the risk of masking of undiagnosed vitamin B_{12} deficiency in older adults would be negligible. These levels of addition of folic acid to bread and flour would allow safe consumption of folic acid at current levels from other foods fortified with folic acid and supplements. Foods that are voluntarily fortified with folic acid reduce the risk of occurrence of NTD-affected pregnancies by about 11-14%.

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TERMS OF REFERENCE – FOLIC ACID WORKING GROUP

1. To provide an update on the data relevant to the prevention of pregnancies affected by NTDs in Ireland and to provide recommendations on 'best practice' monitoring systems necessary to generate these data into the future. The update should as a minimum, address the following questions:
   - What is the trend to date in pregnancies affected by NTDs in Ireland and what are the features of a 'best practice' monitoring system for NTDs?
   - What is the trend to date in blood folate status of the target group (women of childbearing age) and other population groups and what are the features of a 'best practice' monitoring system for blood folate status?
   - What is the dietary intake of folate, folic acid from fortified foods and food supplements among all sub-groups and what are the features of a 'best practice' monitoring programme for such dietary intake assessments?
2. To provide an update on the latest scientific developments relevant to safe and effective dietary intakes of folic acid for the target group (women of childbearing age) in addition to other population groups exposed.
3. To provide recommendations on suitable risk management options for the prevention of NTDs in Ireland.

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