

Report of the National Committee on Folic Acid Food Fortification

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Foreword

Message from the Chairperson

I am very pleased to present this report of the National Committee on Folic Acid Food Fortification (the Committee) to An Tanaiste and Minister for Health and Children, Mary Harney, T.D. The Committee was established in March 2005 by then Minister for Health and Children, Micheál Martin, T.D., with a remit to review evidence and to find the best solution to reduce the prevalence of neural tube defects (NTDs) in the national population.

Ireland has one of the highest rates of NTDs in Europe with between 49 and 93 babies affected every year. NTDs, the most common of which is spina bifida, are among the most frequently occurring human congenital malformations throughout the world. The physical, emotional and financial costs of NTDs are enormous and, can lead to lifelong stress and trauma for families.

Since 1991, it has been known that up to 70% of NTDs can be prevented by the consumption of folic acid. Ireland currently has had two key policies to increase folic acid intake in women of childbearing age: consumption of folic acid supplements and voluntary fortification of selected foods with folic acid. Experience over the past few years has shown that these policies have only been marginally successful in reducing the incidence of NTDs. The Committee considered other solutions to reduce the incidence of these debilitating diseases.

The Committee is recommending mandatory fortification of all bread on sale in Ireland, (with the exception of some minor bread products) at a level of 120µg per 100g of bread. This recommendation was considered to be the most effective public health intervention to prevent the occurrence of NTDs in women of childbearing age in Ireland. Similar levels of fortification in the US and Canada have safely reduced NTD levels by between 20 and 70%. Mandatory fortification will require changes to the legislation and minor modifications to the bread-making process. It will also require the introduction of comprehensive surveillance and monitoring programmes, to assess safety and efficacy of this public health measure, and recommendations to introduce these measures are included in the report. Also included are recommendations to improve the health promotion messages targeted at sexually active women of childbearing age.

It was an honour and most interesting experience to Chair the Committee. I would like to thank the members of the Committee for their invaluable contributions and for giving freely of their time and for the conscientious manner in which members approached their tasks. Thanks also to all those who made submissions to the Committee and contributed to the wide consultation process. The response to the consultation process from members of the public was excellent and we have endeavoured to address the various issues raised in this report.

Finally, I would like to thank the Food Safety Authority of Ireland (FSAI) for its administrative support and for pulling the various strands of the report together.

Ms Maureen Lynott

Chair
May 2006

Acknowledgements

The Committee would like to thank the many scientists, health professionals, communications and administration staff, both in Ireland and further afield, who contributed to this report.

The Committee is grateful for the advice provided by staff at the Centers for Disease Control and Prevention and Emory University in Atlanta, Georgia; the US Food and Drug Administration, Washington DC, and the National Health Institutes, Bethesda, Maryland; Health Canada, the Public Health Agency of Canada and the Canadian Food Inspection Agency, Ottawa, Ontario; Food Standards Australia New Zealand, Canberra; the Food Standards Agency, UK; the Folate Group in the Northern Ireland Centre for Food and Health, University of Ulster and the Dublin EUROCAT Registry of Congenital Anomalies, HSE - Eastern Region. The Committee is also thankful for the cooperation of the major bread-makers, millers and supermarket chains in Ireland.

The Committee greatly appreciates the contributions made by speakers and delegates at the National Seminar on Folic Acid Food Fortification held on the closing day of the public consultation (24th June 2005). Speakers included Dr Mary L'Abbé (Director, Bureau of Nutritional Sciences, Health Canada), Professor Hélène McNulty (University of Ulster), Dr David Wald (Cardiology Department, Southampton University Hospital), Dr Louise Sullivan (Food and Drink Industry Ireland, IBEC), Mr Reg Fletcher (Director of Scientific Research, Kellogg's Europe) and Professor John Scott (Department of Biochemistry, Trinity College, Dublin).

Finally, particular thanks are due to Dr Karen Harrington, Dr Maureen McGowan, Dr Peadar Kirke and Dr Evelyn Hannon for their assistance in the completion of the report.

Executive Summary

Background

Neural tube defects (NTDs) are severe abnormalities of the central nervous system that develop in babies during the first weeks of pregnancy. The most common NTD is spina bifida. NTDs are a major cause of mortality and morbidity especially in childhood with high proportions of those who survive having disabilities. Ireland has one of the highest incidence rates of NTDs in Europe with evidence of between 0.8 and 1.5 cases recorded per 1,000 births in Ireland, that is to say, between 49 and 93 babies affected per year. In addition, the genetic background for increased risk of developing NTDs is prevalent in the Irish population.

In the 1990s, the B vitamin, folate, provided in its synthetic form, folic acid, was proven to be effective in helping to prevent first occurrences of having a baby with a NTD and recurrences of having a second baby with a NTD in up to about 70% of cases. This led to recommendations to women of childbearing age in many countries to take an additional 400µg of vitamin folate daily to reduce the risk of developing NTDs if they were likely to become pregnant, in addition to meeting their individual adult needs (Recommended Dietary Allowance) for the vitamin.

As further evidence of the role of folic acid in the prevention of NTDs became available and a greater understanding of the different forms of the vitamin folate was gained, Irish recommendations to women on taking folic acid became more specific, as in many other countries. Women of childbearing age were specifically advised that if there was any possibility of becoming pregnant, the best way to take the recommended additional 400µg of folic acid daily, was in the form of a supplement.

However, advice to women of childbearing age, to take folic acid supplements if there is any possibility of becoming pregnant, has had little impact on reducing the incidence of NTDs in Ireland. Many challenges have been found in achieving these recommendations for additional folic acid, the

greatest being that less than 50% of pregnancies are planned. Thus, many women learn they are pregnant without having had the opportunity to follow recommended advice for planning a pregnancy.

Such findings led some countries, including Canada and the US, to implement a policy of fortification of cereal grains/flour with folic acid to reduce the risk of NTDs. This ensures an increased intake of folic acid by all women in the population at the time of conception. Compelling evidence from countries implementing mandatory folic acid fortification programmes has recently demonstrated that such a policy leads to significant reductions (ranging from 20-78%) in the incidence of NTDs. The amount of folic acid added to the food supply does not, however, provide enough to fully protect the unborn child, so Canadian and US women have been advised to continue to take folic acid supplements.

In 2002, the Department of Health and Children asked the Food Safety Authority of Ireland (FSAI) for advice with regard to folic acid fortification. In 2003, the FSAI recommended a policy of mandatory fortification of flour with folic acid. In 2004, the National Committee on Folic acid Food Fortification was established by the Minister for Health and Children under the secretariat of the FSAI to further examine the option of a mandatory folic acid fortification policy for Ireland for the prevention of NTDs given the high incidence in Ireland.

The Committee was tasked with:

- reviewing options for the fortification of foods with folic acid
- addressing the broader aspects of policy implementation, including technical issues on folic acid food fortification, risk assessment and examination of reported health benefits associated with increased levels of folic acid in the diet.

The following tasks were completed to fulfil the terms of reference and to produce the conclusions and recommendations of the Committee:

- consultation and dialogue with relevant industries to develop viable options for folic acid food fortification in Ireland
- obtaining international expertise and advice from countries that have implemented national folic acid food fortification programmes
- consultation with stakeholders in Ireland on the best options for moving forward
- exploring strategies for addressing technical issues arising from folic acid food fortification
- developing a comprehensive evaluation plan, designed to monitor the effectiveness and safety of the folic acid fortification intervention
- hosting a national seminar for health professionals, food scientists and industry technologists on folic acid food fortification in Ireland.

Issues Addressed

The following points summarise the issues considered and researched as part of the work of the Committee:

- **The role of folic acid in the prevention of NTDs in Ireland**

Since scientific evidence became available in the early 1990s that folic acid (the synthetic form of the B vitamin folate) could help prevent first occurrences of NTDs and recurrences of NTDs in up to about 70% of cases, countries (including Ireland) made recommendations to women of childbearing age to take folic acid supplements with 400µg of folic acid daily. This amount of folic acid was to be taken to prevent NTDs in a potential pregnancy and was in addition to a woman's daily adult needs (RDA) for vitamin folate.

In Ireland, as in other countries, this recommendation has not been easily achieved by women and thus the incidence of NTDs has not declined in Ireland with this advice. Evidence

highlights many reasons for this and a major reason is that less than 50% of pregnancies in Ireland are planned and NTDs occur in the early weeks of pregnancy when a woman may not realise she is pregnant.

Thus, an alternative option of supporting women of childbearing age, who are sexually active to try and take in the special requirement of folic acid for prevention of NTDs was needed. As mandatory folic acid fortification of cereal grains/flour is used in the US and Canada with successful reductions in the incidence of NTDs, this option offers potential to Ireland.

- **The food sources of vitamin folate: natural folates and folic acid**

The B vitamin, folate, exists in different forms - folic acid, the synthetic form that is added to some foods and is found in supplements and natural folate that exists naturally in food. Natural folate is less easily absorbed into the body than folic acid taken as supplements or in fortified foods. Thus, increasing a woman's intake of vitamin folate through food sources with natural folate only is unlikely to reduce the risk of a NTD affected pregnancy. Folic acid food sources are, however, important.

- **Current food sources of folic acid in Ireland**

Foods that have folic acid added to them (referred to as fortified foods) are currently available in Ireland (some varieties of breakfast cereals, cereal bars, milks, yogurts, fruit drinks, bread and rolls). They are, however, found to contribute only small amounts of folic acid to the diets of women of childbearing age, with many women consuming none of these foods. Generally, these foods are fortified with folic acid to provide between 20 and 33% of an adult's daily needs for vitamin folate.

Taking steps to increase the range of foods fortified with folic acid or the amount of folic acid added to these foods could lead to over-consumption by some groups of the population and would not cover the needs of those women who choose not to eat these foods.

- **Folic acid intakes in Irish women of childbearing age**

Over a third (35%) of women of childbearing age living in Ireland consume no folic acid at all, according to a recent study on food intakes of Irish adults (58). They did not choose foods with added folic acid (fortified foods) or folic acid supplements.

- **The risk of NTDs is reduced with improved folate status**

There is evidence in Ireland that the number of pregnancies affected by NTDs decreased with improved folate status of the mothers. Thus, with mandatory folic acid food fortification which can result in improved dietary intakes of folic acid, the folate status of mothers at the time of conception would be improved. This is important, given that many women forget to take the recommended folic acid supplement.

- **Selection of a suitable food vehicle for folic acid fortification**

Staple foods, such as bread or flour are chosen for mandatory folic acid food fortification programmes because they meet the necessary criteria of being:

- a) consumed regularly, and in sufficient quantities by women of childbearing age, to ensure the intake of folic acid will be sufficient to reduce the incidence of NTDs
- b) a food that is encouraged as part of a healthy diet
- c) a food product that can offer consumer choice by omitting some varieties from the fortification programme.

The Committee recommend bread rather than flour or all flour-containing foods, as the vehicle of choice for a mandatory folic acid fortification programme in Ireland.

Other flour-containing foods such as cakes, biscuits, crackers and confectionery products are food categories that are advised in limited amounts daily to avoid high fat, salt, sugar and energy intakes in accordance with healthy eating guidelines.

A survey of bread consumption, commissioned by the Committee, confirmed that women of childbearing age eat bread. This helps to ensure a fairly even distribution of intake of folic acid among all women, which is of particular importance for women from disadvantaged backgrounds for whom other sources of folic acid may be economically out of reach.

The analysis work by the Committee found that folic acid can be added to bread in amounts that can reduce the incidence of NTDs in Ireland without risks to other sub-groups of the population.

- **Consultation to consider the views and concerns of Irish consumers and industry**

A public consultation was conducted to receive comments from the widest possible number of people on ways to increase the average folic acid intakes of women of childbearing age to reduce the incidence of NTDs in Ireland. This was crucial to address if there would be support, in particular from the public and food industry, for mandatory folic acid food fortification. The results of the consultation highlighted support for mandatory folic acid fortification of bread or flour by over three-quarters (77.1%) of the submissions made.

- **Technical issues involved in folic acid fortification of bread in Ireland**

All relevant industry sectors (flour millers, improver/flavouring ingredient suppliers and large bread manufacturers) are willing to participate, as required, in a national folic acid food fortification programme and have attended meetings where technical issues associated with the implementation have been identified.

The technology for fortifying bread with folic acid exists in Ireland but the best method for implementing the mandatory folic acid fortification of a specific range of breads needs to be identified and tailored to meet the specific needs of the Irish market.

It is recommended that a committee, charged with the implementation of the fortification programme, should be established to decide on technical and logistical details involved, including the point of addition of folic acid, labelling, trade and cost issues, consumer acceptability, communication, promotion and advertising.

- **Consideration of the risks and benefits of folic acid fortification**

Analysis was conducted to find a folic acid fortification level for Ireland with maximum benefits and minimum risks involving careful consideration of the latest evidence in relation to folic acid and various conditions and situations. The main benefit of interest was the prevention of NTDs in Ireland and the potential risk considered in the analysis was the masking of vitamin B₁₂ deficiency.

The full recommended amount of folic acid (400µg) to prevent risk of NTDs cannot be added to bread, as this would result in excessive intakes by others in the population. A dual approach is thus needed for protection against NTDs - folic acid food fortification together with taking folic acid supplements by all women of childbearing age who are sexually active.

- **Very high intakes of folic acid can mask a deficiency of vitamin B₁₂**

A deficiency of vitamin folate and vitamin B₁₂ has the same clinical effects in the body, megaloblastic anaemia. Very high amounts of folic acid can actually correct the anaemia associated with B₁₂ deficiency, and therefore hide the presence of the deficiency but allow the other problem of B₁₂ deficiency (neurological disease) to continue. This fact was considered by the Committee in its analysis of a suitable fortification level of folic acid for Ireland.

- **Monitoring**

As part of mandatory folic acid food fortification, the need for a science-based monitoring plan has been highlighted, through the experience of others to date. This is crucial to ensure long-term effectiveness and safety of the intervention.

- **Health promotion**

The Committee revised current recommendations to women regarding folic acid supplements to specifically advise all women of childbearing age who are sexually active to take an additional 400µg of folic acid daily in the form of a supplement.

The need for an integrated national health programme to be launched as part of the introduction of mandatory folic acid fortification was recommended.

- **An understanding of the true incidence of NTDs in Ireland**

The Committee reports that the true incidence of pregnancies affected by NTDs in Ireland is likely to be underestimated, due to the absence of a national birth defects register and due to the complete lack of data on affected pregnancies that do not reach term.

The current NTD incidence rate at birth of between 0.8 and 1.5 cases per 1,000 births is thus an underestimation of the total number of pregnancies affected by NTDs.

Despite this underestimation, Ireland has one of the highest incidence rates of NTDs in Europe. Recent evidence of the Irish population having a genetic make-up that is vulnerable to the development of these birth defects, contributes to this high incidence. Each year no preventive action is taken, the number of babies affected by NTDs continues to increase.

Conclusions and Recommendations of the Committee

The broad conclusions of the Committee are that:

- It is established that consumption of folic acid on a daily basis, before conception and during the first 12 weeks of pregnancy, can protect up to about 70% of pregnancies from the development of a NTD. Public health policy recommends women take 400µg of folic acid prior to conception and for the first 12 weeks of pregnancy in order to reduce the risk of these serious birth defects. It should be noted, however, that folic acid does not protect against the development of all NTDs. It is known that approximately 30% are related to other unknown causes and are not prevented by taking folic acid

- A national policy of mandatory fortification of bread with folic acid will contribute significantly to the reduction in the numbers of babies born with NTDs in Ireland. This approach represents the most effective means of increasing women's folate status at the time of conception. It will significantly reduce folate deficiency and ensure that all women of childbearing age consume at least 25% of their special folic acid requirements for the prevention of NTDs on an on-going basis. This policy will require legislative change
- The best and most reliable scientific evidence indicates that enriching most bread with folic acid at a level that delivers 120µg per 100g of bread as consumed, will be both effective and safe. It will reduce the incidence of NTD-affected pregnancies by about 24% and will ensure that older adults do not consume excessive amounts of folic acid. In addition, it will yield other health benefits associated with eradicating folate deficiency, in particular, prevention of anaemia due to a shortage of vitamin folate in older adults. Available evidence indicates a possible (modest) reduction in cardiovascular disease risk in adults at this level of folic acid fortification, but this requires further confirmation
- While the level of addition of folic acid to bread will significantly reduce the incidence of NTDs, it will not, however, provide women of childbearing age with the full amount of folic acid they are recommended to consume for protection of their pregnancies. This means that the policy of recommending folic acid supplements for women of childbearing age needs to continue, in conjunction with a policy of mandatory fortification. Prevention of NTDs in Ireland, therefore, requires the dual approach of mandatory folic acid fortification of most breads and provision of advice to women who are sexually active and may become pregnant about the importance of taking folic acid supplements
- Folic acid fortification of bread is technically achievable for the main types of bread marketed in Ireland. Labelling, nutrition and health claims can be accommodated within existing or proposed national and European Regulations. Trade issues may arise, but can be managed
- Consumer choice can be accommodated by the exclusion of some minor bread products and retail flour from the mandatory requirement for fortification
- Monitoring is essential to ensure the fortification programme is implemented in a manner that is both effective and safe. Monitoring the levels of folic acid added to bread will be necessary to ensure compliance with food regulations. Monitoring the levels of folic acid added to foods voluntarily fortified with folic acid and to supplements will be necessary to ensure the maximum levels currently being set, in association with food regulations, are not exceeded. Monitoring dietary intake of the B vitamin, folate, and blood levels of folate within the various population sub-groups will provide an overall assessment of the programme's impact on folate intake and status. Finally, monitoring the incidence of NTDs will assess the effectiveness of the programme in terms of the main intended outcome.

Recommendations of the Committee

The recommendations of the Committee are that:

Recommendation 1: Policy Aspects of Folic Acid Food Fortification

- All bread (white, wholemeal and brown) manufactured or marketed in Ireland, with the exception of minor bread products, should be fortified on a mandatory basis with folic acid at a level which provides 120µg per 100g of bread as consumed.
- Consumer choice should be accommodated by excluding minor bread products as well as retail flour, from the mandatory fortification programme.
- An implementation group should be established to oversee the operational issues associated with these recommendations and to advise the Minister for Health and Children on progress.

Recommendation 2: Legislation and Folic Acid Food Fortification

- The Department of Health and Children should make new Regulations that would introduce mandatory fortification of all bread marketed in Ireland, with the exception of minor bread products.
- The new Regulations should provide for upper and lower tolerance limits around 120µg folic acid per 100g bread which will be set by the implementation group following consultation with the industry.
- The new Regulations should address labelling and health and nutrition claims for breads fortified with folic acid.

Recommendation 3: Technical Aspects and Folic Acid Food Fortification

- The implementation group should consult with industry to determine the most appropriate point(s) in the bread-making process to add folic acid.
- Technical guidance and codes of practice should be developed to support ongoing quality assurance of the folic acid fortification process.

- External assessment procedures should be put in place to monitor the folic acid fortification levels of all fortified breads, compliance with the labelling format and health claims provided for in food regulations.
- An adequate lead in time before enactment of the legislation on folic acid fortification should be given to allow for adequate preparation by industry.

Recommendation 4: Monitoring the Effects of Folic Acid Food Fortification

- An assessment of all pregnancies affected by NTDs, including those that do not reach term, should be undertaken immediately to establish a baseline for monitoring.
- A national congenital birth defects register, that records all pregnancies affected by birth defects, including those that do not reach term, should be established without delay for ongoing surveillance purposes.
- To assess the impact of the fortification programme on the population, the measurement of blood parameters relevant to folate status of all age/sex groups should be undertaken immediately to establish a baseline for monitoring and this should be repeated at regular intervals.
- Dietary intakes of the B vitamin, folate, in all population sub-groups should be monitored regularly and these assessments should distinguish between intakes of naturally occurring food folate and folic acid from fortified foodstuffs and supplements.
- Monitoring of folic acid levels in breads should be included as part of the national food monitoring and surveillance programme.
- Monitoring of folic acid levels in foods that are voluntarily fortified with folic acid and in supplements available in Ireland, should be included as part of the national food monitoring and surveillance programme.
- The implementation group should report to the Minister for Health and Children on the overall impact of the fortification programme as identified by the monitoring programmes.

Recommendation 5: Health Professionals and Folic Acid Food Fortification

- All relevant health professionals should be updated on the implications of the mandatory folic acid food fortification programme and on the need to continue to advise women of childbearing age who are sexually active to take folic acid supplements.
- Written and web-based material outlining the implications of the folic acid fortification programme for women's health should be made widely available by health professional representative bodies and agencies.
- The implementation group should address barriers to folic acid supplement use, including cost and availability.
- All relevant health professionals should be aware that high dose folic acid supplements may increase the risk of masking B₁₂ deficiency.

Recommendation 6: Folic Acid Supplements

- While the level of addition of folic acid to bread will contribute to a reduction in the incidence of NTDs, it will not, however, provide women who could become pregnant and are sexually active, with the optimal level recommended for protection of their pregnancies. Therefore, the policy of recommending folic acid supplements for women needs to continue.

Recommendation 7: Health Promotion Needs

- Awareness of the need for women of childbearing age who are sexually active to take folic acid supplements should be actively and vigorously promoted through a national integrated health promotion programme involving all stakeholders across all settings.
- Awareness of the need for women of childbearing age who are sexually active to take folic acid supplements should be promoted by the relevant Government departments.

1. INTRODUCTION

1.1 Background

Neural tube defects (NTDs) are severe abnormalities of the central nervous system that develop in babies during the first weeks of pregnancy. NTDs are a major cause of mortality and morbidity, especially in childhood. High proportions (85%) of the babies who survive have disabilities that can include major limitations in mobility, bowel and bladder incontinence, hydrocephalus or intellectual disability. Despite a marked decline in incidence of NTDs over the past three decades, Ireland continues to have one of the highest incidence rates in Europe. Between 49 and 93 babies are born with NTDs each year in Ireland and many more affected fetuses are lost as miscarriages. The most common NTD is spina bifida.

Since the early 1990s, it has been known that folic acid taken by women before conception and for the first few weeks of pregnancy can prevent up to about 70% of NTDs. Recommendations that all women capable of becoming pregnant should take 400µg of folic acid every day were issued by the Governments of many countries, including Ireland. Thus, since 1993, women of childbearing age in Ireland have been advised by the Department of Health and Children, if there is any chance that they may become pregnant, to take folic acid tablets (supplements) and also to eat foods that are rich in natural folate or fortified with folic acid.

However, similar to the experience in other countries, this policy has not proved to be effective in reducing the number of pregnancies affected by NTDs (6). In 2001, research in Ireland among pregnant women, indicated that only about one in five take folic acid supplements during the recommended timeframe. There are three main reasons for this:

1. About half of all pregnancies are unplanned and these women are unlikely to consume folic acid supplements.
2. There is inadequate knowledge among women of the benefits of folic acid to a healthy baby. Even when women know about folic acid, not all of them take the necessary action.
3. The cost of folic acid supplements may be a barrier for women from disadvantaged backgrounds - a population sub-group where pregnancies affected by NTDs are more common.

In the late 1990s, this situation led some countries, including Canada and the United States (US), to implement a policy of fortification (the addition of vitamins and minerals to foods) of cereal grains/flour with folic acid - a step that ensures an increased intake of folic acid by all women at time of conception. The amount of folic acid added into the food supply does not, however, usually provide enough to fully protect unborn children. Therefore, Canadian and American women of childbearing age continue to be advised to take folic acid supplements. In recent years, Canada and the US have issued several reports that show that fortification of cereal grains has been very effective - resulting in reductions in the birth incidence of NTDs by 20-78% (45,55,72,98).

Data from Canada indicate that about 50% of pregnancies affected by NTDs are terminated (45,72,98). Recent data from European countries, where folic acid food fortification programmes do not exist, would suggest that the true incidence of NTDs is even higher (Botto *et al* 2005). In Ireland, however, termination of pregnancy is illegal. Therefore, in Dublin, the proportion of pregnancies affected by NTDs that are delivered as live-births is much higher (81%) compared with other European centres, e.g. 10% in London or 20% in Barcelona. Thus, NTDs have a considerably greater impact in Irish society than elsewhere, placing a greater onus on Ireland to maximise the primary prevention of these conditions.

Vitamin Folate is a B vitamin needed by the body. It exists naturally in some foods (natural folate). A synthetic or man-made form of the vitamin called folic acid is added to some foods (fortified foods) or is found in supplements.

Folic acid food fortification - the addition of folic acid to foods.

In June 2002, the Department of Health and Children asked the Food Safety Authority of Ireland (FSAI) for advice with regard to folic acid food fortification. Following consideration by the FSAI Scientific Committee and Nutrition Sub-committee, the FSAI reported policy advice to the Department in June 2003, which recommended the mandatory fortification (the obligatory addition of folic acid to food by legislation) of flour with folic acid. The Chief Medical Officer concluded in his fourth Annual Report that *“the case for fortification of flour is sufficiently robust to recommend moving to the next stage, namely a consultative process to deal with the technical and other aspects of implementing policy.”*

1.2 Terms of Reference

The Minister for Health and Children set up the National Committee on Folic Acid Food Fortification in late 2004 and requested the FSAI to act as the secretariat to the Committee. The Committee was tasked with reviewing options for the fortification of foods with folic acid in view of the relatively high level of NTDs in Ireland. In carrying out its work, the Committee was requested to address the broader aspects of implementing this policy, including the technical issues surrounding folic acid food fortification, risk assessment, and examination of other reported health benefits that are linked to increased levels of folic acid in the diet.

1.3 The Main Work Carried out by the Committee

The Committee developed a workplan and carried out tasks that ensured that the terms of reference were fulfilled. The work undertaken involved the following:

- **consultation and dialogue with relevant industries to develop viable options for folic acid food fortification in Ireland**
- **obtaining international expertise and advice from countries that have implemented national folic acid food fortification programmes**
- **consultation with stakeholders in Ireland on the best options for moving forward**
- **exploring strategies for addressing technical issues arising from folic acid food fortification**
- **developing a comprehensive evaluation plan, designed to monitor the effectiveness and safety of the folic acid fortification intervention**

- **hosting a national seminar for health professionals, food scientists and industry technologists on folic acid food fortification in Ireland.**

1.3.1 Consultation and dialogue with industry

The food industry was represented on the Committee and a special Sub-committee was established to explore the technical issues involved in folic acid food fortification. One of the first tasks of this Sub-committee was the identification of the most suitable food vehicle for folic acid food fortification in Ireland. Once the food vehicle was established, the Sub-committee met with representatives of the relevant industries involved, with a view to exploring the technical issues involved and how to deal with them.

1.3.2 Obtaining international expertise and advice

Over 40 countries fortify flour or bread with folic acid for the purpose of prevention of NTD birth defects. Communication links were established with many experts in these countries in order to benefit from their knowledge and experience to date. In particular, the experience, expertise and the reliable evidence of the impact of folic acid food fortification in the US and Canada were considered of paramount importance for guiding best practice in Ireland. National programmes for the mandatory folic acid fortification of flour and all flour-containing products have been ongoing in these two countries since 1998.

Direct contact was established with experts in the US and Canada. In addition, links were established with Food Standards Australia New Zealand which is currently engaged in public consultations on mandatory folic acid food fortification. Finally, dialogue on the issue was initiated with Member States in the European Union.

Communications with international experts were very helpful to the overall process. Apart from ensuring that all relevant issues around folic acid food fortification were covered comprehensively, there was tremendous interest in the Irish venture. There was unanimous agreement that the situation in Ireland, where the incidence of NTDs is relatively high and there is no option for secondary prevention, represented a special case for a most serious consideration of folic acid food fortification. The international evidence available over recent years on the effectiveness of public health measures made the case even more compelling.

1.3.3 Consultation with stakeholders in Ireland

A formal public consultation process was launched on 21 March, 2005 and continued over a period of three months until 24 June, 2005. During the process, advertisements were placed nationally in newspapers and on television, aimed at encouraging all who wished to do so, to make submissions. In addition, presentations were mounted with a view to raising awareness and leaflets were distributed outlining how a submission could be made. Groups who could bring a particular expertise to the debate were directly invited to make submissions (see Chapter 5) and a total of 513 submissions were received.

1.3.4 Exploring strategies to address technical issues

Following the identification of bread as the most suitable food vehicle for fortification, the Sub-committee on technical issues met with representatives of the relevant industries involved. This led to the development of a comprehensive outline of the technical issues involved. One segment of the public consultation dealt with specific questions for the food industry on the technical issues identified. Discussion and debate on these issues took place at the National Seminar on Folic Acid Food Fortification, where a special session was devoted to the food industry perspective. Having completed the public consultation process and hosted the national seminar, meetings were convened with wider groups of food industry stakeholders to establish how the technical issues involved in a mandatory folic acid food fortification programme could be best addressed (see Chapter 6).

1.3.5 Monitoring the effectiveness and safety

One of the key lessons learned during the implementation of national folic acid food fortification programmes in the US and Canada concerned the need for a comprehensive evaluation plan to monitor the effectiveness and safety of the fortification intervention. Such an evaluation plan should extend beyond assessments that ensure that the fortification programme is being implemented

in accordance with the relevant legislation (food monitoring) and the main outcome (incidence of NTDs), to include actual changes in folate status and related nutrients. Special Sub-committees were established to explore how such an evaluation process could be established in Ireland (see Chapter 7).

1.3.6 National seminar on folic acid food fortification

A national seminar was held for health professionals with a particular interest in women and child health issues and public health, food and nutrition scientists and technologists, researchers in epidemiology and surveillance, and representatives of consumer and food industry stakeholder groups. The seminar was held on the closing date of the public consultation, the results of which were not available for delegates. The seminar was held in closed session and was designed to facilitate debate on folic acid food fortification.

A keynote speaker from Health Canada outlined the effects and experience of mandatory national folic acid food fortification, as initiated in Canada in 1998. The rationale for, and the development of, policy for the addition of minerals and vitamins to foods in Canada since then, was also described. Finding the best policy for health in regard to folic acid food fortification continued with an exploration of the issues around dietary folate intake and status in terms of bioavailability of the natural and synthetic forms of the vitamin in the context of strategies to prevent neural tube defects. This session concluded with a presentation on the potential of folic acid to prevent heart disease and stroke. A session on the 'Food Industry Perspective' involved presentations by speakers from the food industry on foods that are suitable for a national folic acid fortification programme and on the role of other folic acid fortified foods in the Irish diet. The seminar concluded with a presentation outlining research needs for monitoring and evaluation as we move forward on the prevention of NTDs in Ireland.

2. NEURAL TUBE DEFECTS AND THE ROLE OF FOLIC ACID

Key Conclusions

- Ireland has one of the highest incidence rates of NTDs in Europe, with evidence of between 0.8 and 1.5 cases recorded per 1,000 births in Ireland (between 49 and 93 babies affected per year).
- The true incidence of pregnancies affected by NTDs in Ireland is likely to be underestimated due to the absence of a national congenital birth defects register and due to the absence of data on pregnancies that do not reach term.
- The genetic background for increased risk of developing NTDs is prevalent in the Irish population (recently, 50% of pregnancies in Ireland were estimated to be vulnerable).
- It is proven that folic acid can help prevent the first occurrence of NTDs (having a NTD affected baby for the first time) and recurrence of NTDs (having a subsequent affected baby after already having one affected baby), in up to about 70% of cases.
- Current policy advising women to take folic acid supplements has not been effective in reducing the incidence of NTDs in Europe or in North America and folic acid food fortification is now used in over 40 countries to address the risk of NTDs.

2.1 Background

Neural tube defects (NTDs) are serious birth defects, which constitute an important public health problem in terms of mortality, morbidity, social cost and human suffering (56). Overwhelming evidence exists since the early 1990s that increased intakes of the vitamin folate in its synthetic form, folic acid, can prevent up to about 70% of these birth defects (23,83). Since that time, there has been intense debate in many countries about what might be the most effective strategy to increase women's intake of folic acid and so reduce the risk of developing NTDs in such a large number of cases.

Many countries, including the US and Canada, since 1998, have implemented folic acid food fortification programmes to reduce the risk of NTDs. Recent reports outline the tremendous success of these mandatory food fortification programmes in reducing the incidence of NTDs in these countries, leading to the need to consider this option in Ireland. Ireland currently has a high incidence of NTDs and a population that is vulnerable to the development of these birth defects, due to the Irish genetic make-up.

This section of the report describes NTDs, including information on the incidence in Ireland and the associated burden of disease in this country compared with others. An outline of the genetic basis for the development of NTDs in Ireland and how increased intakes of folic acid can help protect against the development of NTDs is given. Finally, an overview of folic acid food fortification in other countries is given in the context of the different public health options for addressing the high incidence of NTDs in Ireland.

2.2 What are Neural Tube Defects (NTDs)?

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 are just beginning to suspect 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 a NTD.

NTDs can involve the brain, spinal cord, meninges (covering membranes), skull and spine (91). There are many different malformations involved and the terms used to describe them are based on clinical descriptions and the presumed embryological defect. The terminology in the literature may vary. These defects include spina bifida (accounting for approximately 51% of NTDs), anencephaly (40%), encephalocele (8%) and iniencephaly (1%).

Further details describing NTDs are outlined in the following section:

The Morbidity and Mortality Associated with NTDs

About 80% of babies with spina bifida and encephalocele survive the new-born period but the vast majority (85%) of these children have lifelong moderate or severe handicap. Spina bifida, which accounts for half of all NTDs, involves incomplete formation of the spine during the first four weeks after conception (see Figure 2.1). The vertebrae (bones in the spine) do not completely fuse around the part of the spinal cord they are meant to protect. The unprotected part of the spinal cord may protrude through the defect. Although the spinal defect can sometimes be repaired through surgery, any nerve damage that has already occurred may be permanent. This initial surgery can be followed by more surgeries during the child's first years. Other complications may also develop. These include:

- hydrocephalus, an accumulation of cerebrospinal fluid surrounding the brain
- foot and knee deformities caused by an interruption of spinal nerve pathways, requiring leg braces, crutches, and other devices to help children walk
- learning disabilities and slight to severe mental retardation, which can affect up to 30% of children
- chronic bladder and bowel malfunctions which may lead to chronic bladder infections and kidney problems requiring life-long medical attention (69).

Despite their need for medical attention, children with spina bifida can learn to care for many of their own needs and lead fulfilling lives.

The most severe forms of NTDs, anencephaly and iniencephaly, are fatal. During the period of neural tube development, an extension of the spinal cord forms the brain. Failure of this process results in anencephaly - a condition incompatible with survival - which accounts for up to 40% of NTDs in Ireland. Babies affected by anencephaly die later on during pregnancy or shortly after delivery. Severe NTDs tend to occur with disproportionate frequency in areas of overall high incidence (7). During the late 1970s and early 1980s, Ireland was a high incidence area for NTDs, with an elevated rate of severe NTDs (18). A decline in rates of severe forms such as anencephaly is particularly evident within the overall decline in rates of NTDs in Ireland (18).

The short timeframe for the normal development of the neural tube means women need increased intakes of folic acid before the pre-conception period.

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 even 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 to intervene in order to ensure normal closure of the neural tube. 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. Studies in Ireland have revealed that only between 40 and 45% of women plan their pregnancy (77-80,88,113). To reduce the numbers of babies born with NTDs, therefore, all women of childbearing age who are sexually active, need to take folic acid supplements.

2.3 Incidence of NTDs

While there has been a decline in many parts of the world in the incidence of NTDs, in Ireland the decline observed in the 1980s appears to have levelled off during the early 1990s. In Ireland, accurate and reliable data on the pregnancies affected by NTDs in Ireland are currently lacking. This is due mainly to the absence of a register that provides national cover and to the complete lack of data on affected pregnancies that do not reach term. Unlike missed cases at birth, affected pregnancies that do not reach term can never be accounted for and there is no estimation of the number of cases involved. Furthermore, the increasing diversity in the Irish population over recent years is likely to contribute to this source of bias over time.

The current incidence rate at birth of between 0.8 and 1.5 per 1,000 births suggests that between 49 and 93 babies are born with NTDs each year in Ireland (61,684 total births in Ireland in 2004), but this is an underestimation of the total number of pregnancies affected by NTDs. The fact should be borne in mind, however, that every year no preventive action is taken, the numbers of babies

affected by NTDs continues to increase. Thus the numbers of babies affected by NTDs is cumulative. During the period of 14 years since 1991, when it was established that up to about 70% of NTDs could be prevented through increased intake of folic acid, the number of preventable cases rests between 480 and 911 in Ireland.

Information on the incidence of NTDs in countries across the world and in Ireland is provided in detail in section 2.3.

2.3.1 Trends over time in the incidence of NTDs

There has been a decline in many parts of the world in the incidence of NTDs. This decline appears to have begun earlier in some places than in others, e.g. The Netherlands in the 1950s (108), and the United Kingdom in the 1970s (60).

Serum screening for alpha-fetoprotein in pregnant women has been introduced in many countries for the detection of open neural tube defects. Roberts *et al* (107) reported on the impact a prenatal screening programme in Atlanta (Georgia, US) had on the incidence of NTDs for the two years 1990 and 1991. Due to selective termination of affected pregnancies detected prenatally, the incidence of anencephaly was reduced by 49% and spina bifida by 23%, with a total reduction in NTD births of just 32%. This type of prevention programme is a secondary action as it does not address the prevention of the NTD, which is obviously the most important issue.

Although the decline in NTD birth incidence in the UK and Ireland since the early 1980s is partly due to prenatal diagnosis and selective termination of affected pregnancies, nonetheless, a decrease in incidence is still apparent when terminated pregnancies are included. However, this trend towards decreasing incidence of NTDs appears to have levelled off during the early 1990s. For example, between 1974 and 1994, the estimated total incidence per 1,000 births in the United Kingdom and Wales decreased from 3.35 to 0.79, then remained static through the early 1990s (93). The crude birth incidence per 1,000 in Dublin also decreased from 4.69 to 1.16 between 1980 and 1994, then remained static through early 1990s (78-80). It is not known why this decline has occurred in so many countries, but improved nutritional awareness, better prenatal detection and increased use of prenatal screening programmes to terminate affected pregnancies have contributed.

2.3.2 Incidence of NTDs in Ireland

Accurate data on the incidence of pregnancies in Ireland affected by NTDs are lacking. This is mainly due to the fact that there has never been a national register for Ireland that collects information for the entire country on the pregnancies affected by NTDs. In addition, there are a lack of data on pregnancies that do not reach full-term. Unlike missed cases at birth, affected pregnancies that do not reach full-term can never be accounted for and there is no estimation of the number of cases involved.

The only available data on the incidence of NTDs in Ireland are provided through the European Surveillance of Congenital Anomalies (EUROCAT)*. The EUROCAT data for Ireland however, does not have information on all births in the country, it only covers approximately two-thirds of births (see Figure 2.2).

* EUROCAT is a network of registries of birth abnormalities involving 17 countries in Europe that work together in the area of surveillance and monitoring. EUROCAT includes 36 registries which are registries from different areas of the countries in Europe involved. The EUROCAT central registry database dates from 1980. The registries are based on live-births, still-births and terminations in European countries. Data on terminations are not included in the Irish registries.

There have been up to five EUROCAT registries in Ireland providing data on the live-births and still-births affected by birth abnormalities. The data provided collectively from these EUROCAT registries for incidence of NTDs in Ireland are limited however, as described by McDonnell *et al* 2004 (76):

- data are not available regarding early foetal loss or termination of pregnancy and
- births in the geographic areas of the North, West and Midlands are largely excluded from these registries (see Figure 2.2).

A recent report, which focused mainly on information from the three registries operating along the east of Ireland (76), provided the following information:

- the incidence of NTDs in Ireland has been declining over the past two decades from a high of 4.8 per 1,000 births in 1980 to the current rate of 0.8-1.5 in every 1,000 births in 2001 (see Figure 2.3). Please note this figure presents data on rates of NTDs per 10,000 births i.e. 8-15 NTDs in every 10,000 births

- the registries for areas in the eastern region of Ireland¹ recently reported that during the five-year period between 1997 and 2001, 163 children were born with NTDs in this region. Overall, 52% had spina bifida (83 out of 163), 33% (54 out of 163) had anencephaly and the remainder (16%) had encephalocele. The overall rate of NTDs in this region of Ireland for the five-year period was 1.04 in every 1,000 births, a rate which was generally stable in that time. There was, however, some variation in the rate within the region. The rate of NTDs was 1.0 in every 1,000 births in the former Eastern Regional Health Authority in 2001 while the rate in the former South Eastern Health Board area was 1.3 in every 1,000 births in 2001.
- in Ireland, NTDs account for more perinatal (around the time of birth) deaths than any other group of birth defects. In 1999, for example, there were 23 perinatal deaths due to anencephaly and eight due to spina bifida, while congenital abnormalities of the heart accounted for 19 deaths and DNA abnormalities accounted for 14 deaths.

2.3.3 Geographic variation in the incidence of NTD

There is marked geographic variation in the incidence of NTDs with reports of Ireland and the UK having the highest rates in Europe for many decades (28;97). Data published by the coordinators of the 1980-1992 EUROCAT register, in European countries, demonstrated total incidence ranging from 0.53 per 1,000 births in Switzerland to 2.9 per 1,000 births in Glasgow (17). Excluding therapeutic abortions (terminations), which are not legal in Ireland, the sub-set of live-birth and still-birth incidence varied similarly, from 0.2 per 1,000 births in Paris to 1.88 per 1,000 births in Dublin (17).

Recent data confirm the particularly high rate of pregnancies affected by NTDs in Ireland compared to other countries (6). Of 13 birth defects registries monitoring rates of NTDs from 1988 to 1998 in 11 countries², Ireland was shown to have the highest rates of NTDs (see Figure 2.4). In the report by Botto *et al* (6) cases of NTDs were ascertained among live-born infants, still-births, and pregnancy terminations (where legal). Ireland is the only country in this report to have no data on terminations of affected pregnancies, therefore, a higher incidence rate, due to not accounting for terminated pregnancies, is almost certain.

¹ The region served by the former Eastern Regional Health Authority, North Eastern Health Board and South Eastern Health Board.

² Norway, Finland, Northern Netherlands, England and Wales, Ireland, France (Paris, Strasbourg, and Central East), Hungary, Italy (Emilia Romagna and Campania), Portugal and Israel.

There is an association between social disadvantage and higher risk of NTDs.

Data are available from several countries up to the mid-1970s which strongly demonstrate a higher incidence of NTDs in babies of women of low socio-economic status: Britain (1,27), Australia (32), Finland (49) and the US (94). More recent data concerning the relationship between socio-economic status and NTDs are limited (128).

2.4 The Burden of Disease Associated with NTDs in Ireland

For a number of reasons, NTDs are a larger health issue in Ireland than in other countries. Despite a marked decline in incidence during the past three decades, the incidence at birth of these conditions remains higher in Ireland than in many other countries. As noted above, many countries in Europe and elsewhere, use the secondary prevention approach of termination of pregnancy as a means of dealing with affected pregnancies, but this intervention is illegal in Ireland.

A recent analysis of data on the incidence at birth of NTDs is presented in Table 2.1 for all of the birth defect registries in Britain and in other selected European centres, including Dublin, for different categories of NTD births (65). The proportion of pregnancies affected by NTDs that are delivered as live-births is much higher in Dublin (81%) than elsewhere (for example 13% in North Thames and 18% in Barcelona). This reflects the use of termination of pregnancies in the other centres and its non-use in Dublin.

Also, shown in Table 2.1, is the live birth rate for babies born with spina bifida or encephalocele. The vast majority of these babies who survive to their first birthday will survive long-term. Currently, about 50% to 60% of these children survive to one year (65). Research conducted by the Health Research Board has found that high proportions (75%) of the babies who survive have major disabilities including limitations in mobility, hydrocephalus, intellectual disability and incontinence. The live birth rate for this group of babies is between 50% and 700% higher in Dublin than in the other centres included in Table 2.1. Therefore, the population incidence of children with disability attributable to spina bifida or encephalocele is similarly much higher in Ireland compared with these other countries.

One can conclude therefore that because termination of affected pregnancies is not provided in Ireland, NTDs have a considerably greater impact on Irish society than elsewhere. This places a greater onus on Ireland to maximise the primary prevention of these conditions.

Table 2.1: The burden of disease associated with NTDs: incidence (per 1,000 births) of NTDs in EUROCAT registries in Britain, Ireland and other selected countries 1993-2002 (65)

	All NTDs LB + SB + T* Rate/1000 births	All NTDs % as live births	Spina bifida & encephalocele % as live-births
Dublin†	1.00	81	61
North Thames	1.22	13	9
Wessex	1.33	14	12
Oxford	1.39	12	8
Trent	1.09	19	16
Merseyside & Cheshire	1.31	18	16
Wales (CARIS)	1.75	22	18
Glasgow	1.72	47	43
Paris	1.30	12	11
Barcelona	0.91	18	14
North East Italy	0.60	17	15
Northern Netherlands	0.85	45	41

*Live-birth (LB) plus still-birth (SB) plus termination (T)
† Data for Dublin is based on live-births and still-births only

2.5 Causes of NTDs

What causes the development of NTDs has been the subject of intense research over many decades. This research has found differences in how the various categories of NTDs evolve, leading experts to believe that the causal factors of NTDs are multifactorial. There is strong evidence that heredity and genetics is a major contributor. In fact, the recurrence rate of having a subsequent affected baby after already having one affected baby is as high as 3 to 5%. In most cases, the inheritance is believed to be polygenic, in other words, potentially involving multiple genes. Such polygenic traits are influenced by environmental factors, such as nutrition.

The most exciting advances, from a prevention perspective, have emerged from research that has focused on the genetic basis of NTDs and research that has evaluated the role of the vitamin folate in its synthetic form, folic acid.

2.5.1 Genetic basis of NTDs

- A significant association has been shown between the mothers of children with NTDs and having variation in some of their genes which determine the use of the vitamin folate in the body.

Folate levels - a measure of the levels of folate in the blood, used to determine if an individual's needs for the vitamin folate are being met.

A study in Dublin found people with this genetic variation had low levels of folate in the body and high levels of another substance, homocysteine (an amino acid), in the body (90). Low levels of folate and high levels of homocysteine in the body in early pregnancy have been found to be risk factors for the development of NTDs (85). High levels of homocysteine in the body may also increase one's risk of heart disease.

- Recent studies have also shown that almost 50% of the Irish population has a genetic make-up which involves variations in their genes which determine the use of the vitamin folate in the body. This genetic make-up may be accountable for as much as one in four (26%) of the NTDs studied by Kirke *et al* (66). The vitamin folate is estimated to be involved in about 50-70% of these defects.

- As the Irish population is at particular genetic risk for the development of NTDs, the issue of folic acid food fortification needs to be addressed for Ireland.

Further details on the genetic basis of NTDs are outlined in the following section.

The Genetic Basis of NTDs

Mothers of children with NTDs and genetic risk

A significant association has been shown between mothers of children with NTDs and a common variation in the gene coding for an enzyme involved in folate metabolism (125,134). The enzyme involved is 5,10-methylenetetrahydrofolate reductase (MTHFR). Two major polymorphisms in the MTHFR gene - C677T and A1298C - have been studied and have been shown to reduce MTHFR activity. A study, based in Dublin, found low red blood cell folate (red cell folate) levels in people with this genetic variation (90), and they also have elevated homocysteine blood levels (62), which may increase their risk of coronary artery disease (61). Previous work in Dublin has shown that low folate and raised homocysteine levels in early pregnancy are risk factors for the development of NTDs (85).

The Irish population is at particular genetic risk

The normal gene encoding for MTHFR is referred to as CC, which indicates that both chromosomes in the pair have the normal gene. Variations within the gene for MTHFR can involve just one of the chromosomes and is referred to as CT (heterozygosity for the T allele of the C677T polymorphism); or it may involve both chromosomes and is referred to as TT (homozygosity for the T allele of the C677T polymorphism). While the CT polymorphism (heterozygous) is more common, occurring in more than a third (38%) of the Irish population, the TT polymorphism is rarer, only occurring in about 10% of the Irish population. Until last year it was thought that the risk of developing NTDs was only associated with the rarer TT polymorphism (8). However, a recent study involving over 300 survivors of NTDs in Ireland, found that the CT polymorphism is also associated with risk of developing NTDs (66). The combined CT and TT genotypes were found to account for 26% of NTDs in this Irish study. Folate or folic acid is estimated to be involved in about 50 to 70% of these defects. Thus, as these researchers point out, up to a half of the folate related NTDs may be explained by this single genetic variant (66). These findings have important implications for food fortification in Ireland, because the population at risk, and by corollary, the population that will benefit from food fortification, is much larger than previously believed. Due to the population distribution of the TT and CT genotypes, this study indicates that almost half (48%) of all pregnancies in Ireland have the genetic background for the risk of developing a NTD.

2.6 Nutrition: Folic Acid and Other Factors in Preventing NTDs

- The vitamin folate, provided in its synthetic form, folic acid, has been proven to be effective in helping to prevent first occurrences of NTDs and recurrences of NTDs in up to about 70% of cases.
- Two randomised controlled trials provide the scientific evidence for the effectiveness of folic acid in preventing NTDs, the Medical Research Council (MRC) UK-based trial on NTD recurrence (83) and the Hungarian trial on NTD occurrence.
- The MRC UK-based trial showed that 4mg of folic acid had a 71% protective effect against the recurrence of NTDs in women with a previously affected pregnancy. Some 29% of NTDs were not prevented by folic acid.
- Successful results from the Hungarian trial (which showed no NTD births in women who received 800µg of folic acid as part of a multivitamin supplement) and from an earlier study using 360µg of folic acid provided the scientific support for the recommended dose of 400µg of folic acid for the prevention of NTD occurrence.
- From these studies, it is estimated that folic acid prevents up to about 70% of all NTDs.
- The cause of the 30% of NTDs that appear not to be related to folic acid are not known. Studies suggest vitamin B₁₂ is important for the protection against the development of NTDs. At this time however, the majority of countries implementing folic acid food fortification programmes for the prevention of birth defects only fortify with folic acid.

- Maternal diabetes and obesity are other nutrition related factors associated with risk of NTDs. It is of concern that both of these conditions are becoming more common in Irish women of childbearing age today.

Further details on the role of folic acid and the prevention of NTDs are outlined in the following section.

Occurrence - having an NTD affected baby for the first time

Recurrence - having a subsequent affected baby after already having one affected baby

Vitamin B₁₂ - a vitamin necessary for the proper functioning of all body cells

Folic Acid and the Prevention of NTDs

The main evidence of the effectiveness of folic acid in prevention of first occurrences (having a NTD affected baby for the first time) and recurrent (having a subsequent affected baby after already having one affected baby) NTDs come from two types of studies. The first are observational studies of dietary folate (natural folate) and folic acid containing vitamin supplements and the development of NTDs. The second are randomised and non-randomised intervention studies. The strongest scientific evidence comes from two randomised controlled trials - the Medical Research Council (MRC) UK-based trial on NTD recurrence and the Hungarian trial on NTD occurrence.

The MRC trial, published in 1991, conclusively established the efficacy of folic acid in a supplement form in preventing NTD recurrence (83). This trial used a research design to investigate the effects of both high dose folic acid (4mg i.e. 4,000µg) and a combination of other vitamins. The recurrence rate in the groups who received folic acid was 1%, which was significantly lower than the 3.5% rate in the groups who did not take folic acid. This established that folic acid had a 71% protective effect against the recurrence of NTDs in women who had had a previously affected pregnancy. It also established that 29% of NTDs were not prevented by folic acid. The multivitamin combination without folic acid had no protective effect. In an earlier randomised trial conducted by Smithells *et al* (119), a multivitamin supplement containing a much lower dose of folic acid, 360µg per day, seemed to be protective against a recurrence. However due to methodological problems in the study, the results were not widely accepted by the scientific community. Given that the subsequent MRC trial conclusively proved the efficacy of folic acid in preventing NTD recurrence, Smithells' findings are interesting in that they suggest that a substantially lower dose of folic acid might also be protective.

The Smithells' results using the 360µg daily dose of folic acid were also important in influencing the decision on the choice of dose for preventing first occurrences of NTDs. In the Hungarian trial (23) on NTD occurrence, a multivitamin preparation containing 800µg folic acid had a significant protective effect in women who had never had an affected pregnancy. There were no NTD births in 2,104 women who received the multivitamin supplement containing folic acid, compared with six cases in the 2,052 women who did not receive the supplement.

There have been several observational studies of the effect of taking supplements containing folic acid on the risk of NTD occurrence, i.e. having a NTD affected pregnancy for the first time (9,86,89,92,118,133,136). These studies show conclusively that women who took a vitamin (usually a multivitamin) supplement containing about 400µg of folic acid per day, reduced their risk of having an affected baby by an average of 60%. These observational studies and the research by the Smithells' group provided the scientific support for the recommended dose of 400µg of folic acid for the prevention of NTD occurrence.

From these studies it is estimated that folic acid prevents up to 71% of all NTDs.

Further details on the role of other nutrition factors in preventing NTDs are outlined in following section.

2.7 Prevention of NTDs

Other Nutrition Related Factors

Vitamin B₁₂

The causes of the 30% of NTDs that appear not to be related to folic acid are not known, but are likely to include genetic and other environmental factors. Studies suggest that vitamin B₁₂, which has an important role in folate metabolism, is important for protection against the development of NTDs (67,122). Insufficient maternal levels of vitamin B₁₂, which are not normally indicative of a classical deficiency nor stem from an inadequate diet, may be an important causal factor in the development of NTDs (122). Support for vitamin B₁₂ in the prevention of NTDs may exist in the 100% protection achieved in the Hungarian trial (23) where this vitamin was included, as well as folic acid (67). In relation to this, Israel has included B₁₂ as well as folic acid in its mandatory food fortification programme to prevent birth defects. At this time, however, the majority of countries implementing food fortification programmes for the prevention of birth defects only fortify with folic acid (Table 2.2).

Maternal diabetes and obesity

Other nutrition-related factors associated with risk of NTDs include maternal diabetes (3) and obesity (132). Both of these conditions are becoming much more prevalent due to the global obesity epidemic, which is also affecting Irish women of childbearing age (58).

When the scientific evidence became available in the early 1990s that folic acid could help prevent first occurrences of NTDs and recurrences of NTDs in up to about 70% of cases, countries made recommendations to women of childbearing age to take folic acid supplements if they were planning a baby or if there was any possibility of becoming pregnant. These recommendations are outlined below. Unfortunately, experience has shown that these recommendations are not easily achieved by women of childbearing age. The potential value of mandatory folic acid fortification as a means to support women of childbearing age, who are sexually active, in reducing the risk of NTDs is introduced in this section.

2.7.1 Recommendations to women to take folic acid supplements

- Immediately after the publication of the findings of the MRC UK based trial in 1991 which showed a protective effect of a 4mg (4,000µg) daily dose of folic acid, the Department of Health in the UK and the Centers for Disease Control and Prevention in the US issued recommendations on the prevention of the recurrence of NTDs. Although expert committees who examined the matter considered that a smaller dose of folic acid might also be protective, the higher 4mg used in the MRC trial was adopted for the recommendation to prevent recurrence.
- The key recommendation was that women with a previously affected pregnancy (who were, therefore, at increased risk of a recurrence in subsequent pregnancies) should be advised to take 4mg of folic acid daily at least four weeks before conception until the third month of pregnancy.
- In 1992, the UK and the US issued recommendations for the prevention of the occurrence of NTDs (13,30). These recommendations advised all women capable of becoming pregnant to consume 400µg of folic acid daily for the prevention of birth defects.
- In 1993, Ireland along with other countries, issued similar recommendations.
- In 1993, the Department of Health and Children advised that all women likely to become pregnant, take an additional 400µg of vitamin folate daily, prior to conception and during the first 12 weeks of pregnancy. They were advised on four possible ways of increasing intake: by eating more foods naturally rich in folate (natural food folate), by eating more foods fortified with folic acid, by taking folic acid supplements or a combination of these.
- During the 1990s, as further evidence of the role of folic acid in the prevention of NTDs became available and a greater understanding of the different forms of the vitamin folate was gained, Irish recommendations to women of childbearing age on taking additional folic acid became more specific, as in many other countries.

- In Ireland, during the late 1990s, women of childbearing age were specifically advised that the best way to take the recommended additional 400µg of folic acid daily was to take a daily supplement. With the realisation that less than 50% of pregnancies are actually planned, women were later advised that if there was any possibility of becoming pregnant they needed to take the additional folic acid daily.
- The recommendations of this report by the Committee are:
 - To prevent the risk of NTDs, all women of childbearing age who are sexually active, are advised to take an additional 400ug of folic acid daily in the form of a supplement.
 - When a woman 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.
 - In addition, women are advised to eat foods fortified with folic acid and natural food sources everyday to meet their individual needs for vitamin folate.
 - Women on long-term medication, e.g. those with diabetes or on anti-seizure medication, are advised to consult their doctor, as they may have higher requirements for folic acid.

The differences between natural folate and folic acid are described in Chapter 3. The need for women to get folic acid from fortified food and supplements is also outlined there.

2.7.2 Recommendations on folic acid are not easily achieved

Challenges have been found in achieving current recommendations on folic acid by women:

- As outlined in section 2.2, the crucial timeframe for the prevention of NTDs is pre-conception because the neural tube closes during very early pregnancy. The greatest challenge arises due to the fact that less than half of all pregnancies are planned. This means that all women capable of becoming pregnant need to take a daily supplement of folic acid 'just in case'.
- There are many reasons why women do not take this advice (106), including:
 - the feeling among those who are not planning a pregnancy that this advice is not relevant to them

- not being in the habit of taking daily supplements
- the ongoing cost of supplements
- confusion among health professionals and the public about the most effective form of the B vitamin (folic acid rather than natural folate) for the prevention of NTDs.

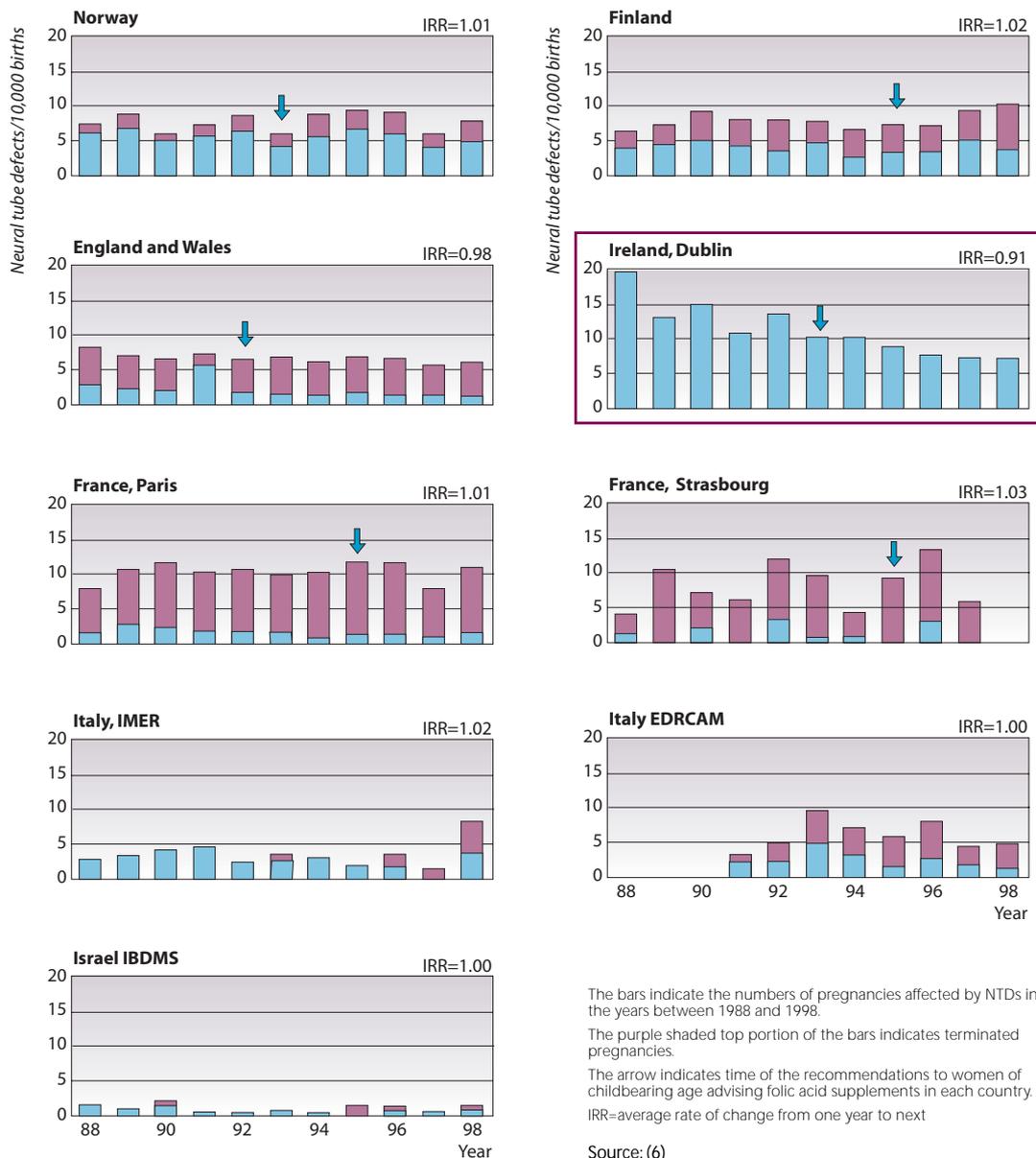
- Studies undertaken among pregnant women attending antenatal clinics in Ireland in the 1990s, indicate that only between 5 and 34% of women took folic acid during the correct time period for prevention of NTDs (35). Recent data from an ongoing study involving women attending the Coombe Women's Hospital in Dublin highlight some of the difficulties around issuing advice to women to take folic acid supplements depending on their potential to become pregnant. While 84% of these women took folic acid, 60% of them did so after discovering they were pregnant - a timeframe which is too late to prevent NTDs (123). A recent report from a GP practice indicates that even systematic and rigorous provision of information on the importance of pre-conceptual folic acid to women of childbearing age has limited effectiveness. While almost all of these women (who had been given both verbal and written advice on the importance of taking folic acid before becoming pregnant) took folic acid during pregnancy, only 45% took folic acid pre-conceptually and in time to prevent the development of a NTD (124).
- A more direct analysis was undertaken recently to evaluate the effectiveness of folic acid supplement policies and recommendations using data on incidence of NTDs according to 13 EUROCAT registries (see section 2.3) monitoring birth defects in several European countries (6). In Figure 2.4, the incidence of NTDs according to the 13 registries, is shown with an arrow indicating the time of recommendations to women to take folic acid supplements to prevent NTDs. Although the rate of NTDs was falling over the time of this study, the analysis shows that these recommendations had no effect on the rate of NTDs (6).

The most likely reason given by the authors for the failure of recommendations concerning folic acid supplements is that they were not implemented to the point of inducing a sustained change in behaviour in a sufficiently large proportion of women to cause measurable effects.

It is noted that two of the countries involved in the study, the UK and The Netherlands, have shown an increased use of folic acid supplements in conjunction with Government sponsored campaigns (114). However, the long-term persistence of such behaviour change is unknown (6). Elsewhere in Europe, folic acid supplement use by women of childbearing age is low, approximately 10% in Norway and 6% in Italy in 2002 (6).

During the same timeframe of this study of 13 birth registries, rates of NTDs were being reduced by more than half in countries with mandatory folic acid food fortification programmes - leading the authors to strongly recommend a food fortification approach (6). As they point out - the element of timeliness is crucial because preventable cases of NTDs accumulate for every year fortification is delayed. As described in section 2.3 on the incidence of NTDs, since 1991, the estimated number of these cases for Ireland alone is between 480 and 911.

Figure 2.4. Rates of neural tube defects (anencephaly and spina bifida) per 10,000 births, 1988-98



Source: (6)

2.7.3 Mandatory folic acid food fortification

In the late 1990s, the failure of advice on supplements led some countries, including Canada and the US, to implement a policy of fortification of cereal grains/flour with folic acid to reduce the risk of NTDs. This ensures an increased intake of folic acid by all women in the population at the time of conception. The amount of folic acid added into the food supply does not, however, usually provide enough to fully protect unborn children. Therefore, Canadian and American women of childbearing age continue to be advised to take folic acid supplements.

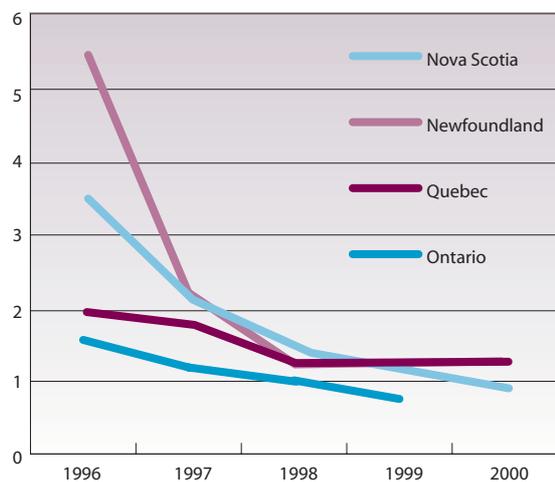
Recently, Canada and the US have issued several reports which show that fortification of cereal grains has been very effective in reducing NTDs. This has led many other countries to implement mandatory folic acid food fortification programmes (see Table 2.2).

In 1996, the US Department of Health and Human Services introduced a policy of folic acid fortification of all cereal grain products at a level of 140µg per 100g of grain in food product as consumed. A similar policy was simultaneously adopted in Canada (fortification of white flour at a level of 150µg per 100g). In both the US and Canada, the birth incidence of NTDs has been reduced by 20% when live-births and still-births only are considered (55) and between 50 and 78% when terminations are also considered (45,72,98). In general, the greatest reductions in incidence of NTDs have been observed in regions where the incidence of NTDs was initially highest. As shown in Figure 5, the immediate effects of folic acid food fortification on the incidence on NTDs is apparent. Although legislation was introduced in 1996, the fortification programme was only mandatory from 1998 to allow time for the food industry to make the necessary changes in its food processing. However, many food companies began to fortify during that two year implementation period and the effects of this are apparent in the declining incidence of NTDs.

In Newfoundland, Canada, rates of NTDs were highest (3.4 cases per 1,000 births on average for the period from 1976 to 1997), and the effects of folic acid food fortification were greatest (72) - resulting in a 78% reduction in the numbers of pregnancies affected (see Figure 2.5). In this Newfoundland study, the effectiveness of advice to women to take folic acid supplements (policy from 1993) was also analysed and found to be ineffective. The study, in particular, highlights how delaying the implementation of a food fortification programme leads to accumulating numbers of preventable cases, many of which survive but are seriously disabled.

No adverse effects of these mandatory food fortification programmes have been reported. This potential is explored in detail in Chapter 4.

Figure 2.5. Incidence of neural tube defects in four Canadian provinces after mandatory folic acid food fortification was implemented (note folic acid flour fortification was legislated for in 1996 and fully implemented in 1998)



2.8 Folic Acid Food Fortification in Other Countries

Worldwide, over 40 countries have introduced mandatory folic acid food fortification for the prevention of pregnancies affected by NTDs (Figure 2.6). In addition to the US and Canada, many South American and African countries also implement a mandatory folic acid food fortification policy. Australia and New Zealand are currently exploring the option of mandatory fortification for the prevention of birth defects for the first time, while the UK is currently re-examining their policy in this area. All three countries permit a range of foods to be fortified on a voluntary basis. Table 2.2 summarises the situation in these and other countries.

Recommended Dietary Allowance (RDA) is the level of intake of a nutrient that, on the basis of scientific knowledge, that is judged to be adequate to meet the known nutrient needs of practically all healthy persons

- Contains folic acid - used where the amount of the foodstuff likely to be consumed in one day provides one sixth of the Recommended Dietary Allowance (RDA = 200µg/day)
- With extra folic acid - used on food labels where the amount of the foodstuff likely to be consumed in one day provides one half of the Recommended Dietary Allowance (RDA = 200µg/day).

Foods that are currently fortified with folic acid on this voluntary basis in Ireland include some breakfast cereals and cereal bars mainly, some milks and yogurts and some breads and rolls, all of which provide approximately one-fifth of the adult RDA of 300µg in a typical serving. These foods make an important contribution to folate intake. Recently, some fat spreads on the market in Ireland have been fortified with folic acid at higher levels, providing almost 100% of the adult RDA per typical daily amount eaten. These more highly fortified food products are further considered in Chapter 4.

This report outlines the findings, conclusions and recommendations of the Committee. This Committee has examined the option of mandatory fortification for the prevention of NTDs, from the perspective of reducing the high burden of disease such birth defects have on Irish society. Currently, such a policy is not implemented elsewhere within the EU. Other Member States, such as Belgium, France, Germany, Greece and the UK permit folic acid food fortification on a voluntary basis only. Fortified foods include: breakfast cereals and cereal bars, spreads, bread, salt and goat's milk. Conversely, national legislation in The Netherlands prohibits both mandatory and voluntary folic acid food fortification.

Ireland can draw on the experiences of other countries in making its decision regarding the mandatory folic acid fortification of folic acid. In 2002, the UK decided against mandatory fortification of all flour (at a level of 240µg/100g flour), believing it is necessary to first obtain more information from countries where mandatory fortification of flour had

The Folic Acid Flash Labelling Scheme

The Folic Acid Flash Labelling Scheme, operated by the Food Safety Authority of Ireland (FSAI) since 2001, allows manufacturers of food products to use one of two logos on their products regarding the amount of folic acid in the product. This scheme was devised by the former UK Health Education Authority to encourage increased intakes of folic acid in the diet. The flash logo is a blue circular disc with F enclosed in a smaller inner circle. The scheme has been adopted in Ireland to ensure consistent use of the flash logo across a range of foods. The logo also appears on many UK manufactured products on sale in Ireland. Foods that are naturally rich in folate cannot be labelled as 'containing folic acid' and such foods are excluded from using the flash logo. It is the responsibility of the company wishing to adopt the flash logo to ensure that the foodstuff in question satisfies general food labelling and claims Regulations in Ireland. The use of the flash logo is monitored by the FSAI.

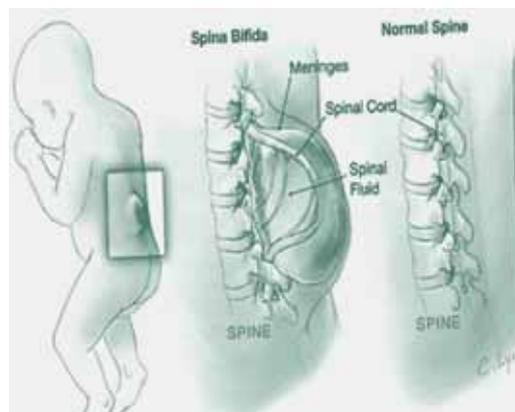


proceeded. Over the last two years, countries have detected a definite benefit. In the US, the folate status (the levels of folate in the body) of the population has increased (99,101) and incidence of NTD-affected pregnancies has decreased (55) following mandatory fortification. In Canada (105) and Chile (53), the post-fortification increase in folate status of the population correlates with a reduction in the incidence of pregnancies affected by NTDs.

In summary

NTDs are serious birth defects, but up to about 70% of such defects can be prevented through increasing intakes of folic acid in women of childbearing age. In Ireland, where the incidence of NTDs is high and the genetic make-up of the population makes it vulnerable to the development of NTDs, efforts to reduce these birth defects are a public health priority. As in other countries, folic acid recommendations are not easily achieved by women in Ireland, thus other options need to be considered for Ireland including mandatory folic acid food fortification which has been successful in other countries.

Figure 2.1. Neural tube defects: spina bifida



Source: (69)

Figure 2.2. Areas in Ireland where data are or have been provided by the EUROCAT registries of birth abnormalities (dark areas on map)

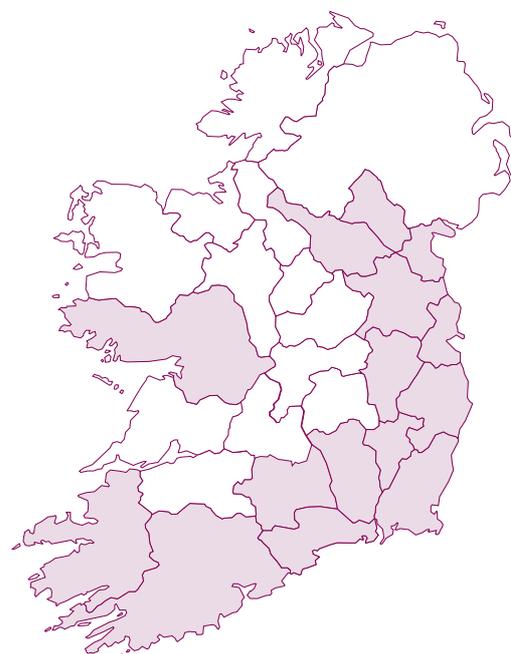
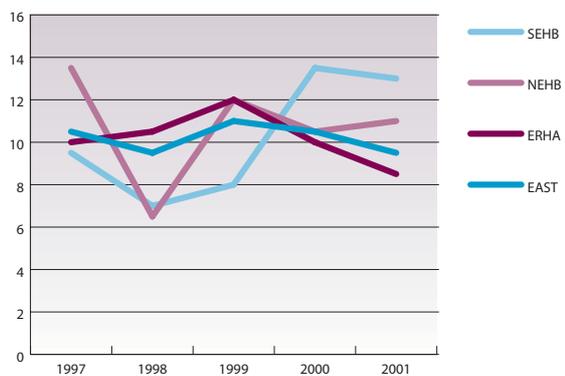


Figure 2.3. Neural tube defects (NTDs) in Ireland: trends in the incidence of birth rates of NTDs per 10,000 births in the eastern region of Ireland (1997-2001)



SEHB: South Eastern Health Board
NEHB: North Eastern Health Board
ERHA: Eastern Region Health Authority

Source: (76)

Figure 2.6. 42 countries have mandatory folic acid food fortification programmes (see dark shaded areas)

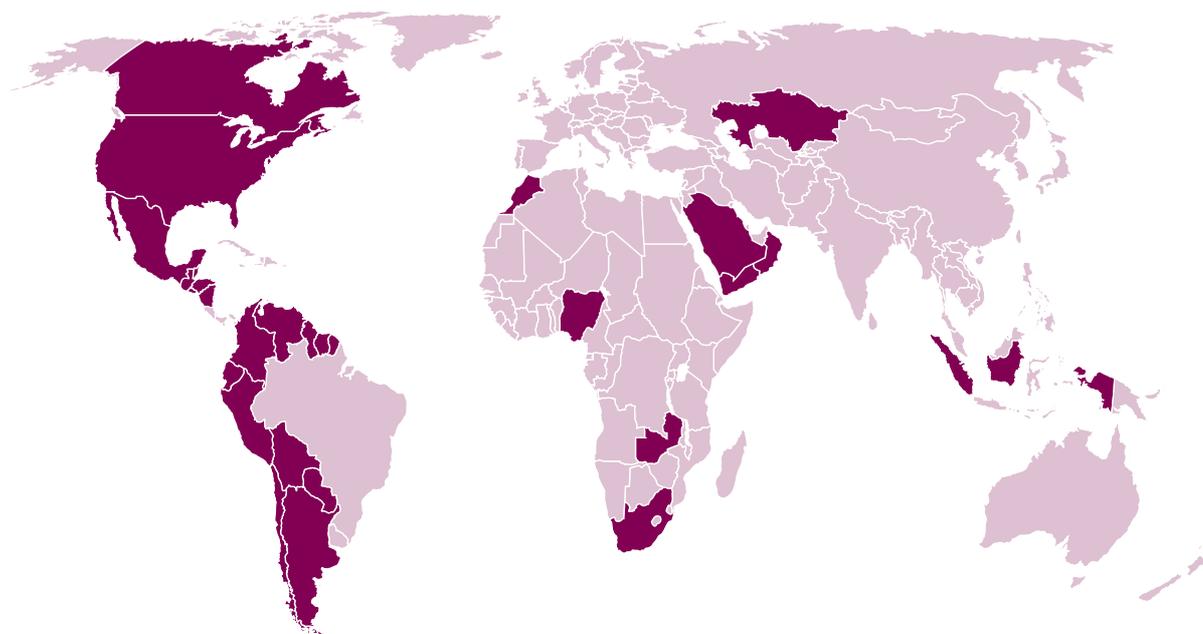


Table 2.2. National Policies on Folic Acid Food Fortification

Country	Fortification Position	Information on Food Fortified and Fortification Level
North America		
USA	Mandatory	140µg/100g grain in food as consumed
Canada	Mandatory	150µg/100g white flour in foods as consumed 200µg/100g enriched uncooked pasta (estimated to provide 150µg/100g cooked pasta)
	Voluntary	150 - 220µg/10g cornflour
Australia and New Zealand		
Australia New Zealand	Voluntary	Folic acid can be added to a maximum claim of 50% recommended dietary intake for adults (100µg) per reference quantity of the following foods: flour; savoury biscuits; breads; breakfast cereals; pasta; fruit and vegetable juices and drinks; fruit cordial; beverages derived from legumes (currently Australia and New Zealand are exploring the option of mandatory folic acid food fortification for the prevention of birth defects)
South America and Caribbean		
Chile	Mandatory	220µg/100g flour
Brazil Argentina Bolivia Colombia Costa Rica Dominican Republic Ecuador El Salvador Guatemala Honduras Mexico Nicaragua Panama Paraguay	Mandatory	150µg/100g wheat and maize flour
Barbados Belize Grenada Guadalupe Guyana Peru Puerto Rico St. Vincent Surinam Trinidad Tobago	Mandatory	All fortify wheat flour (extended to corn flour, rice and milk in some countries). Fortification levels range from 40-300µg/100g

Country	Fortification Position	Information on Food Fortified and Fortification Level
Venezuela	Mandatory	Details of food and fortification levels unavailable
Europe		
Belgium	Voluntary	Foods and food supplements are fortified. For the product to be labelled as fortified with folic acid, a daily portion must contain between 15 and 200% of 200µg
France	Voluntary	Breakfast cereals: only fortified if they are planned to be consumed by children or women (levels unavailable) Goat's milk: 4.5µg folic acid/100g milk
Germany	Voluntary	Breakfast cereals (mainly), beverages, cereal bars and salt (levels unavailable)
Greece	Voluntary	Details of food and fortification levels unavailable
Hungary	Voluntary	In 1998, through a voluntary fortification programme, a bread to prevent birth defects, which was fortified with folic acid and vitamins B ₂ , B ₆ and B ₁₂ , was introduced. This was unsuccessful due to being a higher priced product. In 2005, a group of mill workers have introduced two fortified flours:
		1. for women who potentially could become pregnant (fortified with 350µg folic acid, 10µg B ₁₂ , 500µg B ₂ , and 1600µg B ₆ per 100g flour;
		2. for prevention of cardiovascular disease (fortified with 250µg folic acid, 10µg B ₁₂ , 500µg B ₂ , and 1600µg B ₆ per 100g flour.
Iceland	Voluntary	Breakfast cereals: 30-700µg/100g Flour and rice: 30-100µg/100g
Ireland	Voluntary	Various products fortified under the 'Folic Acid Flash Labelling Scheme' including: milk (70µg/100ml); yogurt (36µg/90g serving); breads 50-263µg/100g bread; flour used to make bread (140µg/100g flour)
UK	Voluntary	Breakfast cereal and breakfast-type products (8-643µg/100g) Some yellow fat spreads: 1mg/100g (currently the UK are re-examining mandatory folic acid food fortification for the prevention of birth defects)
Middle East and Africa		
Israel	Mandatory	Fortifies wheat flour with folic acid and vitamin B ₁₂ (levels unavailable)
Saudi Arabia	Mandatory	Enriched wheat and enriched treated flour (150µg/100g)

Country	Fortification Position	Information on Food Fortified and Fortification Level
Malawi South Africa Zambia	Mandatory	Maize flour (206µg/100g) Maize meal (189 -194µg/100g) White wheat flour (136µg/100g) Brown wheat flour (124µg/100g) White and brown bread (74µg/100g) Enriched maize meal (240µg/100g)
Bahrain Morocco Nigeria Oman Qatar Yemen	Mandatory	Details of food and fortification levels unavailable
Asia		
Indonesia	Mandatory	Enriched wheat flour (200µg/100g)
Kazakhstan Kyrgyzstan	Mandatory	Details of food and fortification levels unavailable
Table adapted from various sources: General information (31,40,114), USA (55,101), Canada (15,72,98,104,105); Chile (52,53), Hungary (22), Australia and New Zealand (40,70, 95;96,120)		

CHAPTER 3. METABOLISM OF FOLATES AND FOLIC ACID: THE NUTRITIONAL AND DIETARY IMPLICATIONS OF FOLIC ACID FOOD FORTIFICATION

Key conclusions

- The B vitamin folate, which is essential to the normal development and functioning of the cells of the human body, exists in different forms, folic acid, the synthetic form that is added to some foods and is found in supplements and natural folate that exists naturally in food. The different forms are absorbed differently in the body which helps to explain the way they are used in the body.
- A deficiency of vitamin folate and vitamin B₁₂ has the same clinical effects in the body, megaloblastic anaemia. Very high amounts of folic acid can actually correct the anaemia associated with B₁₂ deficiency and so hide the presence of the deficiency but allow the other problem of B₁₂ deficiency (neurological disease) to continue. The Committee gave serious consideration to this fact and used the internationally accepted Tolerable Upper Level of folic acid in its decision making on a folic acid fortification level for Ireland.
- Women of childbearing age, who are sexually active, are recommended to ensure they have optimal amounts of vitamin folate everyday to reduce the risk of NTDs. This equates to taking a folic acid supplement daily and meeting their adult needs for vitamin folate (Recommended Dietary Allowance) through food. The food sources of vitamin folate, natural folates (which are less easily absorbed by the body than folic acid) and fortified foods (which have been found to contribute only small amounts of folic acid to the diets of women) are currently not providing adequate amounts of vitamin folate to the diets of women of childbearing age. The fortification of staple foods may be the only way of ensuring adequate intakes of folic acid.

This Chapter describes the B vitamin, folate in terms of its many different forms, its function and the implications of folate deficiency (a shortage of folate in the body). An overview of the metabolism of vitamin folate in its different forms is presented, including details on its link with vitamin B₁₂. This overview aims to provide a basis for understanding the nutritional and dietary implications of a folic acid fortification programme. The different dietary sources of vitamin folate are discussed and information on the bioavailability of these sources is outlined. Finally, the recommended dietary allowances (RDA) for folate are discussed and reasons for the folic acid food fortification programme are presented.

3.1 The B vitamin, Folate

The different forms of folate

Folate(s) is a general term used to describe this B vitamin which exists in many different forms.

Folates include:

- Folic acid - this is the term used to describe the synthetic form of the vitamin. Folic acid is not present naturally in foods. It is present in vitamin supplements (folic acid only supplements and some multivitamin supplements) or is added to foods. Foods that have folic acid added to them are referred to as fortified foods or foods fortified with folic acid. Folic acid has been shown to be the form of the vitamin that is readily absorbed by the body
- Natural folate - this is the term used to describe the many natural forms of the vitamin that exist naturally in foods. Natural folate is not as readily absorbed by the body as folic acid
- Folates - this term includes both folic acid and natural folate.

In this report, all of these terms are used. Dietary folate is another term also used in this report:

- Dietary folates - this term can be used to describe the folate that one consumes through food (both natural folate from foods and folic acid from fortified foods). The use of the term dietary folates may or may not include folic acid consumed through supplements.

The functions of folate

The B vitamin, folate is essential for the normal development and functioning of the cells of the human body.

- Folates are essential for DNA biosynthesis (the making of the most basic pieces of genetic information which determine every characteristic of life) and cell replication (the reproduction and copying of cells which is essential to the formation of human life and the maintenance of health).
- Folates are especially important to the normal functioning of the nervous system at all ages.
- The relationship between a mother's folate status and the risk of NTDs is well established, as described in this report.
- Folate is important in controlling the way the body uses homocysteine (an amino acid). High blood levels of homocysteine in the body are associated with heart disease and stroke. Folate can help to control these high levels of homocysteine in blood.
- There is evidence for a possible beneficial role of folate in the ageing brain, in terms of reducing risk of depression and dementia, including Alzheimer's disease.

A deficiency of folate

A deficiency of folate in the body results in an anaemia known as megaloblastic anaemia. This anaemia results in fatigue, breathlessness and headache.

Low folate status is associated with high blood homocysteine levels, which is recognised as a risk factor for cardiovascular disease. Folate deficiency is also associated with the development of some cancers (see Chapter 4). Folate deficiency is not uncommon, particularly among older adults (see Chapter 4).

Care must be taken when diagnosing folate deficiency. A folate deficiency can be mistakenly diagnosed when the problem may in fact be a deficiency of vitamin B₁₂. Further details are outlined in section 3.2.

Folate deficiency has also been found to be associated with:

- NTDs, which is the focus of this report
- other adverse pregnancy outcomes
- high blood levels of homocysteine which is associated with heart disease
- certain types of cancer
- depression in adults
- dementia, associated with ageing
- altered mood and cognitive function.

Assessment of folate status

The assessment of folate status means determining whether an individual's needs for the vitamin folate have been or are being met.

Folate status is assessed by taking measurements of blood to measure the levels of folate in the body:

- blood levels of folate, known as serum folate levels and often referred to as folate levels
- blood levels of folate in red blood cells known as red cell folate. Red cell folate is a more reliable measure of the body's stores of folate
- raised levels of homocysteine in blood.

Poor or low folate status is associated with:

- low blood serum/plasma folate levels
- low red cell folate levels (RCF)
- raised levels of homocysteine in blood.

Further details on folic acid and natural folates are outlined in the following section.

Folic Acid and Natural Folates

Folate is a generic term for this water-soluble B-complex vitamin, which functions in single-carbon transfer reactions and exists in many chemical forms. Folates include folic acid, the synthetic form of the vitamin, in addition to a wide variety of natural forms of the vitamin. In this report, the following terms are used:

- **Folates:** compounds that have a common vitamin activity, including folic acid (the synthetic form and core molecule) and a wide variety of derivatives
- **Folic acid:** the core molecule (pteroyl glutamic acid) is less reduced than natural folates, only contains one glutamic residue, is heat stable and synthetic. When ingested, folic acid is converted into the same active form of the vitamin which the body derives from natural folates
- **Natural folate(s):** natural compounds in foods that have the same core molecule as folic acid but have, in addition, various levels of reduction of the pteridine ring, one carbon substitution and numbers of glutamate residues (leading to this form of folates being referred to as polyglutamate forms).

Folic acid

Folic acid is more chemically stable than natural forms of folate, because it is less reduced and has just one glutamate residue. These two properties make folic acid more bioavailable when taken as a supplement or in fortified foods. The greater stability of this compound relative to other forms of the vitamin, is the main reason why folic acid is the form used for food folic acid fortification and in folate-containing supplements.

When ingested in amounts that relate to those available naturally in the diet, folic acid is readily absorbed and metabolised in the liver to the natural reduced form - principally 5-methyltetrahydrofolate. It is also converted into a polyglutamate as the cell retains this form. The polyglutamate form derived from folic acid is indistinguishable from those derived from naturally occurring folates in food. However, when ingested in pharmacological amounts (that is, exceeding the amount that could be provided by the diet), the absorption and metabolism of folic acid differs from that of naturally occurring forms of the vitamin (see section 3.2). Therefore, for purposes of food fortification, the levels used relate to dietary, rather than pharmacological amounts.

Natural folates

Natural folates all have the same basic structure that forms folic acid, but differ from folic acid in that:

- they are present in a range of foodstuffs while folic acid is not present in nature
- over 90% of food folates are polyglutamate forms (they have several glutamate residues) while folic acid is a monoglutamate form (it has one glutamic residue only)
- natural folates in foods are readily degraded during storage and preparation while folic acid is relatively stable.

3.2 An Overview of the Metabolism of Folates and Folic Acid and the Link with Vitamin B₁₂

The different forms of the vitamin folate, folic acid and natural folate, are absorbed into the human body in different ways. This helps to explain the different ways in which the vitamin folate is used by the body. Folate and vitamin B₁₂ are linked in the way they are used in the body. A deficiency of folate and a deficiency of vitamin B₁₂ actually have the same clinical effects, anaemia. These facts need to be understood and taken into account when making recommendations to increase folic acid intakes for a population.

- Folic acid is the more bioavailable form of the vitamin folate. This means it is more readily absorbed from food into the body than are natural food folates. Folic acid can be absorbed from food or supplements directly into the body while natural folates can only be absorbed into the body, through the action of an enzyme, as part of digestion.
- Vitamin B₁₂ is needed to convert natural food folate to the active form of the vitamin folate that the body needs. When a deficiency of vitamin B₁₂ prevents this process from taking place, the levels of folate in the body decline and this causes the anaemia which is associated with folate deficiency (known as megaloblastic anaemia). Hence, a deficiency of vitamin B₁₂ has the same clinical effect as folate deficiency.

Megaloblastic anaemia, caused by vitamin B₁₂ deficiency can be corrected by consuming very high amounts of folic acid. This happens because the body can convert the 'spill over' of very high intakes of folic acid into the active form of the vitamin folate, without needing vitamin B₁₂. Thus, if folic acid is consumed in very high amounts (i.e. exceeding the upper limit (UL) of 1,000µg/day) the active form of folate can be made and this can treat the anaemia that was caused by vitamin B₁₂ deficiency. It does not however, treat the other effects of vitamin B₁₂ deficiency. The other problems associated with vitamin B₁₂ deficiency remain untreated by this high intake of folic acid.

- The additional problems (to megaloblastic anaemia) associated with Vitamin B₁₂ deficiency include degeneration of the spinal cord (neurological disease) which is not seen in folate deficiency. While very high intakes of folic acid will clear up the megaloblastic anaemia of vitamin B₁₂ deficiency, the neurological degeneration may progress to permanent nerve damage undetected.
- Anaemia is used as a diagnostic indicator of vitamin B₁₂ deficiency. In cases of undiagnosed vitamin B₁₂ deficiency, consuming very high amounts of folic acid can hide (mask) a B₁₂ deficiency. This masking effect of folic acid, requires three conditions:
 1. There must be vitamin B₁₂ deficiency
 2. The B₁₂ deficiency must be unknown
 3. A very high amount of folic acid must be consumed.
- Vitamin B₁₂ deficiency mainly affects older adults (about 5% of people over 75 years of age may have vitamin B₁₂ deficiency), however, this masking effect of folic acid can only occur in those who do not know they have this deficiency and consume very high intakes of folic acid.

A detailed overview of the metabolism of folates and folic acid and the link with vitamin B₁₂ is provided in the following section and in Figure 3.1.

Metabolism of Folate and Folic Acid and the Link with Vitamin B₁₂

A detailed overview

A diagram describing the main processes involved in the metabolism of folates and folic acid and the link with vitamin B₁₂ is given in Figure 3.1.

When natural folates (polyglutamates) are consumed, absorption into the body occurs in the small intestine through the action of an enzyme, folate conjugase. This enzyme breaks down the natural folate polyglutamates to monoglutamates by reducing the number of glutamic residues to one. This step is not required for absorption of folic acid because it is already in monoglutamate form, which makes folic acid more bioavailable (more readily absorbed from the intestine into the body).

For transport to all cells in the body through the blood circulatory system, the folate monoglutamates are in the 5-methyl-tetrahydrofolate (5-methyl-THF) form, which passes by diffusion from blood into all body cells. While a large proportion of food folates is already in the 5-methyl-THF form, folic acid must be converted to this form.

However, if large doses of folic acid are consumed, the mechanisms converting it into 5-Methyl-THF are saturated and free folic acid appears in plasma. This happens because the capacity for converting folic acid to 5-methyl-THF in the small intestine is limited. If single doses of folic acid exceed 200µg, they are not metabolised immediately resulting in unaltered or free folic acid circulating in the blood (63,82), a phenomenon not encountered from consumption of natural folates.

Cells in the body cannot retain the form of folate usually delivered by blood (5-methyl-THF). In the cells, therefore, through the action of enzymes that also require vitamin B₁₂ to function, 5-methyl-THF is converted to tetrahydrofolate (THF), which is a form that can be retained in cells. In fact, THF is the active substrate for synthesis of forms of the folate vitamin needed by the body (THF-polyglutamates). Normally, any unaltered (or free) folic acid delivered to cells by the blood stream is also converted to THF, first to dihydrofolate by the enzyme dihydrofolate reductase and then to THF inside the cell (see Figure 3.1), or is excreted in urine.

The forms of folate needed by the body (various THF-polyglutamates) function metabolically as

coenzymes and substrates in one-carbon metabolism (see Figure 3.1). One of these pathways involves the conversion of homocysteine to methionine (via methyl transfer from 5-methyl-THF). This is catalysed by the enzyme, methionine synthase, which requires vitamin B₁₂ as a cofactor (see Figure 3.1). Deficiency of either folate or vitamin B₁₂, therefore, results in increased cellular and blood concentrations of homocysteine. Homocysteine is a highly reactive compound and many studies have suggested an association between high blood levels (hyperhomocysteinaemia) and blood vessel wall damage and cardiovascular disease in the general population, although the evidence for this association is not, as yet, conclusive (46, 81, 129). Although three B vitamins, folate and vitamins B₁₂ and B₆ are required to keep homocysteine within a narrow range, in practice, high homocysteine levels are due to low folate status, rather than low status of vitamins B₁₂ and B₆ (16).

How folates and folic acid are linked to vitamin B₁₂

The metabolism of folate and vitamin B₁₂ are linked. The enzyme methionine synthase, which is essential for the conversion of 5-Methyl-THF to THF, is vitamin B₁₂ dependent. Therefore, in the case of vitamin B₁₂ deficiency, conversion of 5-Methyl-THF to THF declines and eventually ceases. The synthesis of 5-Methyl-THF in cells by the enzyme 5, 10-methylene-THF reductase is irreversible. Thus, once formed, 5-Methyl-THF can only be used by a single enzyme - namely B₁₂-dependent methionine synthase. If vitamin B₁₂ is deficient, the enzyme methionine synthase ceases to function and, as a consequence, the folate present in cells becomes 'metabolically trapped' as 5-Methyl-THF. This situation produces a 'pseudo folate deficiency' because although the cells have adequate levels of folate, it is trapped in the single 5-Methyl-THF form. This form of folate will not act as a co-factor for the two folate dependent enzymes involved in purine biosynthesis and for thymidylate synthase, the folate dependent enzyme involved in pyrimidine biosynthesis. Without purine and pyrimidine biosynthesis the replicating cell cannot make DNA and, consequently, cannot divide. This is the mechanism whereby vitamin B₁₂ deficiency causes an anaemia identical to that seen in folate deficiency, megaloblastic anaemia. In the case of folate deficiency the folate co-factors needed to make DNA are deficient, while in vitamin B₁₂ deficiency, they are trapped in a form (5-Methyl-THF) which cannot be used to make purine and pyrimidine.

Furthermore, in vitamin B₁₂ deficiency, the 'build-up' of 5-Methyl-THF in the cell cannot be used in the methylation cycle, which is the other folate dependent process in cells. In order to be utilised by the methylation cycle, 5-Methyl-THF must first be activated by methionine synthase and the activation of this enzyme is absent in B₁₂ deficiency (see Figure 3.1). If folic acid is consumed in high enough doses (>1,000µg per day), it will be delivered in 'free', unaltered form to cells by blood. This 'free' folic acid does not need the B₁₂ dependent enzyme, methionine synthase, to metabolise it and retain it in cells. It is, by contrast, converted directly to THF by dihydrofolate reductase (see Figure 3.1). It is then converted to the forms of the folate vitamin needed by the body (THF-polyglutamates), through pathways that are not dependent on vitamin B₁₂.

Thus, large doses of folic acid and not natural folates, can bypass the vitamin B₁₂-dependent enzyme to ensure folate activity remains normal when vitamin B₁₂ deficiency exists.

Such folic acid will thereby restart DNA biosynthesis and cell division and the anaemia present will be treated. However, free folic acid will not restart the methylation cycle, which needs the action of the vitamin B₁₂-dependent enzyme, methionine synthase. Thus, while the anaemia will be treated by folic acid, the neuropathy seen in vitamin B₁₂ deficiency due to interruption of the methylation cycle will not, and some evidence exists to suggest it may become worse (Institute of Medicine, 1998). This masking of vitamin B₁₂ anaemia by taking folic acid makes the presence of B₁₂ deficiency more difficult to diagnose, allowing the neuropathy associated B₁₂ deficiency to progress. Therefore, the main risk of exposure to large doses of folic acid (>1,000µg) is the masking of megaloblastic anaemia, a diagnostic symptom of vitamin B₁₂ deficiency. Due to this missed symptom of anaemia, irreversible neurological disease associated with vitamin B₁₂ deficiency may proceed undetected. This risk is confined to people who meet three conditions -

1. they have vitamin B₁₂ deficiency,
2. their deficiency is undiagnosed and
3. they consume in excess of 1,000µg of folic acid per day.

It is generally accepted that the minimum dose necessary for masking of megaloblastic anaemia due to vitamin B₁₂ deficiency exceeds the UL (29,56,57). In general, data taken from these reports indicate that intake of 1,000µg/day of folic acid is safe in this respect (i.e. it does not alleviate vitamin B₁₂-associated anaemia in the majority of subjects (16,29,56,57)). As cited in a recent Scientific Advisory Committee on Nutrition report (114): 'The effects of doses between 1-5mg [1,000-5,000µg]/day are unclear, whilst (cited by Chanarin 1994, Bower and Wald 1995) (10:14) supplementation with 5mg (5000µg)/day folic acid is reported to reverse the haematological signs of vitamin B₁₂ deficiency in at least 50% of subjects' (discussed by Chanarin 1994, Bower and Wald 1995, Savage and Lindenbaum 1995) (10,14,112).

3.3 Dietary Sources of Vitamin Folate (Natural Folate and Folic Acid)

In 1931, Dr Lucy Wills, an English missionary doctor working amongst the poor in Bombay, India, demonstrated a cure for megaloblastic anaemia (see section 3.1) by a factor present in yeast (135). Thirteen years later, the vitamin folate was identified in spinach and the name folate was used, because it was derived from leafy vegetables and had reference to foliage (16). Green leafy vegetables including spinach, brussels sprouts, kale and asparagus are rich sources of natural folates (>100µg/serving). Other vegetables and fruit that contain lower, but significant amounts (50-100µg /serving) include broccoli, cabbage, cauliflower, lettuce, parsnips and oranges (16). Folate is concentrated in the liver and thus liver is a rich food source. Yeast and yeast extract are also good sources of folate - this being the factor in Dr Wills' cure for megaloblastic anaemia all those years ago.

In Ireland, the top four food categories contributing to dietary folate (natural folate food sources and folic acid from fortified foods) intake in women are potatoes and potato products (17%), vegetables and vegetable dishes (12%), breads and rolls (12%), and folic acid fortified breakfast cereals (11%) (58). The latter food categories indicate the growing significance of folic acid fortified foods as a source of the vitamin folate in the Irish diet.

Since the North/South Ireland Food Consumption Survey of adults was published in 2001, the array of folic acid fortified foods on the Irish market has expanded beyond breakfast cereals, cereal bars and some milks, to include some breads, yogurts and

fruit juices. Generally, these foods are fortified with folic acid to provide between 20 and 33% of the RDA in a typical serving. Recently, however, some foods on the market in Ireland have been fortified with folic acid at higher levels, providing between 67 and 100% of the RDA depending on the typical daily amounts eaten, e.g. some fat spreads where intake levels average between 20 - 30g per day. These more highly fortified products are further considered in Chapter 4. These changes in composition of foodstuffs available emphasise how important it is to keep up-to-date with what the population is eating and the nutrient content of their diet as part of overall dietary surveillance. In terms of folic acid food fortification, dietary intake surveys, examining actual food consumption, represent the only means of assessing both the folate and folic acid intakes of all population sub-groups. Information on supplement intake must also be addressed as part of such surveys. Such information is required to determine both the adequacy of folate intakes and the risk of any sub-group exceeding the tolerable upper level (TUL) of folic acid intake due to a food choice pattern, involving folic acid fortified foods and is an essential part of the overall evaluation of a fortification programme (see Chapter 7).

3.4 Bioavailability of Vitamin Folate (Natural Folate and Folic Acid)

Bioavailability refers to the rate and extent to which a nutrient is absorbed and is available to the body. Natural folates and the synthetic form of folic acid, have different rates of absorption in the body. Therefore, they differ in terms of bioavailability. Natural folate has much lower bioavailability than folic acid taken as supplements or in the form of fortified foods as highlighted in section 3.2. The availability of dietary folate from a typical North American diet has been suggested as 50 - 75% (51).

3.4.1 Natural folate and folic acid

Natural folate in food has been shown to be only 50% bioavailable compared to folic acid in fortified food which has been shown to be as much as 85% bioavailable. Folic acid from supplements has been shown to be almost 100% bioavailable.

Further details on the bioavailability of natural folates and folic acid are outlined in the following section.

Bioavailability of Natural Folate and Folic Acid

Sauberlich *et al* (111) reported that the overall bioavailability of naturally occurring folate in a mixed diet is 50%, compared with synthetic folic acid given in a formula diet. The results of a three-month controlled feeding study, carried out in Northern Ireland, showed that natural folate resulted in a significantly smaller increase in blood folate concentration in healthy young adults, compared with folic acid supplements or folic acid in fortified cereals (20). This study also found that the bioavailability of folic acid in fortified food was not significantly different from that of folic acid supplements (20).

The investigations carried out in North America by Pfeiffer and colleagues (100) found very slight reductions (about 15%) in folic acid bioavailability when it was taken with white and wholewheat bread, pasta and rice compared with folic acid taken in water. These two different studies (20;100) complement each other and strongly indicate that folic acid added to breads and cereal grains is highly bioavailable. This was the evidence for using a value of 85% bioavailability of folic acid consumed in fortified food in the dietary reference value for folate in North America (56,57).

When consumed under fasting conditions, supplements of folic acid are almost 100% bioavailable (44). In a study of 121 women in Dublin, Daly *et al* (25) reported incremental increases in blood folate levels in response to graded doses of folic acid, which provides evidence for high bioavailability of supplemental folate in the folic acid form. The effect of consuming food with folic acid supplements has been reported to reduce bioavailability slightly (about 15%), but insignificantly (100).

3.4.2 Dietary folate equivalent

The dietary folate equivalent is a method that has been devised to take account of the different bioavailability of folic acid and natural folates in food and provide the most accurate assessment of the relationship between the diet and folate status.

Further details on the dietary folate equivalent are outlined in the following section.

Dietary Folate Equivalent

The US Institute of Medicine estimated a bioavailability of 85% for folic acid from fortified foods. Given folic acid taken in fortified food is 85% bioavailable but natural folates in food are only 50% bioavailable, folic acid in food is 85/50 (i.e. 1.7) times more bioavailable than natural folate in food. Thus, if a mixture of folic acid plus food folate has been consumed, dietary folate equivalents (DFEs) are calculated as follows:

$$\mu\text{g DFEs provided} = \mu\text{g of food folate} + (1.7 \times \mu\text{g folic acid})$$

Using this method to account for the different bioavailability of folic acid and natural folates in food provides a more accurate assessment of the relationship between diet and folate status. This has important implications for monitoring because DFEs can only be used where the sources of folate in the diet are known (i.e. to allow for folates naturally present to be distinguished from folic acid in fortified food). Therefore, monitoring dietary folate intake needs to account for food sources of folate (see Chapter 7). Due to their greater accuracy, DFEs have been used to set requirements for vitamin folate in all population groups in North America (National Institutes of Health, 1998). Should future research indicate food folate is more than 50% bioavailable, these recommendations may change in the future towards lower values (Institute of Medicine 2000). The Recommended Dietary Allowances (RDAs)* for Ireland (see section 3.5) are based on earlier European and British data, which do not take account of differences in bioavailability between natural food folate and folic acid in fortified foods. Furthermore, the Irish RDAs do not provide data on tolerable upper levels of intake (see section 3.5).

*The Recommended Dietary Allowance (RDA) is the level of a nutrient that on the basis of scientific knowledge, is judged to be adequate to meet the known nutrient needs of practically all healthy persons.

3.4.3 Recommended Dietary Allowances for Vitamin Folate in Ireland

To protect pregnancies from the development of NTDs, Ireland has a special recommendation that women of childbearing age take an additional 400µg of folic acid per day as a supplement (16, 21,121). This is presented in Chapter 2. This folic acid supplement is to be taken daily, in addition to the recommended dietary allowance (RDA)* for folates for all adults of 300µg per day as recommended by the RDA Working Group in 1999 (36).

In setting the Irish RDA for folate, the RDA Working Group noted that the previous RDAs for folate in Ireland were consistently higher than the levels recommended by the European Union and Britain (36). In view of the high incidence of pregnancies in Ireland affected by NTDs, as outlined in section 2.3, the RDA Working Group retained the higher Irish RDAs for folate and recommended that action be taken to ensure that the population was supplemented with folic acid.

Tolerable upper levels of folic acid

New developments in nutrient intake assessment methodology, which account for differences in bioavailability between natural folates in food and folic acid and provide information on the tolerable upper levels of folic acid, need to be considered. Details on the amount of folic acid that is safe to consume by individuals, known as the tolerable upper level or UL, is outlined below. These issues are particularly relevant in the context of a national folic acid food fortification programme. For these reasons, the Committee used more recent and reliable available data in making its recommendations. This includes the following:

- The UL is an estimate of the highest level of intake which carries no appreciable risk of adverse health effects in a population, including the most sensitive individuals. The adverse health effects of concern with high intakes of folic acid, is the risk of masking the diagnostic indicator of B₁₂ deficiency (megaloblastic anaemia) and thus allowing the neurological disease associated with B₁₂ deficiency to progress.

Two expert panels who have independently established a UL for folic acid and have suggested that supplementation with the UL for folic acid is safe in the respect that it does not alleviate megaloblastic anaemia associated with B₁₂ deficiency - the European Scientific Committee on

Food (2000) and the US Food and Nutrition Board (56,57). These expert panels both set the UL for folic acid intake in adults at 1,000µg of folic acid. This was calculated by dividing the lowest observed adverse effect level (LOAEL) of 5,000µg by a factor of five.

The LOAEL is the lowest level of folic acid at which an adverse effect was observed - an amount of folic acid that can mask B₁₂ deficiency by correcting the megaloblastic anaemia associated with B₁₂ deficiency. The LOAEL for folic acid in adults is 5,000µg of folic acid. Indeed, a recent Food Standards Agency, UK report (FSA, 2002) has stated the effects of amounts of 1-5mg (1,000-5,000µg) are currently unclear.

- In other words, the UL for folic acid of 1,000µg has a five-fold safety margin to protect the masking of vitamin B₁₂ deficiency in individuals most sensitive to this adverse effect.
- The UL is internationally accepted and has been used by the UK Committee on Medical Aspects of Food and Nutrition Policy in its risk-benefit assessment of folic acid fortification of flour (16), by the Food and Drug Administration in the US and by Health Canada in considering the decision to fortify all grain products with folic acid in the US and Canada (56, 57).
- The Committee therefore used this well-established UL as the critical upper limit in the modelling exercises which were undertaken to establish what level of folic acid should be used in the national folic acid food fortification programme in Ireland. This is discussed in more detail in Chapter 4.

3.5 Why Should Folic Acid Food Fortification be Considered Necessary?

The recommended intake of vitamin folate advised to women of childbearing age, who are sexually active is 700µg of the vitamin. This is made up of their individual needs for the vitamin as adults (300µg of folate for adult women or men) plus their special recommendation of additional folic acid to protect pregnancies from the development of NTDs (400µg). To meet these needs women are advised to take a folic acid supplement (400µg) daily and to ensure they consume foods containing vitamin folate (both natural food folate and folic acid) everyday.

In this section, the fact that natural food folate alone is unlikely to increase a woman's body level of folate (blood levels of folate) sufficiently to reduce the risk of NTDs is discussed. The fact that Irish women of childbearing age obtain only small amounts of folic acid, if any, from available fortified foods is also discussed. The value of considering a staple food as part of a national programme to increase women's intake of folic acid and reduce the risk of NTDs is presented.

3.6 Natural Food Foliates and Women's Recommended Intake for Preventing NTDs

3.6.1 Natural food folates and women's recommended intake for preventing NTDs

Studies have shown that women consuming very high intakes of folates from dietary sources have a lower risk of having an NTD-affected pregnancy. Major sources of food folates are:

- green leafy vegetables
- citrus fruits and juices
- wholegrain breads
- legumes.

Due to the fact that natural folates in food are half as bioavailable as synthetic folic acid consumed through supplementation or fortified foods (see 3.4), women would need to consume about 800µg of natural food folate every day to meet the equivalent of 400µg of folic acid. Using actual examples, in terms of food which women would need to consume in order to take in enough natural food folate to reduce the risk of an NTD-affected

pregnancy, every day they would need to consume the equivalent of:

- 500g of raw spinach or
- 900g of boiled spinach or
- 900g of raw broccoli (10) .

Furthermore, the actual daily intake of natural food folate might need to be even more than 800µg in view of the fact that natural folate is lost through cooking and processing. Overall, therefore, increasing vitamin folate intake purely through natural food folate sources is unlikely to increase a woman's folate levels (blood levels of folate) sufficiently to reduce the risk of an NTD-affected pregnancy.

3.6.2 Folic acid in fortified foods and women's recommended intake for the prevention of NTDs

While a range of foods can be fortified, in practice, breakfast cereals represent about three-quarters of foods that are fortified with folic acid. Other foods fortified include cereal bars, some milks, yogurts, fruit drinks and some breads and rolls (59). As mentioned previously, generally these foods are fortified with folic acid to provide between 20 and 33% of the RDA. Analysis of dietary intake patterns in Ireland (using data from the North South Ireland Food Consumption Survey) indicates that while fortified foods can contribute to women's requirement for vitamin folate, intake is quite uneven in that, there are significant numbers of women who do not consume fortified foods at all (59). These fortified foods tend to be more expensive and therefore, are likely to be economically out of reach for women from disadvantaged backgrounds, whose folate status is likely to be more marginal. It is this very uneven distribution of fortified foods, that gives rise to concern about having highly fortified food products freely available on the market. This issue is further considered in Chapter 4.

The North South Ireland Food Consumption Survey of adults found that over a third (35%) of women of childbearing age living in Ireland consumed no folic acid at all (59). In other words, these women neither choose foods that are fortified with folic acid or take supplements. Overall, women in this age group only get an average of 30µg of folic acid every day from fortified foods (59). This falls well short of the goal of 100µg of folic acid per day on average, which was set by the fortification programmes in the US and Canada. Increasing Irish women's intake of folic acid

to 100µg of folic acid per day through voluntary fortification would mean a three-fold increase in the current rate of fortification. However, such an increase through voluntary fortification is likely to expose some consumers to excessive intakes (depending on their food choices) because the unstructured nature of voluntary fortification leads to an uneven and random distribution of fortified foods in the food supply. New European legislation is currently being adopted which will provide for voluntary food fortification.

In summary, only some people in the population eat foods that are fortified with folic acid. These foods tend to be more expensive and as such, are less likely to be consumed by women from disadvantaged backgrounds who may be at higher risk of having a pregnancy affected by NTDs. Finally, there is recent evidence that encouraging voluntary folic acid food fortification by industry has not been successful in reducing rates of pregnancies affected by NTDs. The recent analysis by Botto *et al* (6) found no reduction beyond the well documented natural decline in NTDs over the past two decades, a timeframe during which a wide range of folic acid fortified foods were introduced in the countries studied.

3.6.3 Suitable foods for a national folic acid fortification programme

As outlined in Chapter 2, women of childbearing age are not easily achieving the recommendation to take a daily folic acid supplement (if there is any chance they may become pregnant) to reduce the risk of NTDs (see section 2.6.2). Thus other ways of supporting women of childbearing age, who are sexually active, to meet this special recommendation of folic acid for a healthy baby, in addition to their individual needs for the vitamin folate, are urgently needed if NTD risk is to be reduced in Ireland. The fact that less than 50% of women plan their pregnancy (the risk of NTDs is in the very early weeks of pregnancy) and that Irish women are generally consuming inadequate intakes of vitamin folate further highlight the need for action.

A mandatory folic acid food fortification programme offers this opportunity to support women of childbearing age, without risks to others in the population (see section 2.6.3). Staple foods such as bread or flour are chosen for national food fortification programmes because they ensure a fairly even distribution throughout the population;

almost everyone eats bread or flour, which makes either ideal as food vehicles for fortification.

Bread is a staple food that Irish women eat and has been shown to be a food that can be fortified with folic acid in sufficient amounts to reduce the risk of pregnancies affected by NTDs in Ireland (see Chapter 4). Bread meets the necessary criteria to become a suitable food vehicle as part of a mandatory fortification programme in Ireland as discussed in detail in Chapter 6.

3.7 Interactions with Drugs, Vitamin B₁₂ and the Mineral, Iron

A number of drugs have been shown to affect the normal metabolism of folates and may cause folate deficiency. Experience to date in countries with folic acid fortification programmes, indicate no interference with the treatment action of these drugs and have proposed benefits for women using oral contraceptives or people with chronic alcoholism.

The link between folate and vitamin B₁₂ is a very important one to address as part of folic acid food fortification programmes as outlined earlier (see section 3.2), due to the potential masking of vitamin B₁₂ deficiency with high intakes of folic acid.

There is some evidence that iron deficiency and folate deficiency may be related which means if proven, folic acid fortification may have potential benefits for other groups of the population.

Further details on these interactions are outlined below:

Anti-folate drugs - drugs needed for certain conditions that adversely affect folate status

Some anti-folate drugs may be given at low doses to alleviate the symptoms of conditions such as rheumatoid arthritis, whilst high-dose therapy is used for the treatment of cancer. There is no evidence that the level of folic acid provided in food fortification programmes interferes with the action of anti-folate drugs. In fact, many thousands of patients have been, and are, treated with a high dose of folic acid (5mg) when they are taking methotrexate, with no effects on its efficacy.

Anti-convulsant drugs

Anti-convulsant drugs (for example phenytoin, phenobarbital, carbamazepine) interfere with folate metabolism and may be associated with low folate status. However, experience in the US and Canada indicates that folic acid food fortification does not pose problems for people treated with anti-convulsant drugs.

Anti-inflammatory drugs

Salicylazosulfapyridine (Azulfidine, sulfasalazine), an anti-inflammatory drug used for the treatment of inflammatory bowel disease, inhibits enzymes involved in folate absorption and metabolism. Other commonly used nonsteroidal anti-inflammatory drugs have anti-folate activity via their action as inhibitors of enzymes involved in folate metabolism. Although the dose-response relationships with respect to antagonistic effects on folate metabolism have not been established, folic acid food fortification has not been reported to cause any interference in the treatment actions of these drugs.

Oral contraceptives

Some investigators have reported an association of oral contraceptive use with marginally reduced folate status, although others have found no effect of these drugs on folate status. Folic acid food fortification would have a beneficial effect should oral contraceptives reduce women's folate status.

Alcohol

Folate deficiency is common in people with chronic alcoholism. In addition to low dietary intake in such individuals, studies have shown that folate absorption and metabolism (use in the body) are impaired by chronic alcohol use. Folic acid food fortification would have a beneficial effect on folate status of people with chronic alcoholism. Recently, folic acid was reported to be protective in reducing risk of breast cancer associated with alcohol use (2).

Vitamin B₁₂

The potential adverse effects of high doses of folic acid supplements in relation to vitamin B₁₂ deficiency, relate to intakes above the safe upper intake level of 1,000µg /day. The level of folic acid fortification recommended for a national programme to prevent birth defects in Ireland is set so that no group exceeds the tolerable upper level of 1,000µg/day (see section 3.2).

Iron

Iron and folate deficiencies commonly occur concurrently in humans. Although it is generally assumed that these deficiencies develop independently, some studies in animals have shown that iron deficiency may cause altered folate utilisation (leading to folate depletion), particularly during the reproductive and neonatal stages of the life cycle. If iron deficiency does lead to folate deficiency, folic acid food fortification would have a beneficial effect for many sub-groups of the population affected by iron deficiency.

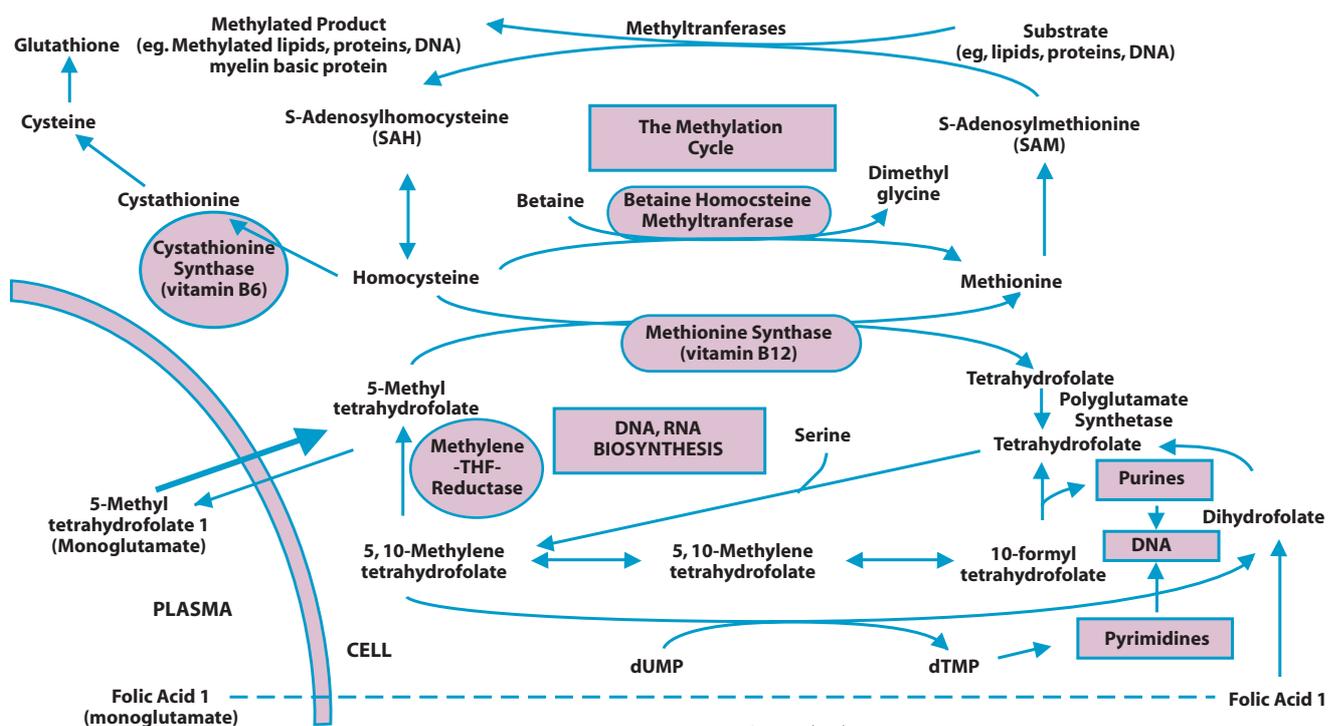
In Summary

The B vitamin, folate, exists in different forms, folic acid, the synthetic form that is added to some foods and is found in supplements, and natural folate that exists naturally in food, with folic acid being more readily absorbed by the body. A deficiency of vitamin folate and vitamin B₁₂ have the same clinical effects in the body, megaloblastic anaemia. Very high amounts of folic acid can actually correct the

anaemia associated with B₁₂ deficiency and so hide the presence of the deficiency but allow the other problem of B₁₂ deficiency (neurological disease) to continue.

Women of childbearing age, who are sexually active, are recommended to ensure they have optimal amounts of vitamin folate everyday to reduce the risk of NTDs. This equates to taking a folic acid supplement daily in addition to meeting their needs for the RDA of folate for adults. To meet this need, women need to firstly ensure they develop a habit of taking a folic acid supplement everyday and secondly need to ensure they consume foods containing vitamin folate, both natural food folate and folic acid, daily. The food sources of vitamin folate, (natural folates and fortified foods) alone, are not able to provide enough of the vitamin for women of childbearing age, who are sexually active. Thus, the fortification of staple foods as part of a national programme to increase women's intake of folic acid is of immediate urgency to reduce the risk of NTDs.

Figure 3.1. The role of folates in DNA biosynthesis and methylation reactions



Source: (115)

CHAPTER 4. FOLIC ACID FORTIFICATION OF BREAD: AN EFFECTIVE AND SAFE LEVEL OF ADDITION

Key Conclusions

- A national policy of mandatory fortification of bread (white, brown and wholemeal) with folic acid at a level that delivers 120µg per 100g of bread, as consumed, will be both effective and safe. It will ensure maximum possible protection of all pregnancies from the development of NTDs without increasing health risks to any other population sub-group.
- This bread fortification programme will reduce the incidence of NTD-affected pregnancies by about 24%. It will provide protection for all women of childbearing age across socio-economic groups, but is likely to disproportionately benefit women from disadvantaged population sub-groups who are less likely to comply with advice on use of folic acid supplements and who are likely to have poorer folate status.
- In addition, it will eradicate anaemia caused by folate deficiency in older adults. Available evidence also indicates a possible (modest) reduction in cardiovascular disease risk in adults at this level of folic acid fortification but this requires further confirmation.
- This fortification level will ensure that older adults do not consume excessive amounts of folic acid, taking into account intakes from other foods fortified with folic acid and food supplements.
- The recommended level of fortification of bread should be kept under review in light of ongoing monitoring of the effectiveness and safety of the fortification measure.
- Due to the fact that the additional amount of folic acid provided by this fortification measure to women of childbearing years (average of 110µg daily) will be less than the additional 400µg currently advised, the continued use of folic acid supplements by this group is recommended.

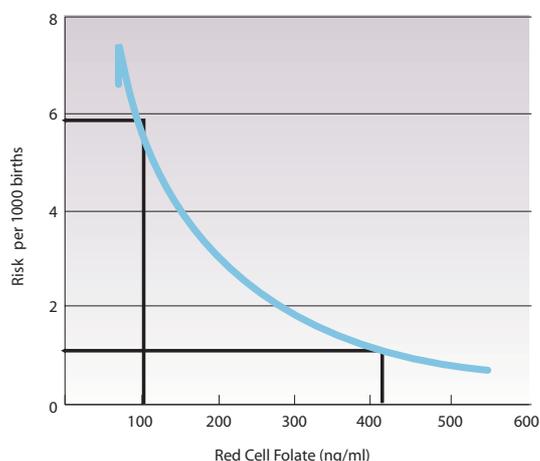
4.1 Reduction in NTDs

The protective role of folic acid in reducing the risk of babies being born with NTDs is well established. Randomised controlled trials and large population studies have shown that increasing folic acid consumption reduces both the occurrence and recurrence of NTDs (4,23,83).

In several countries where mandatory folic acid fortification of staple foods has been introduced, e.g. USA, Canada and Chile, there is strong evidence that this is effective in reducing NTD-affected pregnancies in terms of incidence of NTDs pre and post-fortification. In both the USA and Canada, the incidence of NTDs has been reduced by 20 - 78% (26,45,48,55,72,75,84,98,105). In general, the greatest reductions in incidence of NTDs have been observed in regions where incidence was initially highest. A reduction of 42-51% in NTD-affected births was observed in Chile, following the introduction of folic acid fortification (12,73).

The fortification level of 120µg/100g of bread recommended in this report will provide women of childbearing years in Ireland with an average additional daily folic acid intake of 110µg and will reduce risk of pregnancies being affected by NTDs by about 24%. Keeping in mind that the incidence of pregnancies affected by NTDs in Ireland is underestimated, as outlined in Chapter 2, the level of fortification means that at the very least, 12 to 23 newborn babies would be protected from NTDs every year in Ireland. As shown in Figure 4.1, there is a much greater benefit in terms of reduction of pregnancies affected by NTDs among those with poor or low folate status. Thus, increasing the folic acid intake levels beyond the point at which folate deficiency and low folate status are eliminated, is associated with diminishing returns in terms of prevention of NTDs. Folic acid fortification is likely to disproportionately benefit disadvantaged population sub-groups, that are less likely to comply with advice on use of folic acid supplements and who are more likely to have poorer folate status.

**Figure 4.1. Relationship of early pregnancy
* maternal RCF status to risk of NTDs**



FA - Folic acid,
NTD - Neural tube defect,
P99 - 99th percentile,
UL - Tolerable upper level of 1,000µg of folic acid

Source: (24)

The evidence from countries where mandatory folic acid fortification of food has been implemented shows clearly that such food fortification has the potential to eliminate folate deficiency. In a study of women aged 65 years or more in Ontario and British Columbia pre and post-fortification (105) an increase of 64% in mean serum folate concentrations was observed with a concomitant decrease in folate deficiency (serum folate < 6.0 nmol/l) from 6.3% to 0.9% after fortification. In the US, the prevalence of low serum folate concentrations (<6.8 nmol/L) in a nationally representative survey of the population aged three years and over, decreased from 16% before to 0.5% after fortification (99).

4.2 Reduction of Folate Deficiency

Fortification of bread with folic acid is expected to largely eradicate the occurrence of folate deficiency and low folate status in older adults in Ireland. Folate deficiency results in megaloblastic anaemia (116), symptoms of which include fatigue, breathlessness and headache. Low folate status and elevated plasma homocysteine have been associated with increased risk of cardiovascular disease (CVD) and other age-related conditions in epidemiological studies (99).

Although there are no representative data on folate status in the Irish population, based on UK data (114), it is very likely that folate deficiency and low folate status occurs in Ireland, particularly in older adults. In the UK, folate deficiency is rare among children and adults up to age 64 years, while 5% of adults, and 7-9% of young people have red blood cell folate concentrations indicative of an increased risk of deficiency ("marginal status") (43,50,110). However, in people aged 65 years and over, 21% of those who are free-living have a red blood cell folate concentration indicative of marginal status, and 8% have a red cell folate concentration indicating folate deficiency (33). In the institutionalised people over age 65 years, the corresponding figures are 19% and 16% for marginal folate status and folate deficiency, respectively.

* Maternal red cell folate (RCF) status is the mother's folate status (adequacy of intake of vitamin folate) measured via levels of folate in red blood cells, Red Cell Folate (RCF).

4.3 Masking of Vitamin B₁₂ Deficiency

Available evidence indicates that the only established adverse effect associated with high intakes of folic acid is the masking of undiagnosed vitamin B₁₂ deficiency (29,56,57). The level of folic acid fortification of breads recommended in this report will not lead to high levels of intake in susceptible individuals and will not give rise to a risk of this effect in the population.

susceptible individuals and will not give rise to a risk of this effect in the population.

Vitamin B₁₂ deficiency caused by either intrinsic factor deficiency or hypochlorhydria mainly affects older people. Vitamin B₁₂ deficiency presents with anaemia, neurological symptoms or both, and anaemia is commonly used as a diagnostic indicator. As described in section 4.2,

high doses of folic acid (more than 1,000 µg/day), but not naturally occurring folate in foods, may correct the anaemia caused by vitamin B₁₂ deficiency and may lead to a delay in diagnosis of the underlying vitamin B₁₂ deficiency. A delay in diagnosis of vitamin B₁₂ deficiency may lead to irreversible neurological damage if the nervous system has been affected. A detailed outline of the mechanisms involved in these effects is given in Chapter 3.

Vitamin B₁₂ deficiency mainly affects older people. It has been suggested that the estimated prevalence of vitamin B₁₂ deficiency in the UK (about 2-4% in those over 65 years of age as indicated by elevated mean corpuscular volume or megaloblastic anaemia (33)) probably reflects the situation in Ireland (37). Only a small proportion of those with vitamin B₁₂ deficiency would be undiagnosed.

Two expert panels (EU Scientific Committee on Food (2000) and the US Institute of Medicine's Food and Nutrition Board (1998)) have independently established a tolerable upper intake level (UL) for folic acid to protect against masking of vitamin B₁₂ deficiency anaemia. These expert panels both set the UL for folic acid intake in adults at 1,000µg by dividing the lowest observed adverse effect level (LOAEL) of 5,000µg (intake level that can mask B₁₂ deficiency) by a factor of five. In other words, the UL for folic acid of 1,000 µg has a five-fold safety margin in order to protect against the masking of B₁₂ deficiency in individuals most sensitive to this adverse effect.

For the folic acid fortification level proposed in this report, the objective is to increase the average daily folic acid intake of women in the childbearing age group by 110µg (similar to the objective for the fortification of cereal grain products in the US, and pasta and white flour in Canada). This would result in a reduction of NTD risk of approximately 24%. This low level of folic acid addition ensures that average daily folic acid intake in older adults (including that consumed in supplements and other fortified foods) does not exceed the UL even among those who are the highest bread consumers (see section 4.2 and Table 4.1). Thus, this level of folic acid fortification of bread does not create a risk of masking the anaemia in older adults who have undiagnosed vitamin B₁₂ deficiency.

In the US and Canada, where mandatory fortification of foods with folic acid has been in place since 1998, the available evidence indicates that the increased intake of folic acid does not result in masking of B₁₂ deficiency by correcting the vitamin B₁₂ deficiency anaemia (72,87). In this regard, it is noted that the actual level of additional folic acid intake achieved through fortification was higher than that proposed for Ireland.

4.4 Cardiovascular Disease (CVD)

Increasing folate status throughout the population may reduce the risk of CVD. Prospective epidemiological evidence linking dietary intakes and circulating levels of folate with CVD in the general population has been reviewed (114). There is a strong indication that a raised plasma homocysteine increases risk of CVD and that increasing folate status has the potential to reduce homocysteine levels and risk of CVD, including coronary heart disease and stroke (54,129). The evidence in support of a causal relationship of elevated serum homocysteine and CVD (and thus a preventive effect of folic acid) is supported by genetic epidemiology studies (see page 53). It has been estimated that a reduction of about 16% in risk for coronary heart disease and about 20% for stroke could be achieved with an additional 800µg folic acid per day, equivalent to a reduction of 3µmol/l reduction in serum homocysteine (129). It is noted that the level of fortification of bread proposed for Ireland (120µg of folic acid/100g of bread) would lower homocysteine by much less than this (about 0.6-0.8 µmol/L in adults). Thus, any possible effect on risk of CVD would be relatively modest.

Although some randomised controlled trials (RCTs) of the effect of increasing folic acid intake on CVD have been carried out, it appears that these early trials were all underpowered (126), especially in populations where mandatory folic acid fortification had been introduced, e.g. VISP, HOPE-2, WACS (5). Further RCTs are underway and the outcome is awaited. However, because the size and duration of these trials may be inadequate, it has been recommended recently that a prospective meta-analysis of the ongoing trials of homocysteine lowering should be established, to ensure that reliable information emerges about the effects of such interventions on cardiovascular disease outcomes (B. Vitamin Treatment Trialists' Collaboration, 2006).

Given the limitations of RCTs, it may be necessary to place greater reliance on evidence from large population-wide studies. In this regard, a recent report has shown accelerated reduction in mortality from CVD and stroke coinciding with folic acid food fortification in the US and Canada (137). This is particularly evident from a comparison with the mortality rates in the UK, where folic acid food fortification has not been implemented and no acceleration of improvement in mortality rates associated with CVD and stroke is evident (137).

Genetic Epidemiology Studies

Additional evidence from genetic epidemiological studies of the thermolabile C677T methylene tetrahydrofolate reductase (MTHFR) polymorphism has been proposed as a means of resolving the uncertainty about whether the positive association of serum homocysteine and cardiovascular disease is one of cause and effect. When homocysteine is re-methylated, the methyl donor (5-methyl tetrahydrofolate) comes from the metabolism of 5,10 methylene tetrahydrofolate by the enzyme 5,10 methylene tetrahydrofolate reductase (MTHFR) (see Figure 3.1.). Moderately raised serum homocysteine levels (about 25% above average levels) occur as a result of a single mutation in the MTHFR gene (cytosine to thymidine (C->T) at base pair position 677) that renders the enzyme thermolabile with reduced activity (41).

The presence of this polymorphism in the population provides a natural experiment capable of testing whether moderately raised levels cause cardiovascular disease. The C/T mutation is common (about 10% of individuals are homozygous (TT) and have a homocysteine level that is about 2.7µmol/L higher than persons homozygous for the normal allele (CC) (129). Therefore, it has been possible to conduct studies of the risk of coronary heart disease and stroke in persons with and without the mutation. Such studies have been proposed as being analogous to randomised trials (129). This is because the mutation has effectively been allocated at random across the population (a natural process known as Mendelian Randomisation), forming two groups of people, one with a higher homocysteine level (TT) and the other a lower homocysteine level (CC). There is no expectation that any other systematic differences exist between the two groups. It is only recently that sufficient data have become available for meta-analyses with sufficient statistical power, to show if an effect is present.

Four meta-analyses have provided evidence of very similar summary odds ratio (0.8 - 0.86) indicating that the risk of cardiovascular disease is on average 14 -20% lower in CC homozygotes than in TT homozygotes (11,19,68,129). These studies show that the average blood homocysteine levels are between 2.7 - 3 µmol/L lower in CC- compared with TT homozygotes - a reduction level that is achievable by supplementation with 0.8mg folic acid daily leading to a 16% reduction in coronary heart disease risk. The estimates of cardiovascular risk associated with blood homocysteine levels obtained from the meta-analysis of genetically association studies are remarkably similar to those obtained from meta-analysis of non-genetic observational studies (54,68,129). It has been postulated that because the two types of study have different sources of error, their consistency supports a causal relationship of elevated serum homocysteine and CVD (47).

4.5 Cancer

There is evidence that increasing folate intake may reduce the risk of certain cancers, and for colorectal cancer there is moderate evidence from several prospective cohort studies of a protective effect of dietary folate (114). While correcting folate deficiency may be protective against the development of cancer, it has been suggested that intakes of folic acid that greatly exceed normal requirements may be cancer-promoting (64). However, there is no direct evidence to support this hypothesis. Furthermore, the level of folic acid food fortification proposed for Ireland will not lead to excessive folic acid intakes. No randomised controlled trials investigating effects of folate on cancer risk have yet been reported.

4.6 Cognitive Function

Several prospective epidemiological studies indicate an association of high serum homocysteine and low folate intake or blood level with impaired cognitive decline or dementia in older adults (114). However, a recent review of the few RCTs which have investigated this (74) concluded that such a beneficial effect from folic acid has not been established definitively and more studies are needed.

4.7 Twinning

Previous studies raised the possibility that folic acid supplementation might lead to an increase in the rates of twin pregnancies and miscarriages. However, a large population-based study in China has produced evidence that neither of these possibilities are an issue (42,71). A recent retrospective study in Norway indicates that the observed increase in rate of twin pregnancies associated with folic acid supplementation is due to the greater use of folic acid supplements among women whose pregnancies are the result of invitro fertilisation (127). Finally, evidence in countries where mandatory fortification is in place does not support an increased twinning rate (117,130).

4.8 Other Health Effects

Overall, there is insufficient evidence to suggest either beneficial or deleterious effects of folic acid on bone health (114). There are no reports on allergic reactions to folic acid and allergy has not emerged as a problem among the population of the US and Canada, where all cereal grains/flour has been fortified with folic acid since 1998.

4.9 Risk Benefit Assessment of Folic Acid Fortification of Bread

Dietary modelling was used to estimate the benefits and possible risks of increasing average daily folic acid intake of women in the childbearing age group over a wide range. The method has been described in the FSAI's Report on the Mandatory Fortification of Flour with Folic Acid for the Prevention of Neural Tube Defects, 2003, and used the studies of Daly *et al* (1995 and 1997) to estimate the reduction in risk of occurrence of NTD-affected pregnancies for a given increase in average folic acid intake in women of childbearing years. This approach has been used by the UK COMA in its risk-benefit assessment of folic acid fortification of flour (16) and by the FDA and Canadian authorities in the consideration of the decision to fortify all grain products with folic acid in the US and Canada from 1998 (34).

Estimates of the intake by different groups in the population of additional folic acid were made by modelling dietary intake data from the North/South Ireland Food Consumption Survey (58). Estimates were made of 1. the level of folic acid addition to bread needed in order to increase average daily folic acid intake of women aged 18-50 years by specified

Table 4.1. Effects of various levels of folic acid fortification: extra folic acid intakes among women 18-50 years, % reduction in NTDs expected, folic acid intake at the 99th percentile in adults over 50 years and occurrence of intakes > UL

Bread FA level, µg/100g	Extra FA intake µg/g	NTD reduction, %	P99 for >50y, µg/d	Anyone >UL?
110	100	22	558	No
121	110	24	584	No
132	120	26	613	No
143	130	28	644	Yes

FA: folic acid
P99: 99th percentile
UL: Tolerable Upper Limit

amounts 2. the intake of folic acid from fortified bread (as well as other sources - other fortified foods and nutritional supplements) in men and women aged over 50 years.

Addition of folic acid to all white, brown and wholemeal bread at a level of 110 -143µg/100g bread, as consumed, would increase the average daily folic acid intake of women in the childbearing age group by 100-130µg, corresponding to a reduction of NTD risk of approximately 22-28% (Table 4.1). For these levels of addition, 99% of men and women aged over 50 years have daily folic acid intake less than 558-644µg, with maximum average daily intakes ranging from 816-1,062µg. Higher intakes among the older adults were mainly associated with high bread consumption.

4.10 Selection of a Fortification Level for Bread

The Committee agreed that the most appropriate level of addition of folic acid to bread (white, brown and wholemeal) was 120µg/100g bread, as consumed, and this level would be both effective and safe. In selecting this level, a number of considerations were taken into account by the Committee:

- It is recognised that it is not possible to add sufficient folic acid to bread to provide the additional 400µg/day currently recommended for women of childbearing age, because this would result in excessive intake by older adults
- The 2003 recommendation of the FSAI for an additional 200µg/day approximately for women of childbearing age (of a similar order to that proposed by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) in the UK of about 220µg/d) would lead to exposure of a small proportion of older adults to risk of adverse effects (masking of anaemia in undiagnosed B₁₂ deficiency). While this might be justifiable on public health grounds, it would require effective measures to manage this risk in the susceptible group. In the UK, the difficulty in addressing this issue proved to be central to the Food Standards Agency, UK, decision in 2002 not to recommend folic acid fortification of flour to the British Department of Health (38,39)
- The Committee agreed that avoiding levels which could result in folic acid intakes exceeding the UL in older adults who are high bread consumers was an important consideration. Based on the available dietary data, the Committee had confidence that this could be achieved at a level of 120µg/100g bread, taking into account intakes from other foods voluntarily fortified with folic acid and food supplements. This would provide women of childbearing years with an average additional daily intake of 110µg and would reduce NTD risk by about 24%
- Generally, foods that are voluntarily fortified with folic acid provide between 20 and 33% of the RDA. Recently, however, some foods have included the addition of higher amounts of folic acid so that 100% of the folate requirements are provided in a typical daily amount. While fortified foods can make a significant contribution to folate status, there are disadvantages to having highly fortified foods freely available on the open market. Consumption of highly fortified foods may well be associated with consumption of other fortified foods or supplements and result in excessive levels of folic acid intake. New EU Regulations on food supplements (adopted in 2002) and fortified foods (pending adoption in 2006) will establish maximum levels for additional nutrients and thus limit the amount of folic acid added to these products
- The recommended level of fortification of bread should be kept under review in light of ongoing monitoring of the effectiveness and safety of the fortification measure.

In relation to the level proposed, the Committee notes the following:

- Bread fortification is likely to disproportionately benefit women from disadvantaged population sub-groups who are less likely to comply with advice on use of folic acid supplements and who are likely to have poorer folate status
- This level of addition is sufficient to effectively eradicate anaemia caused by folate deficiency in older adults
- This level of addition allows for folic acid intakes from other foods fortified with folic acid at the usual levels (providing between 20 and 33% of the RDA) and supplements, and does not restrict the current marketing of these
- Monitoring folic acid intake and its dietary sources will provide additional data on folic acid intake in older adults which will ensure that levels exceeding the UL are avoided
- Due to the fact that the additional amount of folic acid provided by this fortification measure to women of childbearing years (average of 110µg daily) will be less than the additional 400µg currently advised, the continued use of folic acid supplements by this group is recommended.

In Summary

Finding a folic acid fortification level that would provide maximum benefits and minimum risks for Ireland involved careful consideration of the latest evidence in relation to folic acid and various conditions and situations. The main benefit of interest was the prevention of NTDs in Ireland and the potential risk addressed in the analysis was the masking of vitamin B₁₂ deficiency. A dual approach of food fortification and the taking of supplements is needed to provide women of childbearing age with the optimal level of folic acid to protect against NTDs.

The Committee recommends a fortification level of 120µg of folic acid per 100g of bread which will provide women of childbearing age with an average additional daily folic acid intake of 110µg. This is expected to reduce NTDs by 24% where between 12 and 23 newborn babies would be protected against NTDs in Ireland each year. It is also recommended that all women of childbearing age who are sexually active are advised to take an additional 400µg folic acid daily in the form of a supplement.

To support industry in implementing the fortification programme, a limit in terms of a range around the 120µg of folic acid per 100g of bread will need to be set. As more data on dietary intake levels of the folate vitamin and on blood levels on folate status become available, the current level of fortification should be reviewed to assess if an increase is warranted.

CHAPTER 5. PUBLIC CONSULTATION ON FOLIC ACID FOOD FORTIFICATION

Key Conclusions

- It is clear there is broad support for the proposed change in national policy to promote the addition of folic acid to bread or flour as more than nine in every ten (91.4%) people who made a submission to the consultation process believed that action needed to be taken to reduce the number of pregnancies affected by NTDs in Ireland.
- Support was expressed for the mandatory fortification of bread or flour by over three-quarters (77.1%) of the submissions made. The fortification method selected by the largest number of submissions (57.8%) was the addition of folic acid to all flour so that a targeted or standard amount of folic acid is present in all flour-containing foods as eaten.
- Concerns regarding the safety or long-term side effects of the proposed change in policy were raised by both those supportive and opposed to the change in fortification policy.
- The Committee gave serious consideration to the concerns raised which is reflected in their advice to allow for consumer choice in the mandatory folic acid fortification programme recommended and in the consideration given to individual concerns addressed in Chapter 4.

This Chapter of the report describes the public consultation that took place as part of the work of the Committee. The purpose of the consultation was to obtain comments from the widest possible number of people on ways to increase the average intake of folic acid by women of childbearing age to reduce the risk of NTDs in Ireland. The proposed means of adding folic acid to flour or bread is presented in this Chapter. Details on the way the public consultation was conducted are presented, followed by the results of the consultation process.

5.1 Background

A public consultation was undertaken by the Committee, the purpose of which was to seek comments from the widest possible number of people on three policy options to increase the intake of folic acid (by adding it to flour or bread) among women of childbearing age in order to reduce the incidence of NTDs in Ireland.

To inform stakeholders, a consultation document was prepared by the Committee to provide information on all of the issues involved. This document:

- outlined the background in terms of incidence rates of NTDs in Ireland
- included evidence of the role of folic acid food fortification in reducing incidence of these birth defects and compared it with the lack of effectiveness of current policy for increasing folic acid supplement use among women
- outlined the possible risks and benefits associated with folic acid intake.

Three policy options for moving forward were outlined as follows:

Option 1. Structured Voluntary Fortification of Flour or Bread - A Change in Current Policy

This would involve the voluntary addition of folic acid by flour millers/bakers in a structured way, as opposed to a random way. The bread/flour industry, following consultation with relevant Government agencies, would fortify bread with folic acid at a specific level which would be recommended by the Committee (to provide 120µg per 100g of bread as consumed). These breads would carry a special logo/label and would be allowed to make a legitimate claim about being a healthy choice. The current practice of allowing voluntary fortification of other foods with folic acid would continue, as discussed in Chapter 2.

Ongoing health promotion would also need to continue, to increase public awareness about the need for women to take a folic acid supplement.

Option 2. Mandatory Fortification of Flour or Bread - A Change in Current Policy

This would involve the compulsory addition of folic acid by flour millers/bakers to some flour (bread-making flour) or to all flour. Mandatory folic acid fortification is possible via these two routes. This fact was presented to those who participated in the consultation as a method of increasing folic acid intakes:

- mandatory fortification of some flour (bread-making flour), ensuring a targeted level or standard amount of folic acid is present in all breads or
- mandatory fortification of all flour ensuring a targeted level or standard amount of folic acid in all flour-containing foods.

The bread/flour industry, following consultation with relevant Government agencies, would fortify bread-making flour with folic acid at a specific level which would be recommended by the Committee (to provide 120µg per 100g of bread as consumed)

Ongoing health promotion would also need to continue to increase public awareness about the need for women to take a folic acid supplement.

Option 3: Continue with Current Policy

This would involve current policy staying the same. Current policy involves intermittent health promotion campaigns to raise public awareness about the need for women of childbearing age to take a folic acid supplement. In addition, this policy allows for unstructured voluntary fortification of foodstuffs with folic acid, as presented in section 2.7.

The advantages and disadvantages of the three policy options were outlined in the consultation document and submissions were invited via a standardised questionnaire, which was structured with open-ended questions to facilitate feedback on concerns and viewpoints not covered in the questions posed (see Appendix 2).

The main objective of the public consultation was to invite submissions from interested parties with a view to gaining a solid understanding of public attitudes to the fortification of food with folic acid.

5.2 Methodology

The public consultation was formally launched on March 21st, 2005 and continued until June 24th, 2005. It was widely promoted by means of a comprehensive media campaign, which included print and television advertising.

Interested parties, either individuals or organisations, were encouraged to make submissions as part of this public consultation:

- through the dedicated website: www.folicacid.ie or
- by contacting the Food Safety Authority of Ireland.

Stakeholder groups that could bring a particular expertise to the debate were directly invited by email to make submissions. Twenty-one groups were invited in this way including:

- Public health specialists
- Nutritionists and dietitians, food scientists
- Primary care physicians and nurses
- Obstetricians and gynaecologists, Faculty of Pediatrics, geriatricians, cardiologists, cancer specialists and researchers.
- National Council on Older People, the Women's Health Council
- Irish Association for Spina Bifida and Hydrocephalus, Disability Federation of Ireland*
- Coeliac Society of Ireland*
- European Surveillance of Congenital Anomalies (EUROCAT) registry

* A presentation on the public consultation was made to members at the Annual General Meeting of these organisations in May 2005

Opportunities for making a submission included completion of:

- (1) a self-administered online questionnaire (www.folicacid.ie) or
- (2) a self-administered questionnaire submitted by post or
- (3) an interview assisted questionnaire by telephone.

A copy of the submission sheet is contained in Appendix 2.

MORI Ireland managed the online submissions and collated the results of all submissions made. The

online portal was designed by MORI's online technology team in collaboration with the FSAI to ensure it mirrored the look and feel of the www.folicacid.ie. The FSAI posted out questionnaires in response to requests. The postal method was especially appropriate for interested parties who wished to make particularly detailed submissions. In addition, the FSAI facilitated telephone submissions by talking through the online questionnaire with respondents who were not in a position to make a submission either online or by post.

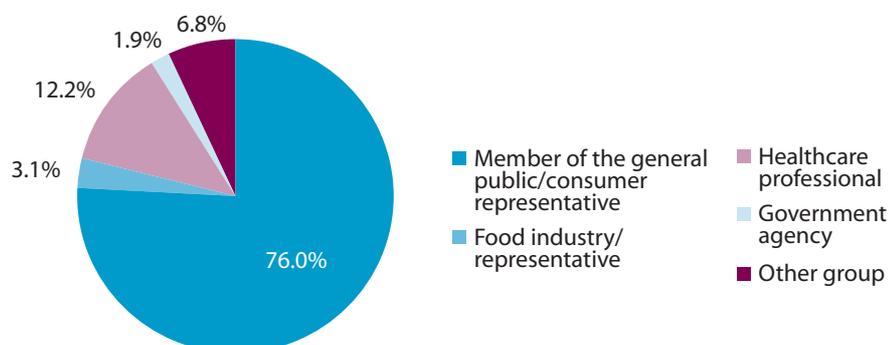
Logic checks and data cleaning were then carried out on the full dataset before analysis commenced. This was to ensure that there was no duplication of responses and that all submissions had been included.

5.3 Response

A total of 513 submissions were made as part of the public consultation, which included both complete and partial submissions*. There were five submission types suggested in the submission to allow categorisation of submissions (see Question 1, Appendix 2).

Over three-quarters of the submissions came from the general public. The second highest number of submissions came from healthcare professionals. Four hundred and seventy eight submissions were made via the online portal, either directly or facilitated by FSAI staff. A total of 35 submissions were made by post, which were then forwarded to MORI Ireland for data entry. Figure 5.1 summarises the submissions according to the category of respondent.

Figure 5.1 Submission Type (Q.1)



* Partial submissions are defined as those submissions that did not provide answers to all questions contained in the questionnaire but did register an opinion or response related to the reduction of NTDs.

5.4 Attitudes to Folic Acid Food Fortification

The submission questionnaire of the public consultation included four sections, sections A-D (Appendix 2), which collected information on the following:

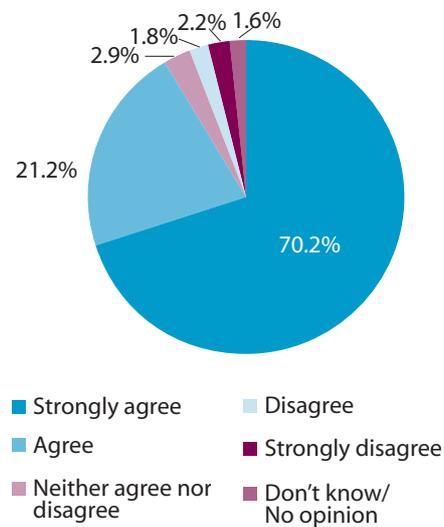
- A. Views were gathered on whether the public agreed there was a need to take action to reduce the number of pregnancies affected by NTDs in Ireland. Views were also gathered on the different methods on how this could be achieved via folic acid food fortification. The consultation also provided respondents with an opportunity to voice their concerns or opposition to this idea.
- B. The opportunity to detail any research or information other than that provided in the consultation document on the incidence of NTDs was given to respondents. An awareness of health risks or benefits associated with the addition of folic acid to foods that were not presented in the consultation document was also invited.
- C. Questions targeted at the food industry were also included. This allowed for the inclusion of information on production process issues.
- D. The final section provided all respondents with the opportunity to voice concerns regarding the fortification of flour or bread that had not been addressed in the consultation document.

This section of the report summarises the responses to the questions of the questionnaire under each of these four sections.

5.4.1 Section A - Crucial questions and your comments on policy

The responses to the six questions included in section A are presented below. This section gathered views on whether the public agreed there was a need to take action to reduce the number of pregnancies affected by NTDs in Ireland. Views were also gathered on the different methods on how this could be achieved via folic acid food fortification to flour or bread. The consultation also provided respondents with an opportunity to voice their concerns or opposition to this idea.

Figure 5.2. Action needs to be taken to reduce the number of pregnancies affected by NTDs in Ireland (Q.2)



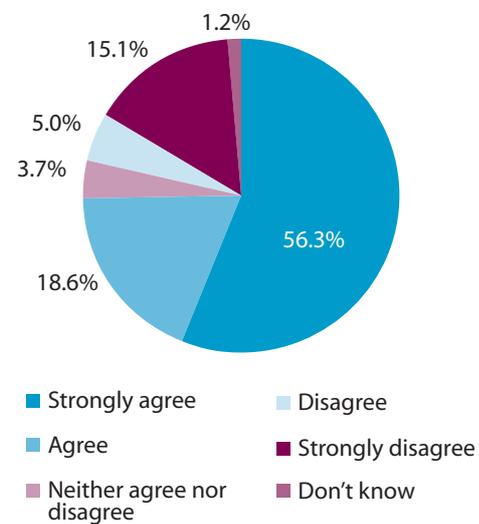
As depicted in Figure 5.2, seven out of ten (70.2%) of those who made a submission indicated that they strongly agreed with the statement that 'Action needs to be taken to reduce the number of pregnancies affected by NTDs in Ireland'. A further, one in five (21.2%) agreed with this statement. Overall, only four percent of respondents disagreed or strongly disagreed with the statement.

This indicates that there is very strong support from those who made submissions for some form of action to be taken to reduce the number of pregnancies affected by NTDs in Ireland.

Q.3 National policy should be changed to promote the addition of folic acid to bread or flour

The next question in the consultation assessed support for the specific action of adding folic acid to bread or flour as a means of reducing the number of NTD-affected pregnancies.

Figure 5.3. Agreement with a change in national policy (Q.3)



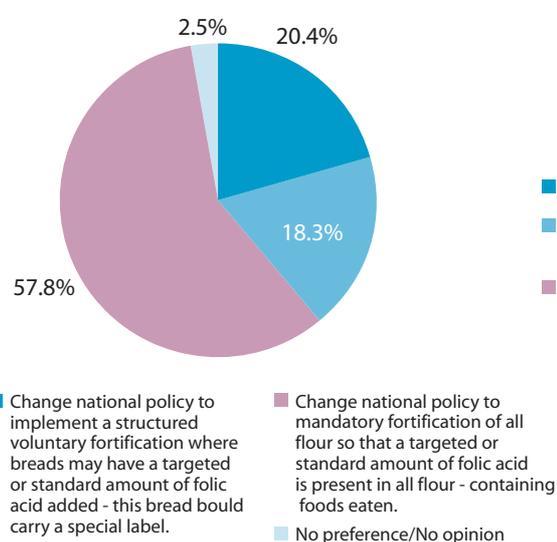
Again, among those who made submissions, support for the change in current national policy to promote the addition of folic acid to bread or flour was high.

Almost three-quarters of respondents (74.9%) to this question indicated that they strongly agreed or agreed with the statement that 'National policy in Ireland should be changed to promote the addition of folic acid to bread or flour'. However, it is worth noting that one in five people (20.1%) disagreed with this statement, most of whom indicated having strong disagreement with the statement.

Q.4a Methods to change national policy to promote addition of folic acid to bread or flour

Respondents who agreed with the above statement (Q.3) were then asked what they believed to be the most suitable method of achieving this objective (those who disagreed were automatically routed to Q.5).

Figure 5.4. Method of achieving a change in national policy (Q.4a)

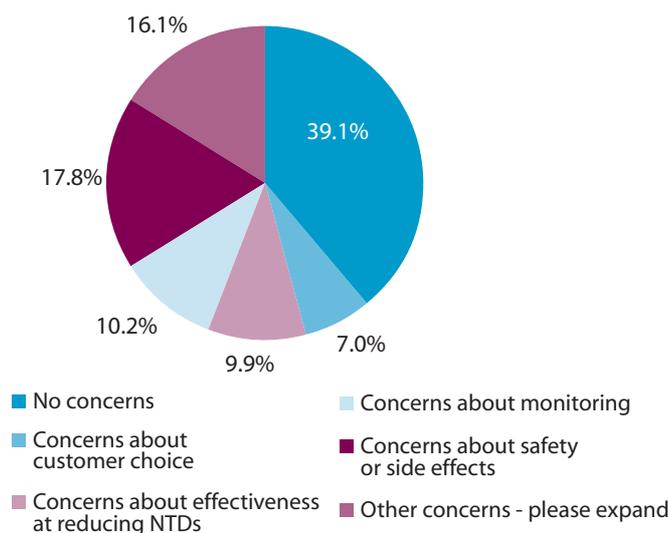


In terms of the three options with which respondents were presented, the option that received most support was Option III "Change national policy to mandatory fortification of all flour, so that a targeted or standard amount of folic acid is present in all flour-containing foods as eaten". Over half (57.8%) of those who provided a response to this question felt that this was the most suitable option.

Option II, which suggested the mandatory fortification of bread-making flour so that a targeted amount of folic acid is present in all breads was favoured by 19.3% of respondents. Option I, which recommended structured voluntary fortification received support from one in five (20.4%) of respondents. Respondents were given the option of recording any reservations or comments they had regarding their choice (Q.4b).

Q.4b Concerns of respondents in favour of folic acid food fortification

Figure 5.5. Concerns of respondents in favour of folic acid food fortification



As shown in Figure 5.5 above, respondents indicated a number of concerns about their 'in favour of fortification' option. While almost one in four (39.1%) indicated that they had no concerns about their choice, six in ten (60.9%) respondents did have concerns.

Concerns about safety or side effects, made by 17.8% of these respondents, represented the majority of reservations recorded. Concerns about monitoring were raised by 10.2% of these respondents, while a further 9.9% recorded concerns about the effectiveness of food fortification at reducing NTDs and seven percent had concerns about consumer choice. A further 16.1% indicated that they had other concerns and these were recorded as verbatim comments.

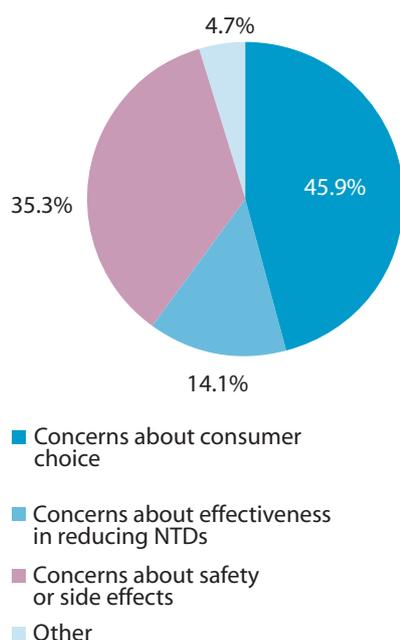
However, analysis of the 'other concerns' revealed that these were mainly expansions on one of the choices listed in Q.4a. An item pertaining to safety or side effects recorded in this section was the possible masking of B₁₂ deficiency by folic acid fortification. Concerns were also expressed over the exclusion of wholemeal bread from the fortification process and that folic acid fortified food would be available to people with Coeliac disease, who are allergic to gluten, therefore must use special gluten free flour and flour products, including bread.

Q.5 Concerns of respondents who were against folic acid food fortification

Those who reported disagreement with the addition of folic acid to bread or flour in Q.3 were routed to Q.5, which examined the reasons for their opposition to fortification. As shown in Figure 5.6, these respondents were most concerned about the programme's implications for consumer choice and about the safety or side effects of fortification.

Just under half (45.9%) reported that they had concerns about consumer choice, while over a third (35.3%) reported concerns about safety or side effects. A total of 85 respondents (17% of those who made a submission) answered this question.

Figure 5.6. Concerns of respondents who were against folic acid food fortification



The following quotation is representative of the concerns voiced by respondents who disagreed with the addition of adding folic acid to food, taken from a verbatim comment provided by one respondent:

"I think this is the wrong approach. Many people are sensitive to food additives and I believe the correct approach is an education campaign to increase awareness. Not everyone has the same folic acid needs, and I fear overdose as much as not enough. I want the right to chose what to consume."

Q.6 Concerns of respondents who neither agreed nor disagreed with folic acid food fortification

Question 6 was presented to respondents who indicated that they neither agreed nor disagreed with the change in national policy to promote the addition of folic acid to bread or flour in Q.3.

Question 6b then asked this group whether there was any additional information that would be useful to them. The principal reason given by the 15 respondents who neither agreed nor disagreed with the change in national policy was the lack of information available to them and their belief that the topic had not been fully researched. Thus, the small number who provided an answer to Q.6b identified further research as a resource that would be helpful to them.

5.4.2 Section B - General questions and comments on the prevention of NTDs

The responses to the three questions included in section B are presented next. In this section, respondents were provided with the opportunity to detail any information or research not discussed in the consultation document that pertained to the prevalence of NTDs in Ireland (Q.7) or the health risks (Q.8) and benefits (Q.9) associated with the addition of folic acid to food. As this section required specialist knowledge of particular areas, the response level to these questions was quite low.

Q.7 Additional information on the incidence of NTDs in Ireland

A number of additional resources were provided by respondents regarding issues relating to the incidence of NTDs in Ireland. These included data indicating that despite increased awareness about the importance of folic acid in the prevention of birth defects, this was not associated with increased uptake of advice to take folic acid supplement pre-conceptually (as highlighted in section 2.6.2)

Data was also submitted on research published in May 2004 by the Health Research Board, Trinity College, National Institute of Child Health and Human Development and the National Human Genome Research Institute which highlighted that up to 40% of Irish people have a certain gene variant that increases the risk of an NTD.

Reference was also made to a survey on folic acid, carried out in seven health boards in Ireland.

Q.8 and Q.9 Other health risks and benefits associated with addition of folic acid

Regarding the health risks and benefits associated with the addition of folic acid to foods not discussed in the consultation document, the following issues were raised but not referenced:

- **The principal health risks identified were possible allergic reactions to folic acid and the masking of pernicious anaemia (vitamin B₁₂ anaemia) referred to previously in responses to Q4b.**
- **In terms of additional health benefits, a reduction in cardiovascular disease and cardiovascular risk factors (with specific mention of homocysteine); a reduction in cancer risk (with specific mention of colon cancer); a reduction in Alzheimer's disease, Parkinson's disease, arthritis, depression and digestive disorders. No references were submitted in support of these submissions.**

All respondents, apart from food industry representatives, were then routed to the final question, Q.17 in Section D of the questionnaire. This section, discussed below, provided an opportunity to voice any other concerns regarding folic acid fortification of flour or bread that was not addressed in the consultation document.

5.4.3 Section C - Questions and comments for the food industry

Section C of the questionnaire was concerned with six specific questions and comments for the members or representatives of the food industry (Q.10-16). The responses to these questions are presented below. This allowed for the inclusion of information on production process issues.

While 3.1% of respondents identified themselves as representatives of the food industry, only six respondents provided answers in this section.

With regard to the technical difficulties posed by the addition of folic acid to flour (Q.10), two responses recorded potential difficulties, both of which referred to experiences of food fortification in other countries.

With regard to the technical difficulties posed by the use of fortified flour in the manufacture of products (Q.11), four respondents indicated that they were not aware of any technical difficulties. The remaining two responses recorded concern over degradation in the levels of folic acid during the baking process, relevant to Q.12, which queried the amount of overage

required to achieve a sufficient level of folic acid in the final product. The concept of 'overage' has been discussed in section 4.2. It highlights the need for a limit to be set as a range around the folic acid fortification level recommended, by the National Committee on Folic Acid Food Fortification, and a final modelling exercise to take place as part of a mandatory fortification programme. These issues will be addressed by the Committee set up to implement the food fortification programme.

For Q.12, regarding the amount of overage needed to achieve a level of folic acid in the final product, five responses highlighted the need for further trials to establish the exact level of the reduction in folic acid levels that occur during the baking process. One respondent suggested a 30µg overage to achieve 120µg of folic acid per 100g of bread as eaten.

For Q.13, regarding the likely variability in the level of folic acid in the final product, four respondents indicated that there would be high variability. One respondent indicated a fairly high level of variability and another indicated that they did not know.

In response to Q.14, three food industry representatives indicated that the level of folic acid in different bakery products (resulting from the fortification of all flour and therefore, of all foods containing flour) is likely to vary, due to the different production processes involved.

For Q.15, regarding the likely cost implications of fortification for industry, the principal cost factor cited related to the purchase of adapted and new technology for the production process.

Finally for Q.16, in terms of the length of time it would take to comply with a requirement of compulsory fortification, three respondents suggested it would take six months to one year, and the remaining three indicated a timeframe of one to three years.

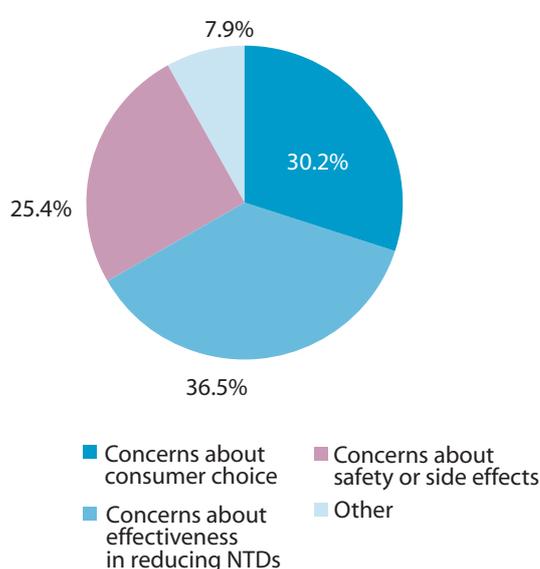
5.4.4 Section D - Final Comments

The final question (Q.17) in this section provided all respondents with the opportunity to voice concerns regarding the fortification of flour or bread that had not been addressed in the consultation document.

There were 63 responses recorded in this section (12% of those who made a submission). However, after analysing the responses, it became clear that respondents had mainly used the final question to

summarise their overall attitude to the proposed fortification policy, rather than adding to their submission. It was also evident that those opposed to the fortification policy were more likely to record their views here than those supportive of fortification. Thus, negative responses fell into one of three main categories regarding concerns about the policy, as illustrated in Figure 5.7 below.

Figure 5.7. Any other concerns regarding folic acid fortification



Following are some examples of the verbatim comments recorded in this section, opposing the overall approach:

"Many younger women (therefore at or pre childbearing age) are diet conscious, so are on diets such as Low Carb or Atkins diet. This would mean using bread as the key fortification medium seem a little short-sighted. Why not look at encapsulating folic acid or including in other food types (e.g. low fat yoghurts/beverages):"*

"I am a person disabled with a neuromuscular condition and I am concerned about any substance put in foods that has a potential neurotoxic effect even indirectly as this proposed fortification does by way of hiding possible vitamin B12 problems. The problems associated with ingesting too much of many vitamins is also an evolving science and it may well be found in the future that certain people may not be able to tolerate the effects of added folic acid in foods."

However, some of those who were positively predisposed to the fortification of food with folic acid also used Q.17 to reiterate their support.

"All bread/flour should be fortified. There are women particularly those in the lower socio-economic group, that would not be aware of the importance of taking a folic acid supplement, possibly through lack of education."

"There needs to be a huge campaign in Ireland in promoting public awareness of the importance of folic acid. There is little or no promotion of this. No doctor, no nurse, no previously pregnant woman, nor people in my family who had given birth to people with spina bifida had ever, during my pregnancies, told me about the importance of folic acid. Health professionals need to be educated and give out advice, or free supplements to women who are on low or no wages. There is very little public knowledge of its importance."

In Summary

Amongst those who made a submission, there is broad support for the proposed change in national policy in Ireland to promote the addition of folic acid to bread or flour. More than nine in every ten (91.4%) people who made a submission to the consultation process believed that action needed to be taken to reduce the number of pregnancies affected by NTDs in Ireland. The fortification method selected most often in the submissions, as the most suitable method for achieving this objective was mandatory fortification of bread or flour over structured voluntary fortification. The mandatory fortification of either all flour or bread only were the methods selected as being most suitable by over three-quarters (77%) of submissions. One in five (20.1%) of those consulted disagreed with the proposed change in national policy which is of significance. The public consultation was valuable in identifying public concerns regarding safety or long-term side effects regarding fortification and these concerns were carefully considered by the National Committee on Folic Acid Food Fortification. Such consideration is reflected in the advice of the Committee to allow for consumer choice in the mandatory fortification programme recommended and in its response to the concerns raised (see Chapter 4).

* A detailed bread consumption survey was carried out among women of childbearing age to ascertain if bread was suitable food for fortification in terms of being eaten by the target group - see Chapter 6, Section 6.8

CHAPTER 6. TECHNICAL ISSUES INVOLVED IN A MANDATORY FOLIC ACID FOOD FORTIFICATION PROGRAMME IN IRELAND

Key Conclusions

Bread is the food vehicle of choice for delivering a mandatory folic acid fortification programme in Ireland to reduce the incidence of NTDs.

- Bread meets the necessary criteria of being:
 - a) consumed regularly and in sufficient quantities by women of childbearing age to ensure the intake of folic acid will be sufficient to reduce the incidence of NTDs
 - b) a food that is encouraged to be taken daily as part of a healthy diet
 - c) technically amenable to fortification and facilitation under existing and future food legislation, and
 - d) a food product that can offer consumer choice by omitting some varieties of breads from the fortification programme.
- Although the technology for fortifying bread with folic acid already exists, the best method for implementing the mandatory folic acid fortification of a specific range of breads in Ireland needs to be developed, in terms of feasibility, cost and legislative requirements.
- It is recommended that a committee charged with the implementation of the fortification programme should be established, to decide on technical and logistical details involved in the programme, including the point of folic acid addition, labelling, trade issues, cost, consumer communication, promotion and advertising.

This chapter describes the issues considered in selecting the most suitable food vehicle (bread) for a national folic acid fortification mandatory programme to reduce the incidence of NTDs in Ireland. Details on the flour and bread market in Ireland are provided followed by an overview of the technical considerations relating to the fortification of bread. The three possible stages for the point of addition of folic acid to bread, (during flour-milling, at the bread-making stage of dough-making or by use of a folic acid fortified flour treatment agent or a flavouring agent) are discussed in terms of the

advantages and disadvantages of each option. The issue of food labelling of breads fortified with folic acid is considered, including recommendations to be addressed by the committee that would implement the mandatory fortification programme. The implications of such fortification to trade and cost are addressed. Finally, the findings of a survey commissioned to examine bread consumption patterns among the target group (women of childbearing age) and among older adults are outlined.

6.1 The Most Suitable Food Vehicle for a National Folic Acid Fortification Programme to Reduce NTD Risk in Ireland

When designing a national mandatory folic acid food fortification programme to reduce NTD risk:

- the vehicle for delivery needs to be a food that is consumed regularly and in sufficient quantities by women of childbearing age to ensure that the intake of the nutrient is sufficient to prevent NTDs
- the vehicle for delivery needs to accommodate prevailing guidance on healthy eating
- it must be technically and financially feasible to fortify the chosen food(s), and be facilitated on a legal basis that accounts for potential conflicts with legislation already in existence
- if it is necessary to facilitate consumer choice it must be feasible to omit fortification of some specific foods within the chosen food category.

In Ireland, folic acid has been added on a voluntary basis to a wide range of foods over recent years. These include breakfast cereals, cereal bars, some milk and yogurts, some bread, rolls and fruit drinks.

The inclusion of folic acid in these products demonstrates that it is technically feasible to fortify these food groups in compliance with current food legislation. However, not all foods that are currently fortified would facilitate increasing folic acid intakes among all women of childbearing age to a specific level.

Consequently, there are only two food categories that are currently fortified with folic acid, that could be considered as being eaten regularly and in sufficient amounts by women of childbearing age across all socio-economic groups to significantly increase their folate status. These food categories include flour, bread and bakery products, milk and milk products.

Many countries allow folic acid fortification of food on a voluntary basis while over 40 countries have implemented mandatory folic acid food fortification programmes to prevent NTDs as discussed in Chapter 2. Without exception, this international experience has focused on flour as the food vehicle of choice for mandatory folic acid food fortification so that all flour-containing foods (bread and bakery products) deliver folic acid to the population.

A suitable food vehicle for folic acid fortification in Ireland

- The food vehicle chosen to deliver folic acid to the Irish population in general, and to women of childbearing age in particular, should comply with current Irish healthy eating guidelines, as outlined above. Otherwise, Irish women choosing to consume food fortified with folic acid to prevent NTDs in their unborn children will be compelled to compromise their own long-term health in terms of their own diet.

In this regard, bread (and not bakery products) fulfils the criteria as a food vehicle of choice for folic acid fortification. It provides energy in a low-fat, high-carbohydrate form and is encouraged as a daily food choice as part of a healthy diet. Furthermore, the inclusion of wholemeal varieties of bread in the food category to be fortified, would also provide fibre, which is of particular importance in Ireland where low fibre intakes are prevalent (58). Low fibre intakes can contribute to risk of cancer and cardiovascular disease.

While bread represents a food category where consumption may be promoted as part of a healthy diet, other flour-containing foods such as bakery products, e.g. such as cakes, biscuits, crackers, and confectionery products represent food categories where consumption needs to be limited. These latter foods are advised in very small amounts daily, in order to avoid high fat, salt, sugar and energy intakes, as recommended by current healthy eating guidelines.

- Examination of the food consumption patterns of Irish women of childbearing age (using data from the North/South Ireland Food Consumption Survey, 2001) as part of the analysis by the Committee identified bread as an effective vehicle for the delivery of folic acid (see Chapter 4). In addition, the Committee commissioned a detailed survey of the bread consumption patterns of women of childbearing age and of older adults, which confirmed bread as a food vehicle of choice for folic acid fortification (see section 6.8). The analysis conducted by the Committee showed that folic acid can be added to bread in amounts that can reduce the incidence of NTDs in Ireland, without risk to any other sub-groups of the population (i.e. risk of masking vitamin B₁₂ deficiency anaemia).
- Furthermore, women from all socio-economic groups consume bread which is important for women from disadvantaged backgrounds for whom folic acid from other sources may be economically out of reach. It is noteworthy that there have been reports of a higher incidence of NTDs in women of low socio-economic status in the past (see section 2.3).
- Finally, as demonstrated by bread products currently on the market in Ireland, it is technically feasible to add folic acid to bread.

Thus, the Committee recommend bread rather than flour and all flour-containing foods, as the vehicle of choice for a mandatory folic acid fortification programme in Ireland.

6.2 The Flour and Bread Market in Ireland

Details on the sources and uses of bread and flour are outlined following:

6.2.1 Flour

Approximately 80% of the flour used in Ireland is milled on the island of Ireland, while 20% is imported - mainly from England and France. The flour milled in Ireland is supplied by one of three major suppliers on the island - Odlums (Republic of Ireland), Allied (Northern Ireland) and Andrews (Northern Ireland).

The predominant use of flour is for the production of bread (60%). Other uses include the manufacture of confectionery, bakery products and consumer foods such as pizza, pies and pastries. A significant proportion of these other products are imported. Almost all (96%) of the flour on retail sale is milled in the Republic of Ireland.

6.2.2 Bread

Approximately 90% of the bread sold in Ireland is produced by domestic bakeries with about 10% imported from Northern Ireland and the rest of Europe. Export of bread from Ireland accounts for only 5% of domestic production and most of this is distributed to Northern Ireland.

The market is divided into branded bread and private (own) label bread with approximately 65% and 35% market share respectively. There are seven main manufacturers of branded bread in Ireland, accounting for 54% of the total market share with the other 11% of branded bread made by a myriad of small bakeries nationwide. In the private label market, the major retailers (Tesco Ireland, Dunnes Stores, Superquinn and SuperValu) hold approximately 74% of the private label market share.

In 2004, the total bread market was estimated to be around 294 million units with loose bread accounting for 25% of that figure. The remaining 75% is composed of wrapped bread (63% of total market), speciality bread (7% of total market) and soft rolls (5% of total market). Consequently, wrapped bread, consisting of 'pan' bread (58%) and Irish traditional bread (5% of total market), represents the majority of bread consumed in Ireland.

6.3 Technical Considerations Relating to the Fortification of Bread - An Overview

There is a range of folic acid fortified breads on the market in Ireland, which is a testament to the existence of the necessary technology for fortifying bread with a prescribed level of folic acid. Such technology is recognised as a crucial element to the design of a national folic acid food fortification programme (see section 6.1). However, the implementation of a national mandatory folic acid fortification programme that targets a specific range of mainstream* white, brown and wholemeal breads requires:

- a comprehensive and reliable process that also takes account of feasibility, cost and legislative issues
- in addition, such a process must consider the implications for medium and small producers where fortification may represent a task of much greater magnitude per unit of bread produced compared with the large producers.

All relevant industry sectors (flour millers, improver/flavouring ingredient suppliers and large bread manufacturers) are willing to participate as required in an Irish national folic acid food fortification programme and have attended preliminary meetings where technical issues associated with the implementation of the programme have been identified. Although the majority of international experience has been to fortify flour with folic acid, the programme developed for implementing this fortification policy in Ireland must be tailored to meet the specific needs of the Irish market (consumer acceptability, point of addition, labelling, trade and cost issues). Therefore, all options need to be considered in detail by a committee responsible for the implementation.

6.4 Point of Addition of Folic Acid to Bread

Using the bread category as the food category of choice for folic acid fortification, fortified products can be achieved by adding a prescribed quantity of folic acid, either:

- during flour milling or
- at the bread-making stage of dough-making or
- by the use of a folic acid fortified flour treatment agent or a flavouring agent, that is a flour treatment agent (improver) or flavouring agent that has folic added to it.

A key determinant of the specific technical issues involved in the implementation of the folic acid food fortification programme, is the decision on which of these stages should be utilised as the point of addition of folic acid to bread. A discussion of some of the technical issues associated with each of these three stages is outlined below, in terms of the advantages and disadvantages of each stage.

6.4.1 Flour fortification

Flour fortification is feasible, as demonstrated in those countries that currently implement mandatory folic acid fortification. UK millers selling into Ireland currently fortify flour with other nutrients, such as iron, but fortification is not currently being carried out in this country.

* Mainstream breads include most wrapped and loose breads sold in Ireland and exclude speciality breads, including traditional Irish soda bread.

Advantages

1. The major advantage of fortifying at the flour milling stage is that the number of participants involved in implementing the actual addition of folic acid would be very limited, involving only the flour millers who supply the bread-makers.
2. This carries major advantages for ease of monitoring and enforcement which, according to international experience, can be undertaken at the flour milling stage. Testing flour for folic acid as part of a quality control process would be a simpler and cheaper option than testing the diverse range of breads on the market. Similarly, any official control activity regarding monitoring would be limited to only a few premises or a limited number of imported batches of flour.
3. There may also be advantages to any legislation that may be required as the range of flours is easier to define than the range of breads.

Disadvantages

1. Flour is not limited just for use in bread manufacture. It is also used for savoury and confectionery bakery products. Although many of the larger bakeries will have specific batches of flour for specific types of products, dividing batches into bread-making flour and other flour is not always practiced in all bakeries. Some bakeries, particularly small/medium sized bakeries, may purchase bulk flour to use for a range of products including bread, scones, cakes, cookies etc. Therefore, the flour miller has no specific control over the final use of folic acid fortified flour.

This has major implications for consumer choice, nutritional health messages and legislative requirements regarding the use of nutrition health claims:

- Consumer choice on accessing bread that is not fortified with folic acid cannot be guaranteed, if folic acid is present in all bread-making flour. In addition, fortifying at the flour milling stage may also mean that other flour-containing foods may have some folic acid present
- New legislation on the use of nutrition health claims is currently being formulated in Europe. Bread that is fortified with folic acid will be labelled and is likely to be permitted to carry a nutrition health claim advising consumers about the benefits in terms of ensuring the healthy early development of babies. As outlined earlier (see section 6.1) the food category/vehicle of choice for folic acid

fortification should accommodate prevailing guidance on healthy eating. In this regard it is likely that foods carrying nutrition health claims will be required under the new legislation to have a nutritional composition that meets specific nutritional health standards in terms of fat, sugar and salt content. Under these criteria flour-containing foods such as cakes and biscuits made from folic acid fortified flour will not be able to carry a nutrition health claim.

2. Approximately 40% of the flour supplied to bread producers in Ireland is imported from the UK and France and this would have to meet the folic acid levels outlined in the new legislation for the fortification programme.
3. As noted earlier regarding consideration to the risk of exceeding the folic acid fortification level, calculating the amount of folic acid that must be added is not an exact science (see Chapter 4) and tolerance limits need to be set round the fortification level to account for losses during processing. Adding folic acid at the flour stage compared with the bread-making stages may result in greater tolerance limits being required, because of the variety of baking processes for the range of breads on the market. Different breads have different recipes concerning the ratios of flour to other ingredients and this has to be allowed for in setting the tolerance limit around the level of folic acid in the final product, as consumed.
4. The main impact on the cost of added folic acid at the flour milling stage is due to the special equipment required by the flour millers, for the controlled addition of folic acid at the specified fortification level. Once installed, the level of folic acid added to flour during the milling process could be controlled within reasonable limits with the appropriate equipment.

6.4.2 Bread fortification

Approximately 90% of bread sold in Ireland is manufactured domestically. The indigenous nature of the bread industry in Ireland provides more scope for a mandatory folic acid fortification programme at the bread production stage. Discussions with several of the major bread manufacturers in Ireland have highlighted that folic acid may be added either directly to the product during dough-making or carried in with the flour treatment agent (improver).

An improver is a standard ingredient, used in the vast majority of bread, for its organoleptic (texture and volume) functionality. It should also be noted

that approximately 15% of bread manufacturers (largely smaller bakeries who aim for the 'homemade' look) do not use an improver. However, these bakeries may use a flavouring agent, which functions in a similar way. Folic acid could therefore be added in the flavouring agent, where an improver is not used.

A major advantage of implementing the addition of folic acid fortification of bread at the point of manufacture is the scope this would provide for consumer choice. Since not all bread products would be included in the programme, consumers could opt for products not labelled as containing folic acid. Alternatively, consumers wishing to avoid folic acid could purchase folic acid free retail flour and bake their own bread.

6.4.3 Bread fortification at the dough-making stage

Folic acid fortification at the dough-making stage is feasible and is currently being carried out on a very limited scale in Ireland.

Advantages

1. The major advantage of fortifying at the dough-making stage of bread production is that with the right dosing equipment the amount of folic acid added can be adjusted, as required, by the various bread-making processes, to ensure the targeted level is achieved in the bread product as consumed.
2. This approach allows scope for facilitating consumer choice (see section 6.4.1).

Disadvantages

Adding folic acid directly during mixing may not be a practical option for the following reasons:

1. In many cases, manufacturers (especially smaller and medium size bakeries) do not have the necessary dosing equipment required for precise addition of folic acid to the bread mix over a prolonged period.
2. The capital costs to include such equipment could be disproportionate to the volume of bread sold (i.e. small bread producers would have more difficulty in covering the capital costs of installing the dosing equipment).
3. The number of participants involved in implementing the actual addition of folic acid at the dough-making stage of bread production would be very significant. In addition to associated

training costs, this increases the potential for human error at the actual addition stage.

4. This approach carries major disadvantages for monitoring which would have to cover multiple bread producers across the country.

6.4.4 Bread fortification at the flour treatment agent (improver) or flavouring agent stage

Folic acid fortification at the flour treatment agent (improver) stage is feasible and is currently being carried out on a limited scale in Ireland.

Advantages

1. There are six key improver manufacturers who represent 98% of the improver market in Ireland, therefore the number of participants involved in the actual addition of folic acid is limited.
2. Initial discussions with these companies indicate that addition of folic acid is possible and would be relatively straightforward for the large bread manufacturers who purchase tailor-made improvers for specific product types (i.e. sliced pan bread).
3. A key benefit is that the level of control over the final amount of folic acid in bread products where with tailor-made improvers have been used, would be high. As a result, the tolerance levels required for the amount of folic acid in the final product, as consumed, could be set within relatively tight parameters and avoid the risk of 'overage' as discussed in Chapter 4.
4. As noted above, fortification of bread at the point of manufacture would provide scope for consumer choice and facilitate those wishing to access bread without folic acid.

Disadvantages

1. Difficulties may arise for the smaller bread producers who purchase a generic improver product and need to use different amounts of this depending on the quality of flour used and manufacturing methods for different bread types. This means that these smaller bread producers will not be in a position to achieve a consistent final level of folic acid in their products, as consumed. This is not an issue for any of the larger bread producers using tailor-made improvers for each bread product type. Larger tolerance levels would therefore need to be allowed for bakeries using a generic improver.

2. Approximately 15% of bread manufacturers (largely smaller bakeries who aim for the 'homemade' look) do not use an improver. However, these bakeries may use a flavouring agent, which functions in a similar way. Folic acid could therefore be added in the flavouring agent, where an improver is not used.
3. The main impact on the cost of adding folic acid at this bread-making stage will be due to on-going analysis to determine folic acid content in the supplied improver, and an agreed bread product sampling plan.

6.4.5 Summary

Following detailed discussions, to date, with interested parties, a number of technical and logistical issues have been identified. Pros and cons exist for the three points of the actual addition of folic acid, as outlined previously (during flour-milling, at the bread-making stage of dough-making or by the addition of a flour treatment agent or improver during bread-making). There is agreement that folic acid fortification can be achieved and all relevant industry sectors (manufacturers, suppliers and flour millers) are willing to participate as required.

It is, therefore, recommended that an advisory group, comprising relevant stakeholders, be set up to discuss the implementation details of a mandatory folic acid food programme. These issues will largely be determined by the decision on the point of addition. To facilitate best practice in implementing a mandatory folic acid fortification programme, the committee responsible for implementation needs to consider this and formulate a plan for addressing the technical issues arising.

6.5 Labelling

To facilitate consumer choice, breads that are fortified with folic acid need to carry labelling that clearly indicates this. Therefore, the advisory group responsible for implementing the mandatory folic acid food fortification programme must develop a plan for labelling fortified foods. Current and future legislative requirements governing food labelling in Ireland need to be considered, these are outlined in brief below:

- Currently, the labelling of food is covered by general food labelling legislation (2000/13/EEC as amended) and in addition, there are labelling requirements for foods where a nutritional claim is made (1990/946/EEC). Folic acid would have to be listed in the ingredient list, however, it is not

necessary to make a nutrition claim or label the quantity of folic acid added to a food under current food legislation.

If manufacturers make a specific claim in relation to the folic acid content of the product, they must apply nutrition labelling and a prescribed format to the labelling of the product. This would have to include a declaration of total folic acid content and the percentage recommended daily allowance (% RDA) of total folate provided by 100g of the food.

- Consideration must be given to the discussions underway at European level regarding legislation covering health and nutrition claims and separately, the voluntary fortification of foods. Both of these legislative processes are close to adoption. In addition, nutritional labelling is under review at European level.

In addition to mandatory labelling requirements, a voluntary Folic Acid Flash Labelling Scheme has operated in Ireland over the past number of years as discussed in Chapter 2. In this scheme, food businesses sign an agreement with the FSAI that gives them the right to reproduce the folic acid flash logo on their packaging. The agreement details the types of food and the levels of folic acid fortification that qualify for the Scheme. A similar scheme operates in the UK and hence the same flash logo can be found on many imported products. It may be possible to extend this Scheme, to indicate for consumers, which breads are fortified with folic acid.

In summary, the committee group for implementation of the mandatory folic acid fortification programme must consider what type of compulsory labelling is necessary to satisfy consumer requirements around the mandatory folic acid fortification programme. Such labelling must conform to current and proposed food labelling legislation and determine to what extent, if any, the folic acid flash logo would need to be incorporated into a mandatory labelling requirement. It is likely that new legislation will ensure that all fortified bread must be labelled clearly to indicate it has folic acid added, the amount of folic acid provided per 100g of bread and the % RDA for folate provided per serving. Similar consideration may have to be given to any mandatory labelling of bread sold loose, as current labelling legislation only applies to pre-packaged bread.

As a consequence of labelling requirements, bread labels will have to be changed in order to communicate folic acid fortification to the consumer. In this regard, the provision of an adequate lead-in time is essential for manufacturers to minimise packaging write-offs.

6.6 Implications for Trade

The trade implications of a mandatory national folic acid food fortification programme must be considered. No other Member State of the European Union currently has a mandatory folic acid food fortification programme, however, a number of countries, including the UK, are investigating this due to the significant potential health benefits in relation to protection of pregnancies against the incidence of NTDs, as outlined in this report.

6.6.1 Exports

Only 5% of domestic bread production is exported and this is predominantly to Northern Ireland. Exported product is produced in the same batches as the domestic product and hence it would also contain folic acid. Northern Ireland also has a high rate of births affected by NTDs.

6.6.2 Imports

At present, up to 10% of the bread that is sold in the Republic of Ireland is imported, primarily from Northern Ireland or the UK. This imported product is mainly bread that is sold in major retail stores and is not fortified at levels being proposed by the Committee. Imported product is not currently fortified with the proposed levels of folic acid that are being proposed by the Committee. Should a mandatory fortification programme be implemented, it would not be possible to place unfortified products on the Irish market without a change in their level of folic acid. New legislation on mandatory fortification in Ireland would have to be notified to the European Commission and justified on public health grounds.

6.7 Costs

The provision of fortified bread does not come without significant costs for the bread industry. Both the bread and flour market in Ireland is extremely competitive. The direct costs that can be envisaged at this early stage are:

- procurement of the folic acid ingredient
- labelling and packaging change costs
- process monitoring costs, these comprise costs to establish a quality assurance process and ongoing analysis costs.

While total costs are difficult to quantify, these cannot reasonably be expected to be absorbed by the manufacturers. It is recommended that methods to offset the burden of cost should be investigated by the committee for implementation of the fortification programme. The potential of a nutrition health claim, combined with health promotion of fortified bread, can be expected to increase market share and offset costs to some extent.

6.8 Bread Consumption Survey

Research was commissioned by the Committee to assess the current actual bread consumption patterns of the target population group (women of childbearing age) and also of older adults (both men and women).

6.8.1 Background

The background to the decision to collect this information was due to the perception that bread may not be the best food vehicle for the fortification programme, because women may not consume much bread. Although data from the North/South Ireland Food Consumption Survey confirmed that women are bread consumers, it was recognised that young women are the most likely group to 'diet' and the recent fad for low carbohydrate diets may well have reduced bread consumption patterns since the survey data collection in the late 1990s. This was raised by submissions to the public consultation and echoed by some members of the Committee. In addition, a survey of bread consumption patterns was deemed necessary to confirm which breads are most regularly eaten by women of childbearing age and to consider if fortification of mainstream breads would effectively deliver folic acid to this group. It was decided to include a smaller group of older adults in the Bread Consumption Survey to update information on bread consumption patterns

recorded in the North South Ireland Food Consumption Survey and used by the Committee to model the level of folic acid fortification. This was also an opportunity to examine bread intake patterns of adults over 64 years whose diets have not been assessed in Ireland.

6.8.2 Subjects and methods

Women of childbearing age and older adults were interviewed using computer-assisted telephone interviewing methodology at MORI Ireland's dedicated telephone centre. The sample was drawn so that it was representative of the population in the Republic of Ireland, in terms of social class and geographical region.

A total of 4,000 telephone interviews were conducted with women of childbearing age (aged between 15-45) with quotas by age, so that 1,333 females aged 15-25, 1,334 females aged 26-35 and 1,333 females aged 35-45). A total of 2,000 telephone interviews with males and females aged 50+ with quotas by age and gender so that 400 men aged 50-65, 600 men aged 65+, 400 women aged 50-65 and 600 women aged 65+ were interviewed.

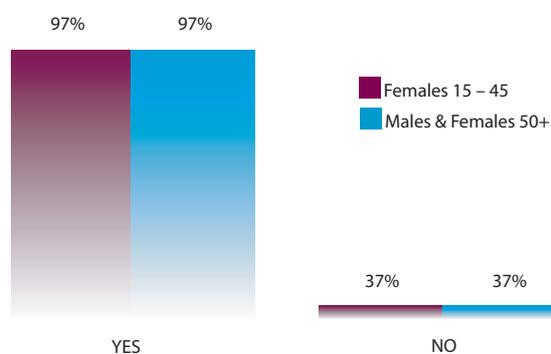
A standardised questionnaire was developed to assess overall bread consumption, type of breads eaten and frequency of consumption. Types of breads were categorised into 22 generic types of bread, which were described to subjects by the interviewer.

6.8.3 Results

Bread consumption

Overall 97% of the women of childbearing years and older adults (males and females aged 50+) interviewed reported eating bread (see Figure 6.1). There were very few differences among age categories within these groups. Ninety-seven percent of all females aged 15-25 eat bread, on some basis, compared to 95% of those aged 26-34 and 98% of those aged 35-45. Ninety-eight percent of all males aged 50-64 eat bread, on some basis, compared to 96% of those aged 65+. 99% of all females aged 50-64 eat bread, on some basis, compared to 97% of those aged 65+.

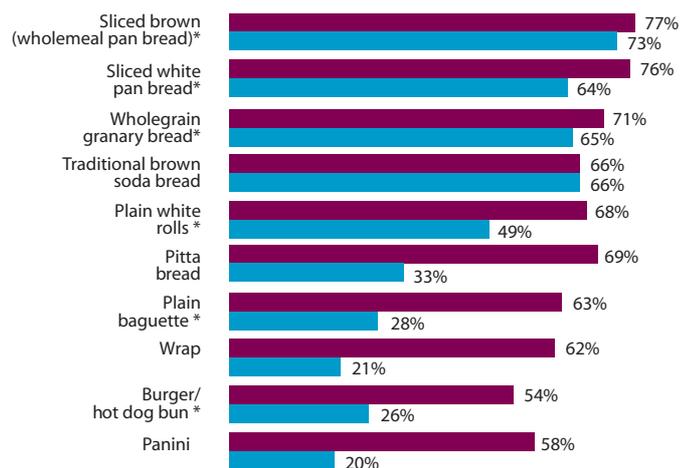
Figure 6.1. Do you ever, or usually, eat bread?



Type of bread consumed

Women of childbearing years reported eating greater variety of breads compared with older adults (see Figure 6.2.). The mainstream breads which are likely to be fortified are indicated with an asterisk (*) in Figures 6.2, 6.3 and 6.4.

Figure 6.2. Do you eat any of the following types of bread?



* denotes bread types that are likely to be fortified with folic acid in the mandatory fortification programme

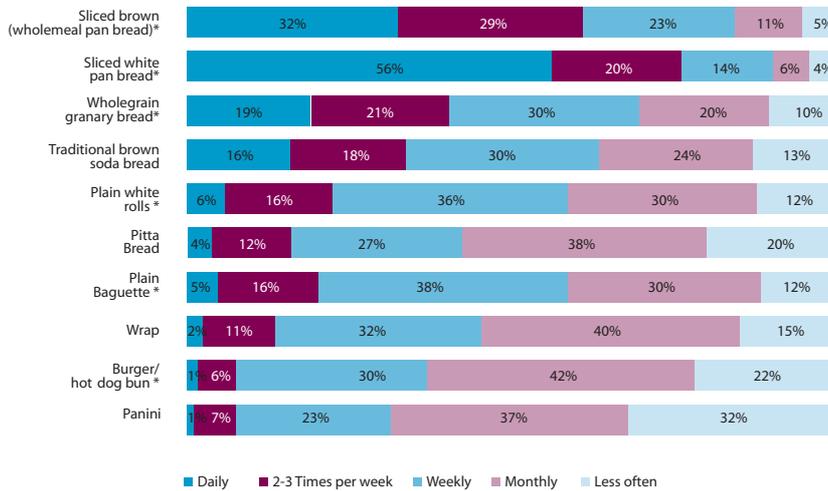
Frequency of bread types consumed

Breads consumed most frequently by both groups (women of childbearing age and older adults) include all types of pan bread and these are included in the mainstream breads earmarked for fortification (see Figures 6.3 and 6.4). Traditional brown soda bread is unlikely to be fortified for technical reasons. This type of bread is eaten more often by older adults. Other breads which are unlikely to be fortified (pitta breads, wraps, panini) are eaten infrequently by both groups.

Frequency of pan bread consumption

In Table 6.1 the proportions of both groups eating pan bread daily or at least 2-3 days per week is outlined. This shows that these bread types are consumed regularly by women of childbearing ages. For example, 91.8% of women aged 15-25 year old eat pan bread at least 2-3 times per week with over 60% of women aged 15-25 eating pan bread daily.

Figure 6.3. How often do women aged 15-45 years, eat the following types of bread?



* denotes bread types that are likely to be fortified with folic acid in the mandatory fortification programme

Figure 6.4. How often do older adults (aged 50+ years) eat the following types of bread?

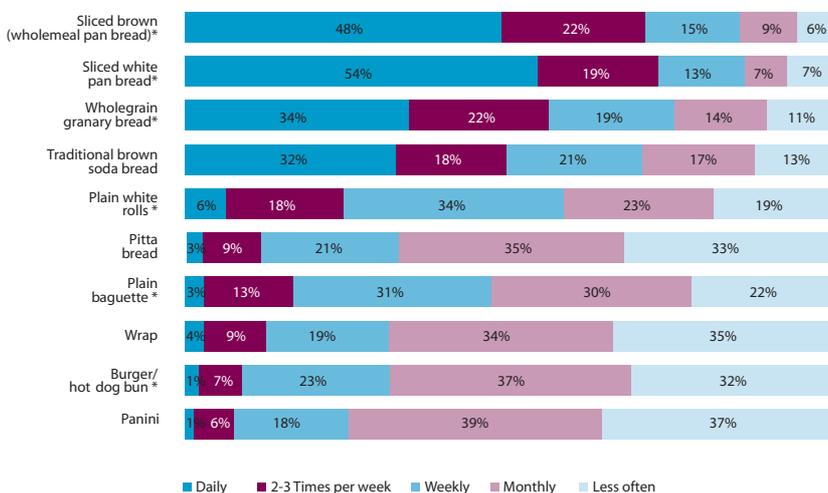


Table 6.1. Proportions (%) of women of childbearing ages (15 to 45 years) and of older adults (aged 50+) who eat any type of pan bread daily or 2-3 times per week

Age (years)	All eat any pan bread daily	All eat any pan bread 2-3 times a week	All eat any pan bread either daily or 2-3 times a week (at least 2-3 times a week)
15-25 Female	63.6%	28.2%	91.8%
26-34 Female	50.9%	30.3%	81.2%
35-45 Female	55.5%	34.7%	90.2%
50-64 Male	63.3%	26.8%	90.1%
50-64 Female	58.3%	26.8%	85.1%
65+ Male	60.5%	22.7%	83.2%
65+ Female	53.5%	21.3%	74.8%

In Summary

Bread is the food vehicle of choice for delivering a mandatory folic acid fortification programme in Ireland to reduce the incidence of NTDs. Bread as a food category meets the necessary criteria of such a programme. All relevant industry sectors in Ireland are willing to participate in a mandatory folic acid fortification programme for Ireland. The establishment of a committee responsible for the implementation of the programme will be of great importance in moving forward. Issues such as the specific needs of the Irish market, the point of addition of folic acid to bread, labelling of fortified breads, trade and cost implications and legislative requirements will need to be addressed by such a committee.

6.8.4 Conclusions

The bread consumption survey shows that women of childbearing age regularly consume the mainstream breads that are under consideration as foods to deliver the mandatory folic acid fortification food vehicles. This survey also confirmed adults older than 65 years are not consuming higher amounts of the breads that may be fortified compared with adults aged 50-65 years, whose bread eating patterns were used to model a safe level of folic acid fortification (see Chapter 4). As this survey was carried out early in 2006, the data are very current.

It should also be noted that the FSAI requested a breakdown of bread sales in major supermarket chains in Ireland as a further means of assessing current bread consumption patterns. Dunnes Stores and Tesco (Ireland) Ltd. kindly supplied the required data from their loyalty cards. These data confirmed the findings of the FSAI Bread Consumption Survey and also provided some details on brand market share that may prove useful at the implementation stage. FSAI acknowledge the contribution of Dunnes Stores and Tesco (Ireland) Ltd to this important work.

CHAPTER 7. MONITORING

Key Conclusions

- **Having a science-based plan in place for monitoring folic acid food fortification is essential for ensuring effectiveness and safety in the long-term.**
- **The collection of baseline data on a number of key areas is crucial for effective monitoring to allow assessment of the impact of the fortification programme on the intended outcome, a reduction in the incidence of NTDs in Ireland.**
- **The key areas on which baseline data are urgently needed prior to any initiation of mandatory folic acid food fortification are: the incidence of NTDs in Ireland, the dietary folate and folic acid intakes of the population, the blood levels of folate of the population and the folic acid content of bread available in Ireland.**

7.1 Background

Much has been learned since mandatory addition of folic acid to enriched flour in the US, and to all white flour in Canada. One of the key recommendations to emerge from the reliable experience of North America is the importance of having a coherent empirical and science-based plan in place for monitoring the effectiveness and safety of such a large-scale intervention in the long-term (103,109). This Chapter of the report outlines the monitoring that is essential in Ireland in order to record the benefits of folic acid food fortification and to ensure that the programme is functioning as intended over the long-term in reducing the incidence of pregnancies affected by NTDs.

Having reliable baseline data to accurately assess the pre-fortification situation in Ireland is crucial for monitoring. The timeline for establishing this baseline is limited as all data must be collected prior to any initiation of mandatory folic acid food fortification. Therefore, there is considerable urgency around undertaking a reliable assessment of the pre-fortification conditions in Ireland. Four essential elements are required for this baseline assessment, namely:

1. Data on the incidence of pregnancies affected by NTDs throughout the Republic of Ireland, including those that do not reach term (outlined in section 7.2)
2. Data on dietary folate and folic acid intakes of sub-groups that are as representative as possible of the age and sex groups within the Irish population (outlined in section 7.3)
3. Data on the blood folate levels of sub-groups that are as representative as possible of the age and sex groups within the Irish population (outlined in section 7.4)
4. Data on the folic acid content of bread, as this is the food vehicle to be used in the national mandatory fortification programme (outlined in section 7.5).

7.2 Monitoring Incidence of NTDs

A reduction in the incidence of pregnancies affected by NTDs is the main intended outcome of folic acid food fortification in Ireland. Therefore, a comprehensive assessment of the incidence of NTDs before and after fortification is necessary to estimate the effects of the fortification programme.

Currently, there is no national register of congenital birth defects in Ireland and no reliable data exist to provide a baseline estimation of the incidence of NTDs. As described in Chapter 2, data on the incidence of NTDs in Ireland are provided through the European Surveillance of Congenital Anomalies (EUROCAT). These data only cover approximately two-thirds of births in Ireland. These registries do not provide cover for the geographic areas of the North, West and Midlands of the country. However, it may be possible to collect live and still-birth data retrospectively from these areas, if the current registries were extended to cover all regions of Ireland.

Another important limitation of the existing registries in Ireland is the exclusion of cases that do not reach 24 weeks gestation. It may be possible to access data on such cases through use of information on prenatal ultrasound scans. Advances in ultrasound

technologies have facilitated the prenatal diagnosis of NTDs and this service is currently available at a limited number of sites in the Republic of Ireland. Cases of NTDs from all of these sites could be recorded to allow assessment of the overall numbers of pregnancies affected by NTDs on a national basis. A network of obstetricians from each unit in Ireland would be required to enable the establishment and maintenance of such a database, as regular follow-up would be needed to minimise missed cases.

Baseline requirements for monitoring incidence of NTDs

- In summary, the long-term best practice for surveillance of NTDs involves extension and development of the current EUROCAT registries, so that they are amalgamated into one register that would be extended to provide national coverage.

This proposed new register should also include data on antenatal diagnosis of NTDs to cover those pregnancies that do not reach term.

The development of such a register would enable long-term trends in the incidence of NTDs to be recorded, along with all other known birth defects.

- However, due to the urgency around establishing a reliable baseline, the amalgamation and extension of the current EUROCAT registries on live and still-births should be initiated separately from the establishment of a system to collect nationwide data on prenatal diagnoses of pregnancies and births affected by NTDs.
- Privacy and ethical issues need to be considered in the operation of both the national register and the data on prenatal cases. This will need to take account of legislative issues also.

7.3 Monitoring Dietary Folate and Folic Acid Intakes

Although women of childbearing age are the target group of the folic acid food fortification programme, many others in the population will consume an increased amount of folic acid due to the fortification of a staple food.

While this is estimated to be of particular benefit to many sub-groups, e.g. folic acid is expected to be protective against cardiovascular disease, which will particularly benefit middle-aged and older groups, the true effects need to be measured. The low level of folic acid fortification chosen means that there is

negligible risk of masking vitamin B₁₂ deficiency, which is the only established risk associated with high intakes of folic acid (see Chapter 4).

Regular monitoring of all population sub-groups in terms of the various forms of dietary folate intake (including folic acid from food and supplements) will provide important information on the level of intake of B vitamin folate and folic acid, food sources and the impact of folic acid food fortification. However, due to incomplete information of the bioavailability of naturally occurring food folate, dietary intake data need to be supplemented by data on actual folate status of the individual, which can be calculated from several parameters in blood as described later in section 7.4.

The food supply is continuously evolving over time and more folic acid fortified foods are expected on the Irish market, which emphasises the need for ongoing monitoring of dietary intakes. This dietary monitoring will enable corrective action to be taken, should voluntary food fortification pose a risk of excessive consumption of folic acid by any particular sub-group in the population. Dietary intake data must be of adequate quality to differentiate between intakes of naturally occurring food folate and folic acid which has been added to foodstuffs. This is necessary to assess the risk of individuals consuming excessive amounts of folic acid due to their food choice.

Baseline requirements for monitoring dietary folate and folic acid intakes

- There are good dietary data available in Ireland for the purpose of establishing a pre-fortification baseline on dietary folate intakes for most sub-groups of the population:
 - recent data from the Irish Universities Nutrition Alliance (59) provide good baseline information for children ages 5-12 years and for adults aged 18-64 years
 - data are currently being collected from adolescents
 - less detailed dietary intake data are also available on large numbers of young women, pregnant women, other adults and children from the SLAN surveys.
- However, information on the dietary intakes of pre-school children and adults older than 65 years is desirable.

7.4 Monitoring Blood Indicators of Folate Status

Recent reports from nationally representative surveys in the US that involve blood samples, demonstrate the significant impact of folic acid fortification on B vitamin status indicators (99). These surveys can contribute valuable information in terms of the adequacy of the levels of folic acid used. For example, monitoring blood folate status can indicate if the national fortification programme is providing women of childbearing age with enough folic acid to minimise folate deficiency.

Other important blood parameters in this regard, include vitamin B₁₂, homocysteine and genetic markers of altered folate metabolism:

- monitoring vitamin B₁₂ blood status will provide valuable information on the risk of deficiency of this important nutrient whose metabolism is closely related to folate (see Chapter 3)
- homocysteine (a protein in the body) is a marker of cardiovascular disease risk and blood levels of this are inversely related to folate status. This is why folic acid is often prescribed to reduce risk of cardiovascular disease (see Chapter 4). Folic acid food fortification is expected to induce favourable changes in blood homocysteine levels in the Irish population and, therefore, monitoring blood homocysteine levels is important
- finally, where possible, blood samples collected should be analysed for known markers of genetic variability in folate metabolism. This may help explain differences that may be detected through monitoring the response to folic acid food fortification in various population sub-groups in terms of blood parameters.

Baseline requirements for monitoring blood indicators of folate status

- Monitoring actual folate status through blood sampling needs to be undertaken, prior to fortification, to establish a baseline estimate of folate status pre-fortification. After food fortification occurs, a sharp rise would be expected in blood parameters such as serum and red cell folate within a relatively short timeframe (three months approximately). Therefore, blood status can provide an early estimation of the impact of food fortification in the various population sub-groups. In addition to this, however, blood data can provide quantifiable information on the effects of folic acid food fortification.

Assessment of the following blood parameters will provide a comprehensive evaluation of pre-fortification status:

- blood levels of folate (serum/plasma total folate levels) or
- blood levels of folate in red blood cells, known as red cell folate are essential.

These are described in Chapter 3.

If possible, the following parameters should also be assessed:

- Blood levels (serum/plasma) of vitamin B₁₂
- Blood levels (serum/plasma) of total homocysteine
- 5,10-Methylenetetrahydrofolate Reductase 677C->T genotype.
- Samples should be collected from as many sub-groups of the population as possible, to ensure the baseline assessment is as representative as possible. A purposeful approach to sampling should be taken to ensure population sub-groups such as infants, children, women of childbearing age, pregnant women, adults and older people are included.
- The opportunity to include blood samples available from on-going research studies of healthy individuals in Ireland could also be availed of.

7.5 Monitoring Folic Acid Content of Bread

Under a mandatory fortification programme in Ireland, folic acid fortified bread will be labelled to facilitate consumer choice. The national food monitoring and surveillance programme of the FSAI will include monitoring of all types of fortified breads marketed in Ireland for compliance with the new legislation on fortification. This food monitoring represents a critical aspect for ensuring folic acid levels added are within the targeted parameters.

Because there is no upper limit for folic acid food fortification in the US, mandatory food fortification there exceeded regulatory requirements - a situation termed as 'overage' (102,103). To avoid this situation, folic acid food fortification in Ireland will use both upper and lower criteria for the level of folic acid added. Such a targeted approach is implemented in Canada.

The committee charged with implementing folic acid food fortification will draw up a comprehensive plan for food monitoring.

7.6 Timelines to Establish Baseline Data

If a decision to implement a fortification policy is announced, the timeframe for establishing a true baseline is very limited due to variation in length of time required to initiate fortification among the various industry processes involved. In effect, once the decision to move forward on fortification is announced, initiation of some fortification processes by industry can be expected as industry moves forward to meet the deadline where fortification legislation is enacted.

Therefore, there is urgency around the data collection needed to establish a baseline on all parameters.

A reliable baseline is essential for on-going monitoring of the effectiveness and safety of folic acid food fortification.

In Summary

A plan for monitoring is a key element of a national mandatory folic acid food fortification programme. Monitoring is the only means by which the effects of the programme can be assessed. The intended effect of this programme is a reduction in the incidence of pregnancies affected by NTDs in Ireland.

Four key areas need to be addressed as part of the monitoring plan. Baseline data on each of these areas will be urgently needed if the decision to implement a fortification policy is announced. That is data on the incidence of pregnancies affected by NTDs in Ireland, data on amounts and sources of dietary folate and folic acid intakes in the population, data on blood levels of folate in the population and data on the folic acid content of fortified bread.

CHAPTER 8. HEALTH PROMOTION

Key Conclusions

- **An integrated national health promotion programme needs to be launched in conjunction with the recommended introduction of mandatory folic acid food fortification.**
- **The policy of recommending folic acid supplements to all women of childbearing age who are sexually active and may become pregnant, needs to continue, alongside a policy of food fortification in Ireland to provide optimal protection for pregnancies against the risk of NTDs.**
- **The development of supportive partnerships between Government departments, the Health Service Executive, voluntary, public and commercial sectors will be central to the success of this important programme for Ireland.**
- **Monitoring and evaluation will be important elements of the national health promotion programme.**

8.1 Introduction

A national policy of mandatory fortification of most bread with folic acid will contribute significantly to the reduction in the numbers of babies born with NTDs in Ireland. While this approach represents the most effective means of increasing women's folate status at the time of conception, it will only provide a little over 25% of their special folic acid requirements for a healthy baby (400µg/day) on an on-going basis.

Fortifying bread to a higher level to provide women of childbearing age, who are sexually active, with all of their special folic acid requirement (400µg/day), would lead to over consumption of folic acid by other population groups who eat greater quantities of bread. Therefore, while the level of addition of folic acid to bread will significantly reduce the incidence of NTDs, it will not provide women of childbearing age with all of what they need to provide optimal protection of their pregnancies.

This means that the policy of recommending folic acid supplements for women of childbearing age

needs to continue. Prevention of NTDs in Ireland, therefore, requires the dual approach of mandatory folic acid fortification of most breads and provision of advice to women of childbearing age, who are sexually active, about the importance of taking folic acid supplements.

The promotion of folic acid, as a means of preventing NTDs, has been ongoing in Ireland since 1993 (35). This has focused on encouraging women to eat foods rich in the B vitamin folate and to take a daily 400µg of folic acid supplement if there is a chance that they may become pregnant. Women are advised to take this action prior to conception and for the first 12 weeks of pregnancy, in order to help reduce the incidence of NTDs. Over the years since 1993, the advice to women about folic acid has become more defined in line with findings from ongoing research. A detailed description of these actual recommendations and how they have become more specific is outlined in Appendix 1.

The initial promotion campaigns involved the compilation and circulation of a leaflet on the beneficial effects of folic acid to health professionals and pharmacies. This was enhanced during 2000-2001 with a public awareness campaign on folic acid undertaken jointly by the Department of Health and Children in the Republic of Ireland and the Health Promotion Agency in Northern Ireland. The campaign included the publication and nationwide distribution of an information leaflet *Folic Acid - One of Life's Essentials* and an accompanying poster, supported by television and radio advertising.

Subsequent evaluation of the campaign, based on a random sample of 2,000 adults, North and South, demonstrated that 62% of adults had heard of folic acid and that 86% of women aged 18 to 45 years (the target group) had heard of folic acid. In addition, of those respondents who had heard of folic acid, 71% could remember seeing, reading or hearing information, advertising or publicity on folic acid over the previous six months. The leaflet developed for the campaign continues to be available in both the Republic of Ireland and Northern Ireland.

With regard to knowledge and practice in relation to folic acid, between 1996 and 2002, 300 women attending their first antenatal booking in each of the Dublin maternity hospitals were surveyed each year (131). Less than half the pregnancies each year were planned. During the period, the proportion of women who had heard of folic acid rose from 54% to 94%. Knowledge that folic acid could prevent NTDs also rose - from 21% to 66%. Although the proportion of women surveyed who took folic acid during pregnancy increased from 14% in 1996 to 83% in 2002, the numbers taking folic acid in time to prevent birth defects (i.e. pre-conceptual intake) did not rise above 24% in any year.

Even the rigorous and systematic provision of information on the importance of pre-conceptual folic acid to women of childbearing age has limited effectiveness as was evident from a recent GP practice-based study. Less than half of the women who had been given both verbal and written advice on the importance of taking folic acid before becoming pregnant, took folic acid pre-conceptually and in time to prevent the development of a NTD (124). As confirmed by several studies in Ireland, this is about the proportion of pregnancies that are planned.

It is evident that the biggest benefits of food fortification will be for women whose pregnancies are unplanned and who are hardest to reach. However the message that all women of childbearing age who are sexually active need to take an additional 400µg of folic acid in the form of a supplement needs to be vigorously promoted to ensure that as many pregnancies as possible in Ireland have optimal protection against the development of NTDs as presented in Chapter 2.

8.2 A National Health Promotion Programme

An integrated national health promotion programme needs to be launched in conjunction with the recommended introduction of folic acid food fortification.

The core objectives of such a health promotion programme will be:

- to increase awareness of the importance of taking additional folic acid for the protection of pregnancies against risk of NTDs, in the general female population and among health professionals. All women of childbearing age who are sexually active are currently advised to take additional folic acid before conception and during the first 12 weeks into pregnancy. As less than half of all pregnancies are planned, the Committee recommends the following:

- To prevent the risk of NTDs, all women of childbearing age, who are sexually active are advised to take an additional 400µg of folic acid daily in the form of a supplement.
- When a woman 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.
- In addition, women are advised to eat foods fortified with folic acid and natural food sources everyday to meet their individual needs for vitamin folate.
- 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.

- to allay concerns among the general public about the fortification of foods with folic acid.

The sub-groups that must be seen as key targets of the national health promotion programme are:

- women of childbearing age who may become pregnant; women from socially disadvantaged backgrounds present a particular challenge because generally speaking, they have a lower folate status and are less likely to take folic acid supplements
- health professionals, doctors, nurses, pharmacists, teachers, journalists and others who have roles that influence behaviour
- the commercial sector, including food retailers, pharmacies, supermarkets and health food outlets
- manufacturers of bread fortified under the mandatory folic acid fortification programme, manufacturers of foods voluntarily fortified with folic acid, manufacturers of folic acid supplements and relevant trade associations.

Central to the success of the national health promotion programme will be the development of supportive partnerships with Government departments beyond the Department of Health and Children, such as the Department of Finance, the Department of Education and Science, and the Department of Enterprise, Trade and Employment. In this regard, the support of the Health Service Executive (HSE) will be vital to the successful implementation of the promotion programme at local and national level. Creative partnerships with the voluntary, public and commercial sectors will also be essential to the effectiveness of the programme, so that different audiences within their own particular settings may be reached and influenced.

It is suggested that measures to be taken in support of the national promotion programme should include:

1. **Developmental research:** this should identify the barriers that can prevent women of different ages, socio-economic and cultural backgrounds from taking folic acid supplements, both prior to conception and in the first trimester of pregnancy. This information is necessary to ensure that the most meaningful and relevant messages are targeted at each of the different groups. Research is also required to identify and allay concerns across all sub-groups about the fortification of food with folic acid.
2. **Monitoring surveys** to cover folic acid supplement use and changes in public attitudes towards folic acid use and fortified foods. These data could be addressed as part of the monitoring of dietary folate and folic acid intakes as discussed in of Chapter 7.
3. **Information compiled and delivered professionally** to the public through leaflets, posters, the internet, dedicated advertising and editorial coverage in the media (local and national).
4. **Widespread dissemination of all evidence (existing and new)** relating to the effectiveness of folic acid in the prevention of NTDs and other health benefits.
5. **Educational materials designed for secondary school teachers** containing guidance for pupils on folic acid use.

8.3 Health Promotion Settings

Several health promotion settings - notably schools, workplaces, communities and health service settings - provide a focus for national promotion of folic acid supplement use by women of childbearing age. In addition, the topics of nutrition and sexual health are key areas for the inclusion of health promotion initiatives on the role of folic acid in the prevention of NTDs.

Schools

The Social, Personal and Health Education (SPHE) curriculum for senior cycle students is being developed at present and affords an opportunity to design appropriate materials for students and teachers in association with the Department of Education and Science, and the National Council for Curriculum Assessment (NCCA). Similar developmental work is needed in out-of-school settings for early school leavers and could be carried out in association with the National Youth Council of Ireland. In addition, schools are workplace settings for many women and provide an opportunity to provide clear focused messages on folic acid supplementation.

Workplaces

Workplaces present opportunities to launch awareness programmes targeted at women about the importance of folic acid. The development and distribution of materials to support such programmes should be included in national health promotion guidelines for workplaces.

Communities

Initiatives to promote appropriate folic acid use in communities could be developed in partnership with local community networks, organisations and groups. Examples include local peer-led programmes in primary healthcare, such as the Community Mothers who work with other mothers mainly in disadvantaged areas and among the Traveller community.

Folic acid supplements are available throughout the country in pharmacies, many supermarkets and health food stores. Measures to promote and widen this availability and accessibility need to be undertaken. The placement and display of supplements with sanitary products instead of with other supplements might increase usage among young women. In addition, because there is currently a relatively large variation in the price among the different brands of supplements, price regulation should be considered as an option to ensure ready access. The cost of over-the-counter folic acid supplements varies between about €2 and €2.75 for a 30 day supply, however, it is important to identify if cost is a barrier to use among women on lower incomes. If cost is an issue, price regulation and/or providing folic acid supplements free of charge needs to be considered (perhaps through the General Medical Service). The labelling of female contraceptives and sanitary products to include messages on the use of folic acid should be considered, to help increase the proportions of women taking folic acid supplements prior to conception.

Home

Support from family members (among parents, partners and grandparents) should be sought by raising awareness about the need for women of childbearing age who are sexually active to take folic acid supplements.

Health services

The community of health professionals, which includes dietitians, nutritionists, pharmacists, general practitioners, practice nurses, public health nurses and antenatal clinic staff, is a key area to be targeted with training and awareness modules on the issue of folic acid and on the concerns of clients in relation to supplement use. The role of all health professionals needs to be developed to maximise the practice of advocacy in promoting the use of folic acid supplementation among women of childbearing age.

8.4 Going Forward

Clearly, a key objective of the national health promotion programme is the creation of a supportive environment for change, aimed at making women more aware of the importance of folic acid, more likely to locate information about it, more ready to acquire it and more likely to take it. Previous campaigns on the promotion of folic acid (2000) have thrown up several issues and challenges:

- low awareness of the relevance of folic acid
- the benefit of taking folic acid is not generally appreciated by young women who are sexually active, but not planning to become pregnant
- concerns about taking supplements
- sensitivity of the nature of the issue
- the key concept of linking folic acid supplementation for all women who are sexually active over their full reproductive cycle from puberty to the menopause is a significant challenge and will need the involvement of teachers, parents, pupils, as well as health professionals.

Currently, only a proportion of women planning to become pregnant take a supplement at the appropriate time. Unplanned pregnancies, which represent more than half of all pregnancies in Ireland, remain unprotected from NTDs. To improve this situation, key messages about folic acid supplementation targeting young women who are sexually active must effect a major attitudinal shift among this sub-group and among those who influence their behaviour. This requires careful research and presentation.

Monitoring and surveillance

Monitoring and surveillance of the effectiveness of an integrated national health promotion programme will hope to identify:

- evidence of greater pre-conceptual use of folic acid supplements among pregnant women in Ireland
- an improvement in knowledge, attitudes and behaviour among all women of childbearing age who are sexually active
- an increase in knowledge and changes in attitudes among the general population
- correct knowledge and positive attitude among health professionals, teachers and other influential groups about the advocacy and promotion of folic acid supplement use
- increased availability and access to folic acid supplements.

In Summary

An integrated national health promotion programme needs to be launched in conjunction with the recommended introduction of mandatory folic acid food fortification. The policy of recommending folic acid supplements to all women of childbearing age who are sexually active, needs to continue alongside a policy of food fortification in Ireland to provide optimal protection for pregnancies against the risk of NTDs. All women of childbearing age who are sexually active, are advised to take an additional 400µg of folic acid every day in the form of a supplement in case they become pregnant. That is, women from the age of reaching puberty through to the menopause. Women are advised to continue taking the supplement until the 12th week of pregnancy or until they receive advice from their consultant or doctor. They should be supported by everyone in their lives; partners, parents, grandparents and the wider community in following this recommendation. The development of supportive partnerships between Government departments, the HSE, voluntary, public and commercial sectors will be central to the success of this important programme for Ireland. Monitoring and evaluation will be important elements of the national health promotion programme.

CHAPTER 9. CONCLUSIONS AND RECOMMENDATIONS

9.1 Introduction

Advising women of childbearing age in Ireland to take folic acid supplements has had little impact on the incidence of pregnancies affected by NTDs, despite the numerous health promotion campaigns that have been undertaken. In contrast to this, compelling evidence from countries implementing mandatory folic acid flour fortification programmes has recently demonstrated that such a policy leads to significant reductions (ranging from 20-78%) in the incidence of NTDs. The Committee has considered all of the issues involved with the aim of making recommendations that will ensure maximum possible protection of all pregnancies from the development of NTDs without increasing risk to any other population sub-group in Ireland.

9.2 Conclusions

The broad conclusions of the Committee are that:

- It has been established that consumption of folic acid on a daily basis before conception and during the first few weeks of pregnancy can protect up to about 70% of pregnancies from the development of a NTD. Public health policy recommends women take 400µg of folic acid prior to conception and for the first 12 weeks of pregnancy, in order to reduce the risk of these serious birth defects. It should be noted, however, that folic acid does not protect against the development of all NTDs. It is known that approximately 30% are related to other unknown causes and are not prevented by taking folic acid.
- A national policy of mandatory fortification of bread with folic acid will contribute significantly to the reduction in the numbers of babies born with NTDs in Ireland. This approach represents the most effective means of increasing women's folate status at the time of conception. It will significantly reduce folate deficiency and ensure that all women of childbearing age consume at least 25% of their special folic acid requirements for the prevention of NTDs on an ongoing basis. This policy will require legislative change.
- The best and most reliable scientific evidence indicates that enriching most bread with folic acid, at a level that delivers 120µg per 100g of bread as consumed, will be both effective and safe. It will reduce the incidence of NTD-affected pregnancies by about 24% and will ensure that older adults do not consume excessive amounts of folic acid. In addition, it will yield other health benefits associated with eradicating folate deficiency, in particular, prevention of anaemia due to a shortage of vitamin folate in older adults. Available evidence indicates a possible (modest) reduction in cardiovascular disease risk in adults at this level of folic acid fortification but this requires further confirmation.

- While the level of addition of folic acid to bread will significantly reduce the incidence of NTDs, it will not, however, provide women of childbearing age with the full amount of folic acid they are recommended to consume for protection of their pregnancies. This means that the policy of recommending folic acid supplements for women of childbearing age needs to continue in conjunction with a policy of mandatory fortification. Prevention of NTDs in Ireland, therefore, requires the dual approach of mandatory folic acid fortification of most breads and provision of advice to women who may become pregnant (all who are sexually active) about the importance of taking folic acid supplements.
- Folic acid fortification of bread is technically achievable for the main types of bread marketed in Ireland. Labelling, nutrition and health claims can be accommodated within existing or proposed national and European regulations. Trade issues may arise but can be managed.
- Consumer choice can be accommodated by exclusion of some minor bread products and retail flour from the mandatory requirement for fortification.
- Monitoring is essential to ensure the fortification programme is implemented in a manner that is both effective and safe. Monitoring the levels of folic acid added to bread will be necessary to ensure compliance with the new regulations. Monitoring the levels of folic acid added to foods voluntarily fortified with folic acid and to supplements will be necessary to make sure the maximal levels currently being set in association with new EU legislation are not exceeded. Monitoring dietary intake of the B vitamin folate (both natural food folate and folic acid from both fortified food and supplements) and blood levels of folate within the various population sub-groups will provide an overall assessment of the programme's impact on folate intake and status. Finally, monitoring the incidence of NTDs will assess the effectiveness of the programme in terms of the main intended outcome.

9.3 Recommendations

The recommendations of the Committee are that:

Recommendation 1: Policy Aspects of Folic Acid Food Fortification

- All bread (white, wholemeal and brown) manufactured or marketed in Ireland, with the exception of minor bread products, should be fortified on a mandatory basis with folic acid at a level, which provides 120µg per 100g of bread as consumed.
- Consumer choice should be accommodated by excluding minor bread products as well as retail flour from the mandatory fortification programme.
- An implementation group should be established to oversee the operational issues associated with these recommendations and to advise the Minister on progress.

Recommendation 2: Legislation and Folic Acid Food Fortification

- The Department of Health and Children should make new regulations that would introduce mandatory fortification of all bread marketed in Ireland, with the exception of minor bread products.
- The new Regulations should provide for upper and lower tolerance limits around 120µg folic acid per 100g bread which will be set by the implementation group following consultation with the industry.
- The new regulations should address labelling and health and nutrition claims for breads fortified with folic acid.

Recommendation 3: Technical Aspects and Folic Acid Food Fortification

- The implementation committee should consult with the industry to determine the most appropriate point(s) in the bread-making process to add folic acid.
- Technical guidance and codes of practice should be developed to support ongoing quality assurance of the folic acid fortification process.
- External assessment procedures should be put in place to monitor the folic acid fortification levels of all fortified breads, compliance with the labelling format and health claims provided for in food legislation.
- An adequate lead in time before enactment of the legislation on folic acid fortification should be given to allow for adequate preparation by industry.

Recommendation 4: Monitoring the Effects of Folic Acid Food Fortification

- An assessment of all pregnancies affected by NTDs, including those that do not reach term, should be undertaken immediately to establish a baseline for monitoring.
- A national congenital birth defects register, which records all pregnancies affected by birth defects including those that do not reach term, should be established without delay for ongoing surveillance purposes.
- To assess the impact of the fortification programme on the population, the measurement of blood parameters relevant to folate status of all age-sex groups should be undertaken immediately to establish a baseline for monitoring and this should be repeated at regular intervals.
- Dietary intakes of the B vitamin, folate in all population sub-groups should be monitored regularly and these assessments should distinguish between intakes of naturally occurring food folate and folic acid from fortified foodstuffs and supplements.
- Monitoring of folic acid levels in breads should be included as part of the national food monitoring and surveillance programme.

- Monitoring of folic acid levels in foods voluntarily fortified with folic acid and in supplements available in Ireland should be included as part of the national food monitoring and surveillance programme.
- The implementation group should report to the Minister on the overall impact of the fortification programme as identified by the monitoring programmes.

Recommendation 5: Health Professionals and Folic Acid Food Fortification

- All relevant health professionals should be updated on the implications of the mandatory folic acid food fortification programme and on the need to continue to advise women of childbearing age, who are sexually active, to take folic acid supplements.
- Written and web-based material outlining the implications of the folic acid fortification programme for women's health should be made widely available by health professional representative bodies and agencies.
- The implementation committee should address barriers to folic acid supplement use, including cost and availability
- All relevant health professionals should be aware that high dose folic acid supplements may increase the risk of masking B₁₂ deficiency.

Recommendation 6: Folic Acid Supplements

- While the level of addition of folic acid to bread will contribute to a reduction in the incidence of NTDs, it will not, however, provide women who are sexually active and could become pregnant, with the optimal level recommended for protection of their pregnancies. Therefore, the policy of recommending folic acid supplements for women needs to continue.

Recommendation 7: Health Promotion Needs

- Awareness of the need for women of childbearing age, who are sexually active to take folic acid supplements should be actively and vigorously promoted through a national integrated health promotion programme involving all stakeholders across all settings.
- Awareness of the need for women of childbearing age who are sexually active to take folic acid supplements should be promoted by the relevant Government departments.

APPENDICES

APPENDIX 1
FOLIC ACID RECOMMENDATIONS IN IRELAND
- THE HISTORY

APPENDIX 2
SUBMISSION SHEET OF THE PUBLIC CONSULTATION

APPENDIX 1. FOLIC ACID RECOMMENDATIONS IN IRELAND - THE HISTORY

In 1993, Ireland, along with many other countries, issued recommendations to women regarding the recommended amount of vitamin folate, to reduce the risk of neural tube defects (NTDs) when evidence became available on the value of folic acid in the prevention of NTDs. During the 1990s, as further evidence on the role of folic acid in the prevention of NTDs and a greater understanding of the different forms of the vitamin folate was gained, Irish recommendations to women on taking folic acid became more specific as in many other countries. The recommendations since 1993, are presented below:

Recommendations of the Department of Health, 1993 are outlined below:

To prevent OCCURRENCE of NTD

For women likely to become pregnant, with no previous history of NTD, take an extra 400µg of folic acid daily prior to conception and during the first 12 weeks of pregnancy.

Four possible means of increasing intake of vitamin folate/folic acid were outlined:

- eating more foods naturally rich in folate
- eating more foods fortified with folic acid
- taking folic acid as medicinal or food supplement (folic acid only, not in a multivitamin)
- a combination of these approaches.

Women who have not been supplementing their folic acid/folate intake and who suspect they may be pregnant should start supplementation at once and continue until the 12th week of pregnancy.

To prevent RECURRENCE of NTD

For women who have already had a baby affected by a NTD, they were advised to talk to their doctor about:

- the increased risk of recurrence
- the need for supplements, 5mg of folic acid per day, if they are at risk of becoming pregnant
- the timing and type of the supplement
- the need for individual medical advice before starting supplements, especially for women on other medications such as anticonvulsant drugs or women with vitamin B₁₂ deficiency.

Source: Health Promotion Unit of Department of Health (1995) leaflet 'What every woman needs to know about the prevention of neural tube defects spina bifida and anencephaly'.

Recommendations of the Food Safety Advisory Board, 1997

In 1997 in Ireland, the Food Safety Advisory Board (Sub-committee on folic acid and NTDs), now the Food Safety Authority of Ireland, prepared a report on the value of folic acid in the prevention of NTDs and made recommendations, including recommendations to women that the best way of preventing NTDs was to take folic acid supplements.

These 1997 recommendations on folic acid are outlined below:

To prevent OCCURRENCE of NTD

Women of childbearing age should be advised that the best way of preventing NTDs is to take a daily supplement (tablet) containing 400µg of folic acid from at least four weeks before conception and to continue until the 12th week of pregnancy.

- Women should also be advised that another way of getting the extra folic acid is to consume foods fortified with folic acid.
- Women should be made aware of the fact that the consumption of foods naturally rich in folate is a much less effective way to increase body folate (and therefore, protection against NTDs) compared with taking folic acid supplements or fortified food.
- Women who suspect that they may be pregnant and who have not been supplementing their diet with folic acid should begin immediately taking supplement of 400µg of folic acid and continue for the first 12 weeks of pregnancy.
- To avoid taking excessive doses of folic acid, women should be advised that it would be prudent not to consume more than 1,000µg of folic acid (1mg) daily.
- Folic acid should be taken from pills containing folic acid only, not from multivitamins because of the danger, particularly to the developing foetus, of taking harmful levels of other vitamins often

contained in these preparations, notably A and D.

- As folic acid can interfere with anti-convulsant drugs, women who have epilepsy and who are on such medication require individual counselling from a medical practitioner before starting folic acid.

To prevent RECURRENCE of NTD

For women who have already had a baby affected by a NTD or have spina bifida themselves, they were advised to talk to their doctor about the increased risk of recurrence and benefits of folic acid.

Women who would become pregnant, should unless contraindicated, be advised to take 4.0mg of folic acid daily from at least four weeks before conception until the twelfth week of pregnancy. As 4.0mg was not available in Ireland at the time, a 5.0mg dose was advised.

The 4.0mg or 5.0mg dose was only to be taken under the supervision of a doctor for two main reasons:

- high doses can complicate the diagnosis of vitamin B₁₂ deficiency
- women with epilepsy who are on anti-convulsant therapy require individual counseling from a medical practitioner before starting folic acid.

The Food Safety Advisory Board, 1997, had three main recommendations

- 1) This specific advice on folic acid intakes to prevent the occurrence and recurrence of NTDs should be distributed through a national health promotion programme to increase the periconceptual use of folic acid.
- 2) The Committee on folic acid should examine the fortification of a staple food or foods with folic acid as an alternative or complementary strategy.
- 3) A study be undertaken to provide the data necessary for a comprehensive evaluation of the periconceptual use of folic acid.

With the realisation that less 50% of pregnancies are planned, the advice to women changed during the 1990s from targeting women who are likely to become pregnant in 1993 to targeting women of childbearing age from 1997 and in the later 1990s, advising women that if there was any possibility of becoming pregnant they needed additional folic acid daily.

Recommendations of the Health Promotion Unit, 2000

In 2000, the Health Promotion Unit in the Republic of Ireland and the Health Promotion Agency in Northern Ireland launched a joint health initiative to promote folic acid. The aim of the campaign was to educate all women on the benefits of folic acid, to ensure there is a clear understanding of what it is and to eliminate any confusion that existed.

To prevent NTDs, women were advised if there was any risk of becoming pregnant, to take an additional 400µg of folic acid daily before conception and until the 12th week of pregnancy to reduce the risk of having a baby affected by a NTD by approximately 70%. Women were advised the best way to get enough folic acid was to take one folic acid tablet with 400µg of folic acid everyday, in the form of folic acid only, not a multivitamin.

Source: Health Promotion Unit (RoI) and Health Promotion Agency (NI) campaign literature, 2000.

Recommendations of the Health Promotion Unit, 2001

In 2001, health promotion literature was even more specific, advising women if there was any possibility of becoming pregnant, that they should be taking folic acid, ideally at least two months before pregnancy and to continue until attendance at the maternity hospital and then to follow the instructions of their consultant or doctor.

Recommendations of the National Committee on Folic Acid Fortification, 2006

- To prevent the risk of NTDs, all women of childbearing age who are sexually active are advised to take an additional 400µg of folic acid daily in the form of a supplement.
- When a woman 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.
- In addition, women are advised to eat foods fortified with folic acid and natural food sources everyday to meet their individual needs for vitamin folate.
- 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.

APPENDIX 2: SUBMISSION SHEET OF THE PUBLIC SUBMISSION SHEET

Your Details

Name:

Name of organisation (if applicable):

Position within organisation (if applicable):

Address:

Phone number:

E mail address:

Q.1 Please select your submission type:

- Member of the general public/consumer representative
- Food industry/representative
- Healthcare professional
- Government agency
- Other group

- Please tick this box if you want your name to remain confidential

Section A - Crucial questions and your comments on policy

Q.2 Expert opinion in Ireland and in other countries is united in the view that adding folic acid to staple foods such as flour or bread is one of the most effective ways to reduce NTDs. Wherever this has been done, it has worked.

To what extent do you agree or disagree with the following statement?

Action needs to be taken to reduce the number of pregnancies affected by NTDs in Ireland.

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree
- Don't know/no opinion

Q.3 To what extent do you agree or disagree with the following statement?

National policy in Ireland should be changed to promote the addition of folic acid to bread or flour

- Strongly agree
- Agree
- Neither agree nor disagree
- Disagree
- Strongly disagree
- Don't know/no opinion

If you answered either 'Agree' or 'Strongly agree', please proceed to Q.4a

If you answered either 'Disagree' or 'Strongly disagree', please skip to Q.5

If you answered 'Neither agree or disagree' or 'Don't know' please skip to Q.6a

Q.4a You agree that "National policy in Ireland should be changed to promote the addition of folic acid to bread or flour".

There are three possible methods for changing national policy to promote the addition of folic acid to bread or flour. The objective of these options is to increase the average folic acid intake of women in the childbearing age group.

Please select the method which you feel would be most suitable for achieving this objective.

- I. Change national policy to implement a structured voluntary fortification where breads may have a targeted or standard amount of folic acid added - this bread would carry a special label
- II. Change national policy to mandatory fortification of some flour (bread-making) so that a targeted or standard amount is present in all breads as eaten
- III. Change national policy to mandatory fortification of all flour so that a targeted or standard amount of folic acid is present in all flour-containing foods as eaten
- IV. No preference/no opinion

Note: Wholemeal and organic flours/breads are excluded from all options.

Q.4b Do you have any reservations or comments on your option of choice?

- No concerns
- Concerns about consumer choice
- Concerns about effectiveness at reducing NTDs
- Concerns about monitoring
- Concerns about safety or side effects
- Other concerns - please expand _____

Now please skip to Q7

Q.5 You believe that national policy in Ireland should not be changed to promote the addition of folic acid to bread or flour. Why do you say this?

Now please skip to Q7

Q.6a You neither agree nor disagree that national policy in Ireland should be changed to promote the addition of folic acid to bread or flour. Why do you say this?

Q.6b Is there any extra information that would be helpful to you?

Section B - General questions and your comments on the prevention of NTDs

Q.7 Do you have any other data on the prevalence of NTDs in Ireland that are not discussed in the consultation document? Please specify below.

No, I do not have any other data

Q.8 Are you aware of other health risks associated with addition of folic acid to foods that were not discussed in the consultation document? Please specify below.

No, I am not aware of any other health risks

Q.9 Are you aware of other health benefits associated with addition of folic acid to foods that were not discussed in the consultation document? Please specify below

No I am not aware of any other health benefits

If you are a member or representative of the food industry, please continue to Q10

If you are not a member or representative of the food industry, please skip to Q.17 on the last page of this document

Section C - Questions and comments for the food industry

Q.10. Does the fortification of flour with folic acid present any technical difficulties? Please specify below.

No, I am not aware of any technical difficulties

Q.11 Are there any technical difficulties associated with the use of fortified flour in the manufacture of products? Please specify below.

No, I am not aware of any technical difficulties

Q.12 What overage is needed to achieve a level of folic acid in the final product at:

- a) 120µg of folic acid per 100g of bread as eaten, or
- b) 120µg of folic acid per 100g of flour-containing foods as eaten, or
- c) 190µg of folic acid per 100g of flour in bread as eaten

Please take into account any problems associated with adding folic acid at the milling stage, and potential losses during storage and during processing of individual products.

Q.13 What is the likely variability in the level of folic acid in the final product?

- High variability
- Fairly high variability
- A little variability
- No variability at all
- Don't know

Q.14 Is the variability in the level of folic acid likely to be different in different types of products?

Q.15 What are the cost implications of fortification for industry, and what is the likely impact on the cost of final products to the consumer?

Q.16. If compulsory fortification were to be introduced, how long would it be before industry could comply with the requirement, given the need to adapt processes, use up stocks of unfortified flour and introduce any necessary changes to product labels?

- Less than 3 months
- Three to six months
- Six months to one year
- One to three years
- More than three years

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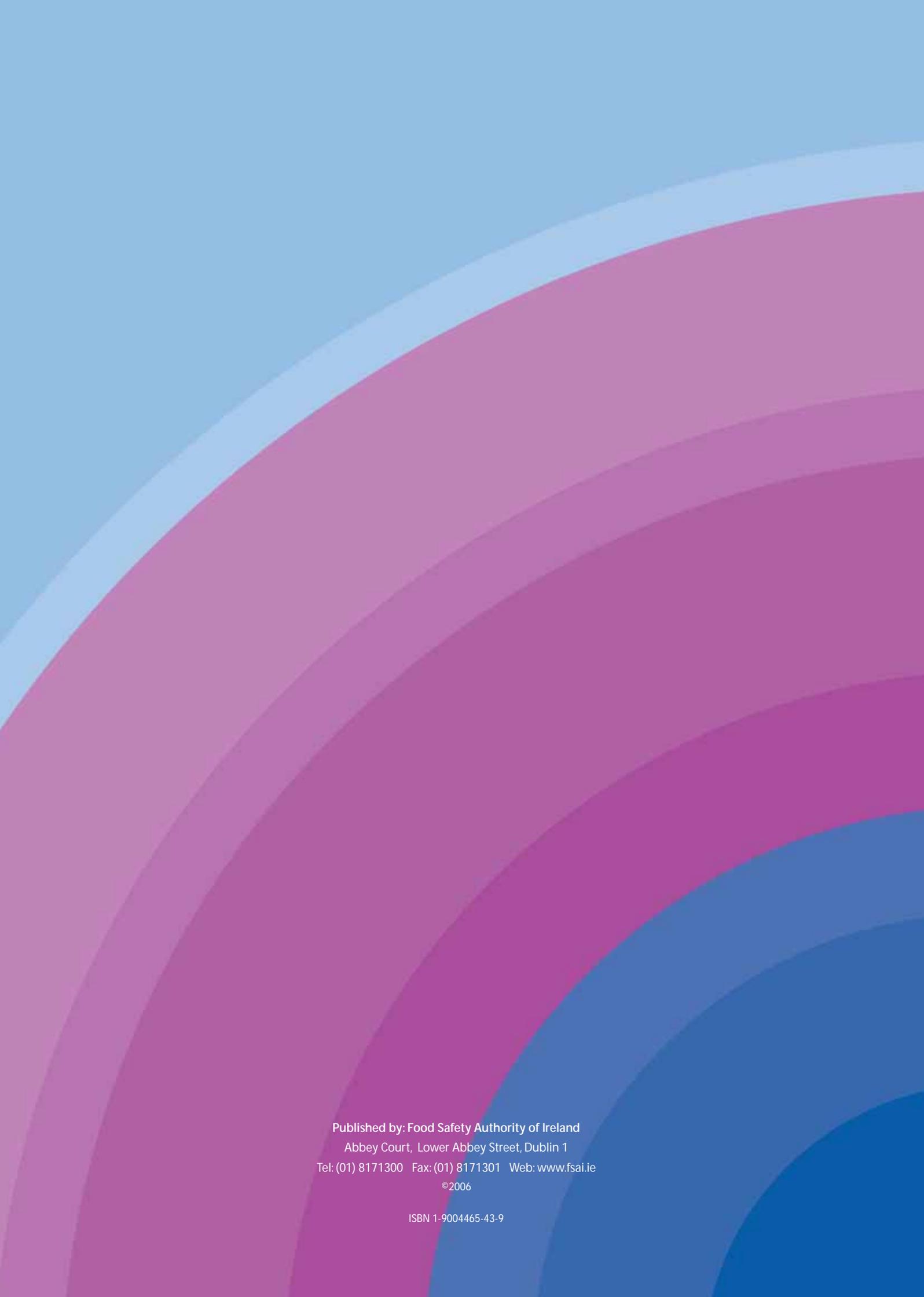
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