Special Report: Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe

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Part I: Overview
Part II: Country-Specific Chapters
Part III: Appendices
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Austria
Belgium
Croatia
Denmark
Finland
France
Germany
Ireland
Italy
Malta
Netherlands
Norway
Poland
Portugal
Spain
Sweden
Switzerland
United Kingdom

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RECOMMENDATIONS

1) European countries should review their policies regarding folic acid fortification and supplementation taking into account available information on benefits and hazards of both. They should pay special attention to results of studies done post mandatory fortification in countries that have introduced it.

2) European countries could prevent most neural tube defects in planned pregnancies by putting in place an official policy recommending periconceptional folic acid supplementation and taking steps to ensure that the population are aware of the benefits of supplementation and the importance of starting supplementation before conception.

3) As many pregnancies are unplanned, European countries could achieve more effective prevention of neural tube defects by additionally introducing fortification of a staple food with folic acid. The particular objectives of this policy would be preventing neural tube defects among women who do not plan their pregnancy, and reducing socio-economic inequalities in neural tube defect prevalence.

4) Health effects of supplementation and fortification should be monitored, and policies should be reviewed periodically in light of the findings.

5) The European population should be covered by high quality congenital malformation registers which collect information about affected pregnancies (livebirths, stillbirths and terminations for fetal abnormality). One important use for the information would be to assess the effect of folic acid supplementation and fortification on NTD rates as well as rates of other congenital malformation
SUMMARY

Background
Approximately 4,500 pregnancies every year in Europe result in a livebirth, stillbirth or termination of pregnancy of a baby/fetus affected by a Neural Tube Defects (NTD), mainly anencephaly and spina bifida. With the publication in 1991 of the MRC Vitamin Study, periconceptional folic acid supplementation was shown to be an effective method of preventing potentially two thirds of cases. In the EUROCAT Special Report 2003, we reviewed progress up to the end of the year 2000 in European countries in terms of developing and implementing public health policies to raise periconceptional folate status, and analysed data on the prevalence of neural tube defects from 36 congenital anomaly registries in 17 countries to determine the extent to which neural tube defects had been prevented. Our findings were disappointing and prompted us to make a number of recommendations including consideration being given by governments to fortifying a staple food with folic acid.

We recognise that the folic acid / neural tube defect story is still being written, and this current report is an update of both folic acid policies and neural tube defect rates. The report will be updated annually.

Methods
EUROCAT is now a network of 43 congenital anomaly registries in 20 European countries collaborating in the epidemiological surveillance of congenital anomalies. Representatives from eighteen countries participating in EUROCAT provided information about policy, health education campaigns and surveys of folic acid supplement uptake in their country. NTD rates (including livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis) were extracted from the EUROCAT Central Registry database for 1980-2002.

Results
We found that there have been some changes in policy and practice since our report in 2003. In Italy, where there was no official supplementation policy at the end of 2002 and no official interest, there is now a lively Folic Acid Network which has succeeded in achieving a supplementation policy and a health education drive. In Belgium, the Association Spina Bifida Belge Francophone was so disturbed by the official indifference revealed in the 2003
EUROCAT Report that they are instigating a health education campaign. In Spain there has been an increase in health education about folic acid. Ireland and Denmark report some movement towards mandatory fortification, but this has not yet happened.

At the beginning of 2005, an official governmental recommendation that women planning a pregnancy should take 0.4 mg of folic acid supplementation daily was in operation in eleven of the eighteen countries. The earliest countries to introduce an official supplementation policy were the UK, Ireland and Netherlands in 1992-3 and the latest was Italy in 2004. In the remaining 7 participating countries, no official government recommendation about supplementation was in place; however, professional bodies had recommended supplementation, and two countries had an official policy of encouraging women to increase their dietary intake of folate periconceptionally. Nine of the eighteen countries had official health education initiatives (either ongoing or in the past): UK, Ireland, France, Italy, Spain, Poland, Netherlands, Norway and Denmark.

Despite all measures taken to date, the majority of women in all countries surveyed are not taking folic acid supplements prior to and for the first weeks after conception.

The situation regarding low uptake of supplementation advice is reflected in the lack of a clear decline in the prevalence of neural tube defects across Europe. Nevertheless, there was some evidence that in countries with a supplementation policy, a small decline in prevalence had taken place. In UK and Ireland, it was difficult to distinguish any effect of supplementation policy against the background of a strongly declining NTD prevalence throughout the 1980s and 1990s, predating folic acid advice.

Conclusion

The potential for preventing NTDs by periconceptional folic acid supplementation is still far from being fulfilled in Europe. Only a public health policy including folic acid fortification of a staple food is likely to result in large-scale prevention of NTDs while avoiding widening socio-economic inequalities in NTD prevalence.
Part I

Overview of Neural Tube Defects
1. **INTRODUCTION**

Across Europe, an estimated 4,500 pregnancies are affected by Neural Tube Defects (NTD) each year. Evidence of a possible association between folic acid and neural tube defects has been described in the scientific literature for more than three decades (Scott et al, 1995). Since the early 1980s a number of intervention trials examining the effects of periconceptional folic acid on the incidence of NTD have been published, with the first unambiguous evidence of the effectiveness of periconceptional folic acid coming in 1991 on the publication of the results of the Medical Research Council (MRC) Vitamin Study (MRC Vitamin Study Research Group, 1991). On the basis of this trial, it has been estimated that improving folate status sufficiently would result in the prevention of 72% of all NTD.

This report examines the periconceptional folic acid policies and implementation strategies across Europe since 1991 and the reported prevalence rates of neural tube defects until the end of 2002. Contributions from EUROCAT (European Surveillance of Congenital Anomalies) members representing 18 countries are included in the form of chapters describing policy and practice in their respective countries in relation to: periconceptional folic acid supplementation, dietary advice, food fortification and women’s knowledge about the advice and compliance with recommendations. These are set within the context of laws relating to termination of pregnancy for fetal abnormality and of what is known about the proportion of pregnancies that are planned. The prevalence of neural tube defects up to the end of 2002 is examined in relation to policies on folic acid supplementation across Europe.

Although there is increasing evidence to suggest that folic acid may also protect against other congenital anomalies (Botto, Olney and Erickson 2004) this report will focus on NTD, as it is for this group of anomalies that the body of evidence for the protective effect of folic acid is strongest.
2. **BACKGROUND**

2.1 **What are Neural Tube Defects?**

The development of the brain and spinal cord is observable at approximately 18 days after conception as a localised thickening of cells collectively known as the neural plate. Following elongation and subsequent formation of the neural tube, closure at the midbrain/cervical region occurs at about day 21 and closure at the cephalic end at about day 26. The closed neural tube then stimulates the development of the bony structures of the vertebral column and the skull. The group of congenital malformations known as NTD are the collective set of malformations which occur if the bone fails to form above any unclosed region of the neural tube. One of the main difficulties regarding the prevention of neural tube defects lies in the fact that NTD occur before most women know they are pregnant.

The location of the defect along the neuraxis determines the specific anomaly presented: if the cephalic end of the tube is affected, the outcome is the lethal condition anencephalus, or more rarely encephalocele or iniencephalus; if any of the remainder is affected, the outcome is spina bifida. Many neonates with spina bifida and encephalocele survive but the vast majority have lifelong moderate or severe disability including lower limb paralysis, poor bladder control, and intellectual impairment.

2.2 **Geographic, Temporal and Socio-economic Variation in the Prevalence of NTD**

There is marked geographic variation in the prevalence of NTD (Little and Elwood, 1992) with the UK and Ireland exhibiting the highest rates in Europe for many decades (Penrose, 1957; EUROCAT Working Group, 1991). There has been a decline in many parts of the world in the prevalence of neural tube defects. This decline appears to have begun earlier in some places than in others, for example: 1950s in the Netherlands (Romijn and Treffers, 1983), and 1970s in the UK (Kadir et al, 1999). While the decline in birth prevalence in UK and Ireland since the early 1980s is partly due to prenatal diagnosis and selective termination of affected pregnancies, decreasing total prevalence is still seen when terminated pregnancies are included (EUROCAT Working Group 91).
Data are available from several countries up to the mid-1970s which demonstrate a higher prevalence of NTD in babies of women of low socio-economic status: (Elwood and Nevin 1973; Anderson et al 1958; Field 1978; Hemminki et al 1981; Naggan and MacMahon 1967). This association may have become weaker more recently, (Vrijheid et al 2000), but there is evidence emerging that women of higher socio-economic status are much more likely to take periconceptional folic acid than are women of lower socio-economic status (de Jong-van den Berg et al 2005, Relton et al 2005, Sen et al 2001; de Walle et al 1999;) and the predicted effect of this is that over time the difference in NTD pregnancy rates between mothers from higher and lower socio-economic backgrounds will increase.

2.3 What is Folic Acid?
The term folate refers to a family of compounds which have common vitamin activity and have a double aromatic ring of a pteridine attached to a \( p \)-aminobenzoate and a glutamate. Folic acid (pteroyl glutamic acid) is the synthetic form of folate (one of the B-vitamin group). It is highly bio-available, stable to heat exposure (eg. during cooking), and not present in nature. In order that folic acid can function enzymatically it must be converted \textit{in vivo} to the natural forms – first to the dihydro and subsequently the tetrahydro form, both reactions being catalysed by the enzyme dihydrofolate reductase (Scott & Weir, 1994).

2.4 Sources of Folic Acid
Folate is found in a wide variety of foods, but liver is the only particularly good source (see Table 1). Cruciferous vegetables such as cabbage, cauliflower and broccoli are rich in natural folate; however, few women have sufficiently high intakes of these foods to offer optimal protection for the fetus. The relatively low bio-availability of natural folate adds to the problem; natural food folate is only half as bio-available as folic acid. (Gregory et al, 1991).

It can be seen from Figure 1 that the folate-rich foods shown in Table 1 do not necessarily contribute the most to overall intake of folate in a population (McNulty, 1997). The main food sources of folate consumed in the UK (as determined in the Dietary and Nutritional Survey of British adults) are shown in Figure 1 below. The paucity of foods eaten on a regular basis which are folate-rich, leads to a problem in
achieving the higher folate status thought to be necessary to reduce the risk of development of NTD in the fetus during pregnancy (Cuskelly et al, 1996).

Mean dietary intake of folate is considerably less than the recommended amount for prevention of NTD in those countries reporting mean values in Part 2 of this report.

Table 1: Folate Content* of Selected Foods

<table>
<thead>
<tr>
<th>Average portion</th>
<th>µg of folate</th>
<th>Folic acid equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken liver (grilled or fried)</td>
<td>500</td>
<td>250</td>
</tr>
<tr>
<td>Asparagus</td>
<td>193</td>
<td>96</td>
</tr>
<tr>
<td>Fortified breakfast cereal</td>
<td>83</td>
<td>41</td>
</tr>
<tr>
<td>Spinach</td>
<td>81</td>
<td>40</td>
</tr>
<tr>
<td>Broccoli</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>Green beans</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Marmite</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Orange juice</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Baked beans</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Fruit yoghurt</td>
<td>24</td>
<td>12</td>
</tr>
</tbody>
</table>

Data from the UK National Food Survey indicate that average dietary folate intakes in Britain have increased substantially since the mid 1980s (the current average daily intake is 311µg for men and 213µg for women) coinciding with the increased proportion of breakfast cereal manufacturers introducing voluntary fortification with vitamins (including folic acid) between the years 1985 and 1991. In addition, bread voluntarily fortified with folic acid first became available in the UK in 1991. National food survey data suggest that steady increases occurred in the consumption of fruit juice and fruits in British households during the past three decades (Rayner, Mockford and Boaz, 1998).
Figure 1: Main Food Sources of Folate*

Women (n=1110)

- veg & potatoes: 31%
- cereals: 23%
- meat, fish, eggs, milk: 24%
- beverages: 12%
- all other foods: 10%

Men (n=1087)

- veg & potatoes: 29%
- cereals: 20%
- meat, fish, eggs, milk: 20%
- beverages: 24%
- all other foods: 7%

* MAFF (1994)
2.5 **Folic Acid and Neural Tube Defects: The Evidence for a Protective Effect**

The possibility that maternal folate status might be implicated in NTD was raised in 1965 when Hibbard and Smithells showed that a test indicating lack of folate or disturbed folate metabolism (the FIGLU test) was more often positive in women carrying a fetus with an NTD than in controls (Hibbard and Smithells, 1965). This finding stimulated a number of studies investigating the role of folic acid in relation to NTDs.

a) **Recurrence studies**

In 1980 Smithells et al reported on a multi-centre (5 UK centres) non-randomised prospective trial of periconceptional multivitamin supplementation (containing folic acid) for the prevention of recurrence of NTD (i.e. mothers who have had a baby with NTD having another baby with NTD). This study found a statistically significant difference between the recurrence risk in supplemented women (0.6%) and that of the controls (5.0%). The lack of randomisation made interpretation of these results difficult. Laurence et al (1981) reported on the results of another intervention study for the prevention of recurrence of NTD. This was a small, randomised controlled trial in which the study group took 4mg folic acid daily while the control group took a placebo. While supplemented women had fewer recurrences, the small size and methodological weaknesses left the question still open.

The MRC vitamin study (1984-1991) conclusively demonstrated a substantial reduction of the recurrence risk for NTD with periconceptional folic acid treatment. This was an international, multi-centre, double-blind randomised trial involving 33 centres of which 17 were in the UK (MRC Vitamin Study Research Group, 1991). The recurrence rate in the folic acid groups was 1.0% and in the non folic acid groups it was 3.5%, yielding an odds ratio of 0.29 (95% CI: 0.12-0.71). This represents a 72% protective effect of folic acid for recurrence among women with a previously affected pregnancy.
b) **Occurrence studies**

Since 95% of NTD are first occurrences rather than recurrences (Department of Health (DOH), 1992), the results in 1992 of the randomised controlled occurrence trial carried out in Hungary were very important. Czeizel and Dudás published the first results in 1992 with further analysis following in 1993 and 1996. There were no NTD in the multivitamin group and six in the trace element group (Fisher’s exact p=0.014). Although unlikely to alter the conclusions of this study, it must be pointed out that the design of the trial does not allow the contribution of the various components of the vitamin tablet administered to be distinguished as there were only two arms (vitamin supplement including folic acid, other vitamins and trace elements versus a trace elements only arm).

In addition to the intervention trials, there have been a number of observational studies. A protective effect of folic acid or dietary folate was found by most of them (Mulinare et al, 1988; Milunsky et al, 1989; Bower and Stanley, 1989; Werler et al, 1993; Berry et al, 1999). One study (Mills et al, 1989) did not find a protective effect of folic acid. While the overwhelming body of literature is supportive of the positive role of folic acid for the prevention of NTD, more cautious views have also been expressed (Kalter 2000).

### 2.6 Folic Acid and Other Congenital Anomalies: The Evidence for a Protective Effect

There is increasing evidence to suggest that folic acid may also protect against other congenital anomalies such as orofacial clefts (Tolarova and Harris 1995, Shaw et al, 1995a, 1998b; Hayes et al 1996, Czeizel et al, 1999; Mills et al 1999, Werler et al, 1999; Itikala et al, 2001), cardiac defects (Shaw et al, 1995b; Botto et al, 1996; Scanlon et al 1998, Botto et al, 2000), urinary tract defects (Li et al, 1995; Werler et al, 1999) and limb reduction defects (Shaw et al, 1995b; Yang et al, 1997). Further studies are required in order to establish whether and to what degree folic acid offers protection against congenital anomalies other than NTD.

### 2.7 Gene-nutrient Interaction  (MTHFR and Folate)

Methylenetetrahydrofolate reductase (MTHFR) is a critical enzyme involved in folate metabolism. There is good evidence that the C677T polymorphism of the
MTHFR gene is associated with an increased risk of NTD (van der Put et al, 1995; van der Put et al, 1996, Wald and Noble 1999). This is a very good example of a gene-nutrient interaction, where the absence of an environmental factor (either folate or folic acid) combined with an abnormal gene (MTHFR) can cause a NTD. In terms of the biochemical effects of the C677T polymorphism of MTHFR, homozygotes show reduced enzymatic activity (Frosst et al, 1995) and this leads to low serum and red cell folate (Molloy et al, 1997) and increased levels of plasma homocysteine (Kang et al, 1993; Engbersen et al, 1995; Kluijtmans et al, 1996). The percentages of various populations homozygous for that MTHFR polymorphism are described elsewhere (Fletcher and Kessling, 1998, Botto and Yang 2000). It has been proposed that folic acid supplementation offers some protection against NTDs in fetuses of homozygotes by partially correcting for the lower activity of the variant form of the enzyme (Whitehead et al, 1995; Shaw et al, 1998b). However, the benefits of increasing folate status are not confined only to women with that MTHFR mutation.
3. **The Public Health Response to Evidence Concerning the Protective Effect of Folic Acid**

3.1 **Possible Methods of Increasing Folate Status**

There are three possible ways in which the recommendation of increasing folate status in women of childbearing age can be achieved:

1. Increased intake of foods naturally rich in folate
2. Folic acid supplementation
3. Fortification of food with folic acid

Cuskelly et al (1996) addressed the question of the relative effectiveness of these three options in an intervention study in healthy young women. They measured change in red cell folate concentration (considered to be the best indicator of folate status) in response to a 12-week intervention study in which women were randomly assigned to one of the following groups: a) folic acid supplements (400 µg per day), b) folic acid-fortified food (400 µg per day), c) dietary advice (qualitative) or d) none of the above. Although women in all four groups increased their folate/folic acid intakes, this change was reflected in increased folate status in *only* those women assigned to folic acid supplements or fortified food.

3.2 **Increase Intake of Natural Folate**

In order to achieve the recommended extra 400 µg, a 3-fold increase in typical intakes of the vitamin would be required (Subar et al, 1989; Gregory et al, 1990; Irish Universities Nutrition Alliance, 2001). Achieving this target by food folate alone would require major dietary modifications unlikely to be accomplished by most women planning a pregnancy, not to mention those women not planning to become pregnant (McNulty et al, 2000).

McKillop et al (2002) indicated the importance of cooking method, especially for green vegetables, a particularly good source of folate. Boiling was found to decrease the folate content to 49% and 44% of the original amount for spinach and broccoli respectively. Steaming of spinach and broccoli, in contrast, resulted in no significant
decrease in folate content. Thus, dietary changes would need to concern both which foods were eaten and whether / how they were cooked.

3.3 Periconceptional Folic Acid Policies in European Countries

Table 2 summarises periconceptional folic acid supplementation policies around Europe. For more detail, the reader is advised to look at individual country chapters in Part II of this Report.

By January 2005, eleven of the eighteen countries contributing to this report had introduced an official policy advising women to take periconceptional folic acid supplementation. The first governments to formulate such a policy were in the Netherlands (1992), UK (1992) and Ireland (1993). Of the other 7 countries: Portugal recommends that health workers should educate women about the benefits of folic acid; Malta and Finland recommend raising folate status by dietary means only; and four countries (Austria, Belgium, Croatia, Germany) have no official government policy at the time of writing, although professional groups within them advise supplementation.

The recommendation for periconceptional folic acid supplements in most countries is for a daily dose of 0.4 to 0.5 mg (except in Poland, where it is 1.0 mg, and Portugal, where no dose is specified). Higher doses, of 4 or 5 mg daily, are usually recommended for women who have had a previous pregnancy affected by an NTD. Some countries also have special recommendations for women on anticonvulsant therapy.

Half the countries have launched some type of health education campaign (Table 2) so that the information about the protective effect of folic acid can reach women directly rather than uniquely through health professionals. This is particularly important as folic acid supplementation must start before conception and therefore before the consultation of health professionals during pregnancy. The details of these campaigns can be found in Part II. There is little evidence as to how often health education campaigns need to be repeated for a sustained effect.
<table>
<thead>
<tr>
<th>Country</th>
<th>Periconceptional Folic Acid Policy</th>
<th>Status</th>
<th>Year current policy introduced</th>
<th>Low risk women</th>
<th>Women with previously affected pregnancy</th>
<th>Health Education Campaign</th>
<th>Year of study</th>
<th>% Women Using Folic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>Official</td>
<td>1993</td>
<td>0.5 mg</td>
<td>5 mg</td>
<td>1995</td>
<td>1995</td>
<td>1998</td>
<td>63% some of advised period 36% for entire advised period</td>
</tr>
<tr>
<td>UK</td>
<td>Official</td>
<td>1992</td>
<td>0.4 mg</td>
<td>4 mg</td>
<td>1995</td>
<td>1995</td>
<td>2001</td>
<td>45% preconceptionally</td>
</tr>
<tr>
<td>Ireland</td>
<td>Official</td>
<td>1993</td>
<td>0.4 mg</td>
<td>5 mg</td>
<td>1993 and 2000/2001 with Ulster</td>
<td>Health Education Campaign with Ulster</td>
<td>1997-8</td>
<td>30% preconceptionally</td>
</tr>
<tr>
<td>Denmark</td>
<td>Official</td>
<td>1997</td>
<td>0.4 mg</td>
<td>5 mg</td>
<td>1999 and 2001</td>
<td>1997</td>
<td>2000-2</td>
<td>22% of women who planned pregnancies took supplements at correct time</td>
</tr>
<tr>
<td>Poland</td>
<td>Official</td>
<td>1997</td>
<td>1.0 mg</td>
<td>4 mg</td>
<td>Yes, but no date given</td>
<td>2001</td>
<td>1999</td>
<td>19% of all women aged 18-45 13% of non-pregnant women aged 18-45</td>
</tr>
<tr>
<td>Norway</td>
<td>Official</td>
<td>1998</td>
<td>0.4 mg</td>
<td>4 mg</td>
<td>1998 (website)</td>
<td>2000</td>
<td>2001</td>
<td>46% perconceptionally</td>
</tr>
<tr>
<td>France</td>
<td>Official</td>
<td>2000</td>
<td>0.4 mg</td>
<td>4 mg</td>
<td>2000 and 2004</td>
<td>1999</td>
<td>2004</td>
<td>1% at recommended time (1 month before until 2 months after conception)</td>
</tr>
<tr>
<td>Italy</td>
<td>Official</td>
<td>2004</td>
<td>0.4 mg</td>
<td>-</td>
<td>2004 regional</td>
<td>1999</td>
<td>2002</td>
<td>3% perconceptionally 5.7% perconceptionally</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Official</td>
<td>1996</td>
<td>0.4 mg</td>
<td>4 or 5 mg</td>
<td>Being prepared</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Official</td>
<td>2001</td>
<td>0.4 mg</td>
<td>4 mg</td>
<td>Yes 2001</td>
<td>2000 2004</td>
<td>2000</td>
<td>4.5% - 17% took FA at recommended time (many studies)</td>
</tr>
<tr>
<td>Sweden</td>
<td>Official</td>
<td>1996</td>
<td>0.4mg</td>
<td>4-5mg</td>
<td>No</td>
<td>1997</td>
<td>2000</td>
<td>8% of pregnant women took FA</td>
</tr>
<tr>
<td>Malta</td>
<td>Official</td>
<td>1994</td>
<td>Women planning a pregnancy should increase dietary intake of folate</td>
<td>No</td>
<td>1999</td>
<td>15% perconceptionally a further 59% at GA &lt;12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>Official</td>
<td>1995</td>
<td>dietary</td>
<td>4 mg</td>
<td>Unofficial</td>
<td>2000</td>
<td>1999</td>
<td>19% took FA before or in early pregnancy</td>
</tr>
<tr>
<td>Portugal</td>
<td>Official</td>
<td>1998</td>
<td>Health workers should educate women about benefits of folic acid</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>Unofficial</td>
<td>1994</td>
<td>0.4 mg</td>
<td>4 mg</td>
<td>No</td>
<td>2000</td>
<td>2000</td>
<td>4.3% preconceptionally</td>
</tr>
<tr>
<td>Austria</td>
<td>Unofficial</td>
<td>1998</td>
<td>0.4 mg</td>
<td>4 mg</td>
<td>No</td>
<td>1998</td>
<td>1998</td>
<td>10% at GA &lt;12 weeks</td>
</tr>
<tr>
<td>Belgium</td>
<td>Unofficial</td>
<td>-</td>
<td>0.4 mg</td>
<td>4 mg</td>
<td>Being prepared</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>Unofficial</td>
<td>-</td>
<td>0.4 mg</td>
<td>4 mg</td>
<td>Unofficial</td>
<td>2003</td>
<td></td>
<td>19% of women with planned pregnancies in the study took FA at appropriate time</td>
</tr>
</tbody>
</table>

1. Policy as of December 2004
2. Recommended dose is as supplements unless otherwise stated
3. Poland recommends that all women of child bearing age take a supplement of 0.4 mg, increasing to 1 mg when planning a pregnancy.
4. Norway recommends >0.4 mg for moderate risk women
5. Since 2004, Finland recommends 0.4 mg folic acid supplementation for women with moderate risk, those with a poor diet or those wishing to be sure they are taking enough folate.
3.4 **Uptake of Recommendations to take Periconceptional Folic Acid Supplements**

Surveys of the use of folic acid supplements periconceptionally in European countries are summarised in Table 2. Details are given in the individual country chapters in Part 2 of this report. A fully informative survey needs to be based on a representative sample of pregnant women, and must contain information about when in relation to conception the folic acid was taken. Unfortunately, many studies that have been done do not meet these minimum criteria. Details of the methodology of each survey, where available, are given in Part II, and figures shown in Table 2 should be interpreted in the light of these details. Readers should note that the studies vary widely in every way and that results cannot be directly compared. Table 2 provides a very imperfect starting off point for looking at compliance in different countries.

In all countries, only a minority of women were found to have taken folic acid supplements during the entire advised periconceptional period. The highest uptake was recorded in Netherlands, UK, Ireland and Norway with 30-46% periconceptional uptake. Extremely low uptakes of less than 5% were found in France, Spain, Germany and Italy. It should be noted that the countries in which the highest uptake rates were found were those with official health education initiatives.

3.5 **Pregnancy Planning Behaviour**

The low uptake of periconceptional folic acid supplements may be because a large proportion of women do not plan their pregnancies and, of those who do plan the pregnancy, many are either unaware of the benefits of periconceptional folic acid, unaware of when they should take it or disinclined to take it (Clark and Fisk 1994; Scott et al, 1994; de Walle et al, 1999). It has been shown that women often modify their behaviour only after pregnancy has been confirmed and this usually occurs after the critical embryonic development of the neural tube is complete (Morin et al, 2002). A group in the Netherlands is attempting to get the message to women prior to conception by using pharmacists as the educators. Initial results are promising. (Meijer et al 2005)
Estimates of the proportion of pregnancies which are ‘planned’ in different countries are shown in Table 3. Since surveys which have asked women whether their pregnancy was planned have not generally employed a definition of “planned”, it is difficult to make meaningful comparisons of reported pregnancy planning behaviour between countries. The concept of ‘planning’ needed in relation to periconceptional folic acid supplementation refers to a conscious decision to stop contraception together with consideration by the woman of possible health and lifestyle changes needed to achieve conception and/or a healthy pregnancy. It may or may not include a consultation with a health professional. The concept of pregnancy ‘planning’ held by women almost certainly differs from this, and is influenced by social status and cultural factors.

There is evidence that women of higher social status are more likely to know of the benefits of taking supplemental folic acid and to be aware of the correct timing (Food and Drug Administration, 1996; Sayers et al 1997; de Walle et al, 1998), potentially leading to widening of socio-economic inequalities in NTD prevalence.
Table 3: Proportion of Pregnancies Thought to be ‘Planned’*

<table>
<thead>
<tr>
<th>Country</th>
<th>Proportion of pregnancies thought to be planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>No information</td>
</tr>
<tr>
<td>Belgium</td>
<td>No information</td>
</tr>
<tr>
<td>Croatia</td>
<td>75% in one small study</td>
</tr>
<tr>
<td>Denmark</td>
<td>68% of ongoing pregnancies in one small study</td>
</tr>
<tr>
<td>Finland</td>
<td>37%-86% depending on definition of planned</td>
</tr>
<tr>
<td>France</td>
<td>No information</td>
</tr>
<tr>
<td>Germany</td>
<td>65-70% in a number of studies</td>
</tr>
<tr>
<td>Ireland</td>
<td>40-45 %</td>
</tr>
<tr>
<td>Italy</td>
<td>No information</td>
</tr>
<tr>
<td>Malta</td>
<td>No information</td>
</tr>
<tr>
<td>Netherlands</td>
<td>estimated to be about 85%</td>
</tr>
<tr>
<td>Norway</td>
<td>estimated to be between 50% and 75%</td>
</tr>
<tr>
<td>Poland</td>
<td>estimated to be 10-20%</td>
</tr>
<tr>
<td>Portugal</td>
<td>thought to be low</td>
</tr>
<tr>
<td>Spain</td>
<td>No information</td>
</tr>
<tr>
<td>Sweden</td>
<td>estimated to be between 50% and 75%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Estimated to be very low</td>
</tr>
<tr>
<td>U.K.</td>
<td>estimated to be about 60%</td>
</tr>
</tbody>
</table>

*none of the authors were confident that their information was accurate. All were either estimates or based on very limited data and with no definition of planning.
3.6 Fortification of Food with Folic Acid

Mandatory fortification of a staple food (usually flour) with folic acid has been seriously considered in seven countries contributing to this report (Denmark, Germany, Ireland, Norway, Poland, Switzerland, and the UK) and the case for it is still being reviewed. As of January 2005 it had not been implemented in any European country although it is now widespread in North and South America and in much of the Middle East.

Food voluntarily fortified with folic acid (mainly breakfast cereals) is available in many European countries. In a recent study investigating the effects of consumption of folic acid-fortified bread compared with folic acid tablets, bread was found to be equally effective in increasing folate status as indicated by both increased red cell and serum folate concentrations (Armstrong et al, 2001). It may be difficult in some countries for women to identify foods fortified with folic acid and to determine the amount in relation to their needs due to limitations/restrictions on food labelling.

NTD prevalence rates over time by country can be found in the Country Specific Chapters of Part II. Registry descriptions can be found in Appendix 3. The majority of registries are population-based and register affected fetuses / babies in livebirths, stillbirths and terminations of pregnancy for fetal abnormality. Laws in each country regarding whether and until what gestational age termination of pregnancy for fetal abnormality is legal are summarised in Table 4.

<table>
<thead>
<tr>
<th>Country</th>
<th>Is it Legal?</th>
<th>Gestational Age Limit for Non-Lethal Serious Anomalies</th>
<th>Gestational Age Limit for Lethal Anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Belgium</td>
<td>Yes</td>
<td>24 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Croatia</td>
<td>Yes</td>
<td>24 weeks</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Denmark</td>
<td>Yes</td>
<td>24 weeks</td>
<td>28 weeks</td>
</tr>
<tr>
<td>Finland</td>
<td>Yes</td>
<td>24 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>France</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Ireland</td>
<td>No</td>
<td>Not legal</td>
<td>Not legal</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>24 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Malta</td>
<td>No</td>
<td>Not legal</td>
<td>Not legal</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes</td>
<td>24 weeks</td>
<td>28 weeks</td>
</tr>
<tr>
<td>Norway</td>
<td>Yes</td>
<td>18 weeks</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Poland</td>
<td>Yes</td>
<td>Viability</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Portugal</td>
<td>Yes</td>
<td>24 weeks</td>
<td>No upper limit</td>
</tr>
<tr>
<td>Spain</td>
<td>Yes</td>
<td>22 weeks</td>
<td>22 weeks</td>
</tr>
<tr>
<td>Sweden</td>
<td>Yes</td>
<td>22 weeks</td>
<td>22 weeks</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Yes</td>
<td>24 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>UK¹</td>
<td>Yes</td>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
</tbody>
</table>

Information as of January 2005

¹ Except Northern Ireland
4.1 Methods

Data for all cases of NTD were extracted from the EUROCAT Central Registry database 1980-2002.

Total prevalence rates were calculated as the number of affected livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis divided by the total number of births (live and still) in the registry population. Livebirth prevalence rates were calculated as the number of affected livebirths divided by the total number of livebirths in the registry population.

Prevalence rates were calculated for anencephalus, spina bifida and all NTD combined. Cases with both anencephalus and spina bifida were classified as having anencephalus.

Data from UK and Ireland were analysed separately from data from the rest of Europe due to the historically higher prevalence of NTD in UK and Ireland, and the well-documented steep decline in prevalence in the UK and Ireland prior to the 1990s (EUROCAT Working Group 91).

Further details of methods can be found in the original EUROCAT special report (2003) on the Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe on this website and in Busby et al 2005 a and b.
4.2 Results

In the UK and Ireland, where periconceptional folic acid supplementation policies (PFAS) were introduced in 1992 and 1993 respectively and where there have been active health education campaigns, all registers combined show a 30% overall mean reduction in NTD total prevalence in 2000-2002 compared with 1989-1991.

Figure 2: NTD rates in UK and Ireland over time

![Graph showing NTD rates over time](image)


In Continental Europe, all registries combined showed a non-significant reduction in NTD total prevalence (2%) for countries with a PFAS policy and 8% for those without. However, in Northern Netherlands, where PFAS policy was introduced early (1993) and an active health education campaign has been ongoing, there is a 43% reduction in NTD prevalence rates in 2000-2002 compared to 1989-1991.

For statistic analysis of the results and discussion, see Busby et al, 2005a and b.

4.3 Discussion
In UK and Ireland it is difficult to distinguish the effect of policy on NTD prevalence rates from the decline in prevalence starting well before the implementation of national policy. It is possible that one explanation for this decline may be the increasing folate content of the British and Irish diet (see Sources of Folate above).

In Continental Europe, notwithstanding the significant decrease in NTD prevalence rates in Northern Netherlands, the decrease for all registries combined is slight and non-significant.

While live birth prevalence has decreased considerably in countries without a folic acid supplementation policy due to the increase in prenatal diagnosis and termination of pregnancy in these countries, the total prevalence has not significantly decreased. This emphasizes two points. Firstly, reduction of livebirth prevalence is still relying more on prenatal screening and termination than on primary prevention with folic acid
supplementation. Secondly, in order to distinguish between decreases in prevalence due to primary prevention and those due to prenatal screening, information on terminations of pregnancy is needed.

The existence of an expanded network of congenital anomaly registries in Europe, collecting data on affected livebirths, stillbirths and terminations of pregnancy, is vital to track progress towards the prevention of neural tube defects. Information on NTD prevalence should be supplemented where possible by surveys of periconceptional folic acid supplementation in the population, and by monitoring of serum levels of folic acid.

Overall in Europe, despite the considerable promise of primary prevention of NTD by raising folic acid levels periconceptionally, little progress has been made, and few of the 4,500 affected pregnancies every year in Europe are being prevented. Folic acid fortification of staple foods is likely to be the only way that significant prevention of neural tube defects will be achieved.
5. **THE CASE FOR FORTIFICATION OF STAPLE FOODS IN EUROPE**

The previous section has shown the disappointing progress of NTD prevention in Europe, even in countries which have a clear supplementation policy implemented by a health education campaign. Fortification of staple foods with folic acid would provide a more effective means of ensuring an adequate intake, especially for those groups of women who are unlikely to plan their pregnancies or to receive or respond to health promotion messages. Fortification together with supplementation is likely to be a more cost-effective option than supplementation only for preventing NTD, since a supplementation only policy requires a health education campaign more extensive and effective and possibly more frequent than those implemented so far.

Spina bifida (including many avoidable cases) carries a high lifetime burden to the affected individual and family and a high economic cost for services. In addition to individuals surviving with spina bifida, there are large numbers of terminations of pregnancy and perinatal losses affected by NTD, causing great distress (Statham 2003; van Mourik 2003) and using health service resources. Evidence continues to mount about the beneficial effects of folic acid for the prevention of other congenital anomalies, cardiovascular disease (Boushey et al, 1995), and cancer. (Branda and Blickenderfer, 1993; Kim et al, 1997; Jacob et al, 1998; Choi and Mason, 2000). Fortification of food with folic acid might therefore have very far-reaching public health benefits beyond prevention of NTDs.

In the US, mandatory fortification of enriched grain products at a level of 1.4 µg per g of product (Food and Drug Administration, 1996) was introduced in 1998. This level of fortification was projected to result in an additional 100 µg per day of folic acid in the population intake. Studies carried out subsequent to the introduction of fortification report increased mean levels of folic acid in serum from 4.8 ng/ml before fortification to 14.8 ng/ml after fortification (Centers for Disease Control and Prevention, 2000). Choumenkovitch et al (2002) estimated that folic acid intake increased by a mean of 190 (95% CI: 176-204) µg per day for non-supplement users and total folate intake increased by a mean of 323 (95% CI: 296-350) µg dietary folate equivalents per day using data collected from participants of the Framingham...
Offspring Cohort Study. As manufacturers of breakfast cereal have also increased the fortification level in many products in recent years in the US, it is not clear how much of the rise in folate status is due to mandatory fortification and how much to the increase in voluntary fortification which was introduced. A 25% lowering of NTD rates in the US since the introduction of mandatory fortification has been reported (CDC, MMWR, May 7, 2004; Williams et al. 2002). Calls have been made for a further increase in the level of fortification (Oakley, 1999), however, others have urged that more information should be available regarding both the benefits and hazards of fortification before this should be considered (Mills, 2000).

Mandatory fortification has also been introduced in Canada, and in many countries in Central and South American and the Middle East. In Canada and Chile, increased serum folate levels have been found following the introduction of mandatory fortification (Hirsch et al. 2002; Ray et al. 2002). NTD rates have declined by about 50% in both countries since fortification. (Liu et al. 2004, Lopez et al. 2005; Hertrampf E, Cortes F, 2004).

In Europe there has been reluctance to proceed to mandatory food fortification which we believe stems from two factors:

1) Lack of recognition of the public health importance of neural tube defects, to the extent that many countries have been exceedingly slow to develop a primary prevention policy and some have still not developed one. This lack of recognition may stem from the fact that the great majority of neural tube defect pregnancies are now terminated, rendering them invisible to all but the family affected.

2) The possibility of health risks related to raising the population folic acid status. (Cornel, de Smit and Jong-van den Berg 2005).

There has been concern regarding the potential risk of masking the symptoms of pernicious anaemia caused by vitamin B\textsubscript{12} deficiency. If undiagnosed, there is potential for irreversible neurological damage in those at high risk of this deficiency, namely the elderly (Savage and Lindenbaum, 1995). However, it is argued that B\textsubscript{12} deficiency can be diagnosed simply with or without the presence of anaemia (Bower
and Wald, 1995). Furthermore, the masking of pernicious anaemia, which has concerned people at a theoretical level, has not been observed in countries with mandatory fortification of flour with folic acid.

There have been some reports of possible increases in twinning associated with periconceptional folic acid (Czeizel et al, 1994; Werler et al, 1997; Ericson et al, 2001). Most of the women in these studies used multivitamins and not folic acid alone. In fact, the increased occurrence of multiple births was not supported in another early, randomised trial of folic acid (Kirke et al, 1992) and has not been confirmed in a more recent, large population-based cohort study with folic acid in China (Li et al, 2003).

The association between folic acid supplementation and twinning is thought by many researchers to be due to the confounding effect of folic acid supplementation being much more common among women using assisted reproductive technology and the fact that use of this technology may be significantly under-reported. (Berry, Kihlberg and Devine 2005)

Although there is evidence that folate may be protective against the development of new cancers, there is concern at the possibility that folic acid may enhance the development of undiagnosed pre-malignant and malignant lesions. This issue was reviewed by Kim in 2004.
6. **Conclusions**

- The evidence that the majority of NTD are preventable by increasing folate status before conception is very strong. Evidence is also accumulating that the protective effect may extend to other congenital anomalies.
- Government response to this evidence has been variable in Europe. Many countries have been slow to introduce policies, and some still have no policy regarding periconceptional folic acid supplementation.
- Only half of the countries contributing to this report have implemented health education campaigns designed to reach all women before conception.
- The majority of women in countries surveyed are not taking folic acid supplements periconceptionally.
- In countries without a policy regarding folic acid supplementation, there has been no discernible decrease in the total prevalence of neural tube defects.
- In countries with a policy to recommend periconceptional folic acid supplementation, there is evidence of some decrease in prevalence, but to a disappointing degree compared to the potential for prevention. In UK and Ireland, it is not clear if the decrease in prevalence is simply a continuation of the pre-existing decline in prevalence already evident in the 1980s.
- There is an immense challenge facing those involved in public health and the care of prospective mothers to replace termination of pregnancy with primary prevention as the chief method of reducing the number of infants affected by this very serious group of congenital anomalies.
- In order to achieve a reduction in NTD prevalence, renewed efforts are needed in all countries to implement a combined strategy to:
  - increase folate status by dietary means
  - increase uptake of folic acid supplements periconceptionally
  - increase availability and identifiability of fortified foods
  - introduce mandatory folic acid fortification of a staple food
- The objective of preventing the majority of NTD is unlikely to be achieved without mandatory fortification of a staple food, which has not yet been introduced by any of the countries surveyed. Mandatory fortification could improve folate
status of all women of childbearing age, substantially reduce NTD prevalence, and reduce socio-economic inequalities in NTD prevalence.

- As countries change their policies and practices regarding prevention of NTD, continued monitoring of NTD prevalence is vitally important, using the data of population based registers of congenital anomalies with high ascertainment of cases among livebirths, stillbirths and termination of pregnancy for fetal abnormality
7. References:


