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Folic acid: from research to public health practice

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Folic acid: from research to public health practice.
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This report is the result of the activities of a working group convened in a workshop organized by the National Centre for Rare Diseases of the Istituto Superiore di Sanità (ISS, the Italian National Institute of Health), in collaboration with WHO Regional Office for Europe, and held in Rome (ISS, 11-12 November 2002). The group objective was to assess scientific evidence on folic acid and prevention of neural tube defects and other malformations in order to recommend public health policies. Participants agreed that since 1991 it was conclusively shown that periconceptional supplementation with folic acid markedly reduced the risk of neural tube defects and also of other birth defects. Whereas it is important to promote healthy dietary habits as a long-range target as well as to ensure folic acid supplements to women planning pregnancy, the only effective way to implement coverage of the whole population is the general availability of staple foods, such as flour, fortified with folic acid. The working group supported the fortification level of 240 µg folic acid per 100 g flour as recommended by the UK Committee on Medical Aspects of Food and Nutrition Policy. Finally, the needs for further research (however useful for a more accurate cost-benefit evaluation) should not delay the implementation of policies to support the general availability of fortified foods.

Key words: Folic acid, Neural tube defects, Anencephaly, Spina bifida, Prevention of birth defects, Food fortification, Folic acid supplementation

Istituto Superiore di Sanità
Acido folico: dalla ricerca all'azione di sanità pubblica.
A cura di Domenica Taruscio
2004, x, 36 p. Rapporti ISTISAN 04/26 (in English)

Questo rapporto è il risultato delle attività di un gruppo di lavoro riunitosi in un workshop organizzato dal Centro Nazionale Malattie Rare dell'Istituto Superiore di Sanità (ISS) in collaborazione con l'Ufficio Regionale per l'Europa dell'Organizzazione Mondiale della Sanità, e tenutosi a Roma (ISS, 11-12 novembre 2002). L'obiettivo del gruppo era di valutare le evidenze scientifiche per l'elaborazione di raccomandazioni sulla prevenzione dei difetti del tubo neurale e di altri difetti congeniti mediante l'assunzione di acido folico. I partecipanti hanno concordato sul fatto che sin dal 1991 è stato dimostrato che l'acido folico è in grado di ridurre il rischio di difetti del tubo neurale ed anche di altri difetti congeniti. Per aumentare l'assunzione periconcezionale di acido folico, è importante sia promuovere, come obiettivo a lungo termine, un'alimentazione ricca ed equilibrata, sia assicurare la supplementazione con acido folico alle donne che programmano una gravidanza. Tuttavia, l'unica via efficace per coprire un'intera popolazione è assicurare la disponibilità di alimenti di base fortificati, come la farina. Il gruppo di lavoro ha concordato con l'impiego di 240 µg di acido folico ogni 100 g di farina, come raccomandato dal *UK Committee on Medical Aspects of Food and Nutrition Policy*. Infine, per quanto ulteriori ricerche siano auspicabili per una più accurata valutazione di costi e benefici, non vi sono motivi validi per ritardare la promozione della disponibilità di alimenti fortificati con acido folico.

Parole chiave: Acido folico, Difetti del tubo neurale, Anencefalia, Spina bifida, Prevenzione di difetti congeniti, Fortificazione degli alimenti, Supplementazione con acido folico

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This report is the result of the activities of a working group on policy for prevention of congenital disorders convened by the WHO Regional Office for Europe and the Istituto Superiore di Sanità on 11-12 November 2002.

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PREFACE

Birth defects are an important public health problem, due to their overall incidence, their major role as a cause of infant mortality in industrialized societies and serious consequences for affected persons, often resulting in permanent disabilities.

Therefore, besides surveillance, treatment and social care, primary prevention is a fundamental component of health policies towards birth defects. Effective prevention strategies are ideally based on an adequate characterization of relevant risk factors. However, risk factors for birth defects are complex (generally involving gene-environment interactions) and often incompletely known.

Nevertheless, research has conclusively identified several issues. Among them, ensuring adequate intake of folic acid by women of fertile age stands as a recognized approach for preventing an important fraction of neural tube defects as well as a variable fraction of other malformations of major public health importance.

Therefore, preventive interventions, already enforced in several countries for many years, should be implemented in the whole European region. On the other hand, research has to answer some further questions in order to increase the effectiveness and efficacy of interventions. For example:

What is the overall preventive impact on the foetus and pregnancy of an increased intake of folates?

What other factors (genetics, diet, etc.) modulate the response to folic acid?

Last but not least, how to integrate the different strategies to promote the intake of folates: education to healthy dietary habits, periconceptional supplementation, availability of fortified staple foods? Furthermore, how to raise the awareness of the health operators and the public?

It is apparent that good will is not enough to plan strategies for the primary prevention of birth defects; the interaction between different cultures and expertises of research and public health is required.

In Italy, interventions and research projects, though valuable, have had a local character till recently and, unfortunately, no action has exerted any adequate impact at national level.

Our Istituto Superiore di Sanità (ISS), and in particular the National Centre for Rare Diseases has assumed a key role in developing a national effort on folic acid since 2001, through the production of several initiatives and documents. Eventually, the Italian Network for Promotion of Folic Acid to Prevent Birth Defects has been established on April 2004.

Being both an important national research institute on public health and an interface with international bodies, the ISS has a responsibility to develop such an up-to-date topic taking into due consideration the experiences of other countries. Therefore, on November 2002, the National Centre for Rare Diseases organized, in collaboration with WHO Regional Office for Europe, one of the most comprehensive workshops on folic acid of the recent years.

Major experts from both European and non-European countries contributed to the meeting, as well as to the following discussion to the finalization of the report.

We are glad to publish the final document from the workshop; we are convinced that this report will be useful for both scientists and health operators involved in the prevention of birth defects.

Prof. Enrico Garaci
President of the Istituto Superiore di Sanità

FORWARD

Folic acid fortification of staple foods has been discussed as a possible mechanism to reach vulnerable population groups, namely women during the pre-conceptional stage, in order to prevent neural tube defects. Fortification with folic acid versus supplementation, has been extensively discussed in the scientific literature, deliberated in the context of nutrition policy decisions, and in some cases, governments have taken action in this area. This meeting, held in collaboration with the Istituto Superiore di Sanità, Rome, Italy brought together a number of experts on the subject with the aim of assessing the scientific evidence and discussing possible public health policy with regards to folic acid in order to protect women of reproductive age and their future children in Europe.

WHO's concern on the effect of diet on the health of the population resulted in a Global Strategy on Diet, Physical Activity and Health adopted in May 2004 by the World Health Assembly. Any approach addressing micronutrients needs to be seen within the overall context of this strategy and must address individual behaviours, the role of industry and that of the public health sector.

As a further development of the Global Strategy on Diet, Physical Activity and Health, WHO has recently initiated activities aiming at the development of a strategy for foetal nutrition, addressing many relevant issues including the best approaches to secure an adequate concentration of folic acid in the diets of women of reproductive age. In this respect, a number of reviews are being carried out and working groups convened to reach consensus on the many issues at stake. This work will form the basis of future recommendations to Member States and possibly to their support and agreement for the development of effective and equitable public health policies in this area.

This report is an important contribution to the preparation of this strategy and an excellent review of the state of the art at the time of the meeting. The recommendations provided in this report are not formal WHO recommendations to Member States and public health authorities but, with the related scientific assessments, should be further discussed and evaluated within the context of the new foetal nutrition strategy as well as and in conjunction with recent scientific developments and evidence in this area. The future adoption of the strategy for foetal nutrition will allow the initiation of adequate activities at different levels, in the scientific, public health and policymaking communities, to ensure that each woman in the fertile age range receives an adequate intake of folic acid for the health and well-being of their children.

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INTRODUCTORY REMARKS

Rare diseases, according to the criteria developed by the European Union, include all conditions affecting no more than 5 out of 10,000 EU citizens. Thus, rare diseases are a wide and diverse group (more than 5,000 conditions altogether) that includes a number of very infrequent diseases as well as a few recognized public health issues.

Birth defects are both a major and a peculiar issue in the field of rare diseases; a major one, due to their overall incidence, the clinical severity, the distress for individuals and families. They affect 2-3% of newborns and may cause up to 40% of total infant mortality in industrialized countries. A few major malformations, namely neural tube defects and cardiovascular defects, may be responsible for up to 50% of the fraction of infant mortality due to birth defects, besides having an impact on disability and long-term hospitalisation yet to be fully estimated. However, because of the important involvement of environmental and dietary factors, malformations represent also a peculiar issue within rare diseases that, otherwise, have mostly a genetic origin. In fact, the complexity of pathogenesis is crucial for the understanding and prevention of birth defects. Genetics is obviously important, but it has to be understood mostly as genetic susceptibility to environmental agents and/or as gene-gene interactions. In particular, considering neural tube defects, risk factors include polymorphisms of a number of genes involved in folate metabolism, metabolic conditions (e.g., fever), pharmaceuticals (the most well-known being the anti-seizure agent valproic acid) and possibly other chemicals as well; the significant recurrence risk also points to complex gene-environment interactions. Therefore, the identification of a single, critical factor in the chain of events provides a vital target for preventive actions. All scientific evidence points to the adequate intake of folic acid as a critical factor to prevent a major fraction of neural tube defects. Moreover, the inadequate uptake/utilization of folic acid (which is critical for nucleic acid synthesis and amino-acid metabolism) is likely to have a role in the pathogenesis of several other birth defects (e.g., heart and limb malformations). Thus, research supports the role of folic acid for primary prevention, and public health agencies are obliged to confront the challenge.

Also, by contrast with many rare diseases, public health activities have given attention to birth defects for many years. In particular, registries have been established throughout Europe, connected by the EUROCAT and International Clearinghouse for Birth Defects Monitoring Systems networks, to which the several Italian regional registries give an important contribution. Italian registries of birth defects are also connected to the National Register of Rare Diseases, co-ordinated by the National Centre for Rare Diseases of the Istituto Superiore di Sanità. Thus, an effective network, using harmonized approaches, may be implemented to survey the extent and effectiveness of preventive interventions, such as promotion of folic acid intake at national level, as well as to interface with similar networks in other countries. Data from Registries have to be fed back to health agencies as a basis to modulate intervention strategies, evaluate their outcomes, plan follow-ups and identify possible groups at risk that may deserve targeted actions. Ideally, monitoring of folic acid intake should be integrated with other strategies to promote the intake of valuable micronutrients. Under this heading, one should not overlook the importance of studying dietary habits in different population subgroups as well as of investigating nutrient intake using biomarkers (e.g., blood folate levels). Multidisciplinary integration between genetics, clinical medicine, pharmacology, nutrition, epidemiology, etc. is therefore required to provide a proper scientific basis for preventive actions.

A most critical point is to integrate in a comprehensive strategy the complementary approaches that are recommended to increase the intake of folic acid in women of fertile age:

- promoting health education towards a well-balanced diet, as a key long-range action;
- making supplementation available to all women planning a pregnancy, an approach that may be particularly effective for groups at higher risk (e.g., women that already had an affected baby or taking certain drugs);
- promoting the widespread availability of fortified staple food, as the only approach that may afford basic coverage to the whole population.

To achieve this objective, it is of paramount importance to raise awareness among health operators, women, and the general public; the active involvement of stakeholders (patient associations, media, food and drug industry, etc.) is also needed. It is the responsibility of the central bodies of the National Health System to issue correct and complete information on the use of folic acid, including recommended dosages and modalities for supplementation. But the role of local services would be as important, i.e., to promote campaigns for information, health education and implementation using resources and approaches adequate to their realities.

Therefore, the primary prevention of defects through folic acid requires a continuous interaction of research and public health expertise. As underlined by the conclusion of the present report, the needs for new research should not delay the implementation of preventive actions, but new research data should be used to refine the adopted strategies. Finally, Health Authorities should take the responsibility of both promoting preventive actions and establishing up-to-date instruments to evaluate their efficacy and outcomes.

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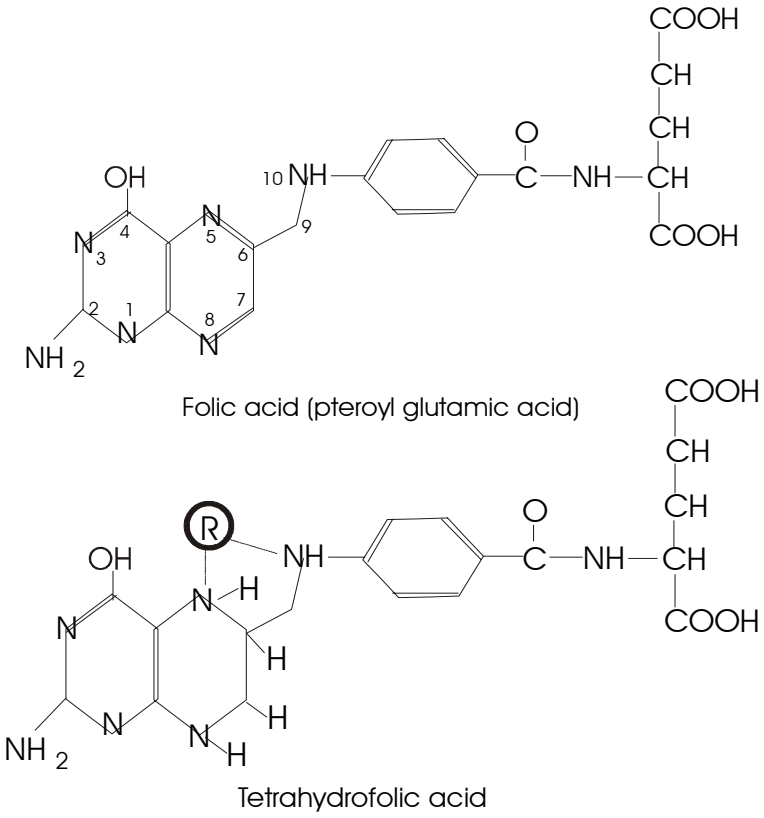
METABOLIC ROLE OF FOLATES

Folate is an inclusive term for biologically active forms of pteroylglutamic acid (Figure 1). Naturally – occurring folates include dihydro- and tetrahydro- folate with up to seven additional glutamic acid residues. Synthetic folic acid is an oxidised form with one glutamic acid residue, which must be reduced to tetrahydrofolate to be biologically active.



* Reduction to tetrahydrofolate generates a reactive site (marked R) capable of binding and releasing single carbon residues.

Figure 1. Structure of folic acid and tetrahydrofolic acid

Tetrahydrofolate is an essential co-factor for metabolic reactions that modify organic molecules by adding or removing a single carbon (methyl) unit (Figure 2). These reactions are crucial in the synthesis of nucleic acids and many other compounds, and in amino-acid metabolism. Vitamins B2 (riboflavin), B6 (pyridoxine) and B12 (cyanocobalamin) are also essential co-factors in some of these reactions.

Dietary folate and folic acid are made available by reduction to tetrahydro (H4) folate by the enzyme methyltetrahydrofolate reductase (MTHFR). Tetrahydrofolate is methylated to N5 methyl tetrahydrofolate in the conversion of serine to glycine. The resulting methylated forms

supply the methyl groups required for many essential metabolic reactions. Of these, the methionine-homocysteine cycle is particularly well understood. Methionine first reacts with adenosine triphosphate (ATP) to produce high-energy S-adenosylmethionine. This donates methyl residues (e.g. in the synthesis of choline, creatine, adrenaline, anserine, N-methylnicotinamide) and breaks down to homocysteine and adenosine-1-phosphate. Methionine is regenerated from homocysteine by transfer of a methyl unit from N5 methyl H4 folate.

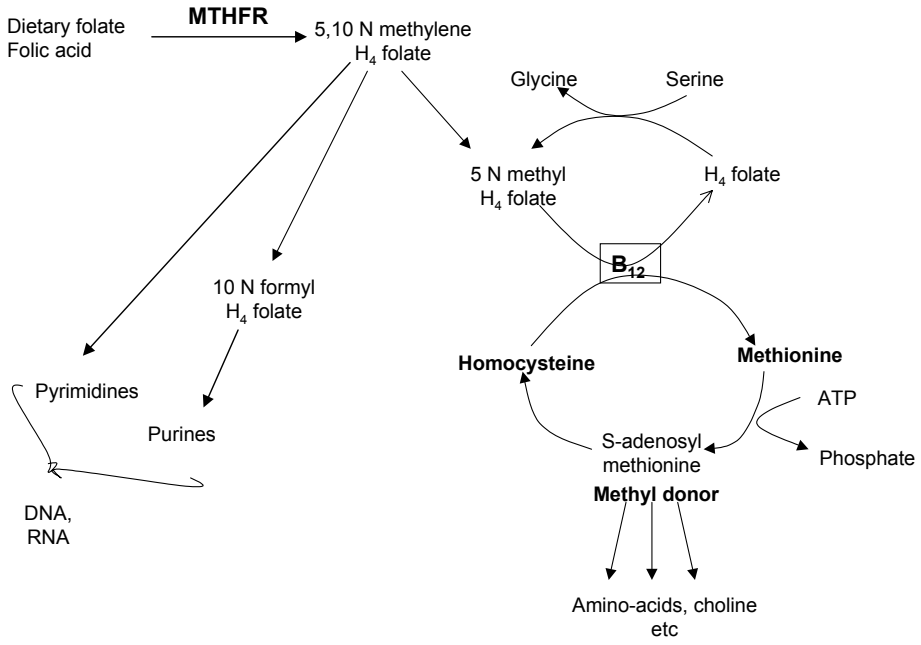


Figure 2. The metabolic roles of folate, and the place of vitamin B12

During the 1940s an intensive search for the active factor in liver extracts that prevents pernicious anaemia showed that both folate and vitamin B12 prevent megaloblastic anaemia, but only vitamin B12 can prevent neurological complications. It is now known that the two vitamins act jointly in regenerating methionine from homocysteine (see Figure 2).

Homocysteine accumulates if conversion to methionine is slowed because of shortage of folate or vitamin B12 or both. A raised plasma homocysteine suggests sub-optimal nucleic acid and amino-acid metabolism. There is also evidence indicating a direct harmful effect in increasing the risk of cardiovascular disease. It may also increase the risk of certain cancers, and possibly of dementia. As reactions catalysed by tetrahydrofolate are crucial for cell growth and multiplication, rapidly dividing cells are particularly vulnerable to deficiency of either folate or vitamin B12. In adults this affects the bone marrow causing megaloblastic anaemia. In the early embryo morphogenetic events may be affected, increasing the risk of congenital malformation.

Single gene disorders caused by rare variants of several enzymes involved in one-carbon transfer cause problems ranging from greatly increased plasma homocysteine levels with very early onset cardiovascular disease, to developmental delay and neurological problems, with or without megaloblastic anaemia (1). Variants of lesser effect in the same enzymes may contribute to genetic predisposition to cardiovascular disease and neural tube defects. For example, about 10% of many populations are homozygous for a common polymorphism of the

enzyme MTHFR (valine replaces alanine at codon 677). In homozygotes this reduces enzyme activity by 50-70%, slows the regeneration of methionine leading to raised plasma homocysteine, and increases risk of cardiovascular disease (2). Foetuses homozygous for the variant are at increased risk of neural tube defect (3-5). Variants of other enzymes, and other vitamins, may also influence homocysteine levels and risk of neural tube defects (4,5). Folate levels may also be influenced by metabolic conditions, such as fever or coeliac disease, and by environmental factors such as drugs or cigarette smoke (6-10). Folic acid supplementation increases the supply of tetrahydrofolate, accelerates most folate-dependent metabolic reactions, and reduces plasma homocysteine levels.

Folic acid and neural tube defects

Over 90% of pregnancies where the foetus has a neural tube defect occur among women without any previous indication of increased risk. Identifiable risk groups include women with a prior affected pregnancy, who have a 3-4% recurrence risk, women who are heterozygous for the MTHFR mutation (4), and women taking certain drugs, such as the antiepileptics valproic acid or carbamazepine (11). However, these groups account for only a small proportion of affected pregnancies.

Trials of the effect of folic acid supplementation on the prevalence of neural tube defects (11-26) summarised by Wald and Noble (27) (Table 1), provide conclusive scientific evidence for the preventive effect of the vitamin, and support the following conclusions.

Dietary supplementation with folic acid or with multivitamin preparations containing folic acid, before and during early pregnancy (periconceptional supplementation) markedly reduces both the first occurrence of neural tube defects, and recurrence among women with a previous affected pregnancy.

The effect is greatest in areas with a high baseline prevalence of neural tube defects, but also applies in lower prevalence areas.

With the exception of claims of increased rates of twins and miscarriages, to be discussed below, no harmful effects have been observed with levels of supplementation ranging from 360 μg to 5 mg of folic acid daily.

The relatively high prevalence and the ease of diagnosis of neural tube defects at birth made it feasible to conduct the randomised trials that conclusively demonstrated a direct preventive effect. The evidence for other types of congenital malformation is weaker, but nevertheless points to a wider preventive effect (28-32).

Other, yet unrecognised, environmental factors may also play a part in the causation of neural tube defects (24). The observed decline in the prevalence of these malformations in the US and Britain over the last 20 years (22, 23), and the difference in prevalence between North and South China (24), are too large to be explained by differences in folate intake alone. Though the research has focused mainly on the role of folic acid, vitamin B12 may contribute to the prevention of neural tube defects. There is also a strong indication that a raised plasma homocysteine increases risk of cardiovascular disease (35). Vitamin supplementation (folic acid, vitamin B12 and vitamin B6) reduces plasma homocysteine levels, and folic acid supplementation reduces recurrence rate in patients with coronary heart disease (36). There is also some evidence that increasing folic acid intake may reduce risk of some other common diseases, including certain cancers (notably colo-rectal cancer) and dementia (37, 38).

Table 1. Summary of randomised and non-randomised studies of the effects of folic acid or multivitamin supplementation on the prevalence of Neural Tube Defects (NTD)

Type of study	O or R*	Authors (Ref.) Year	Folic acid DD	Supplemented women n.	Supplemented women NTD	Unsuppl. women n.	Unsuppl. women NTD	Total NTD	RR	95% CI
RCT	R	Laurence (11) 1981	4 mg	44	0	67	6	6	0.42	0.04-2.97
RCT	R	MRC VSR group (12) 1991	4 mg	593	6	602	21	27	0.29	0.1-0.74
RCT	R	Kirke *et al.* (13) 1992	400 µg	172	0	85	1	1	0	-
RCT	O	Czeizel & Dudas (14) 1992	800 µg	2471	0	2391	6	6	0.06	0.00-0.63
Comm. Inter.	O	Berry *et al.* (15) 1999	400 µg	130142	102	117689	173	275		
Non-RCT	R	Smithells *et al*. (16) 1983	360 µg	454	3	519	23	27	0.14	0.03-0.47
Non-RCT	R	Vergel *et al.* (17) 1990	5 mg	81	0	114	4	4	0	0.00-2.13
Dietary folate	R	Laurence *et al.* (24) 1980	Dietary	141	0	45	8	8	0	0-0.33
Observational study		Winship *et al.* (18) 1984	ca 400 µg	Prescription data for 764 women who had a foetus with an NTD and 764 with an unaffected baby				561	0.14	0.003-1.11
Observational study		Mulinare *et al.* (19) 1988	ca 400 µg	Recall of multivitamin usage by 347 women with an NTD pregnancy and 2,829 with unaffected pregnancy				347	0.41	0.26-0.66
Observational study		Mills *et al.* (20) 1989	ca 400 µg	Recall of multivitamin usage by 571 women with an NTD pregnancy, 546 with stillbirth or other anomaly, and 573 with an unaffected baby.				571	0.94	0.8-1.1
Observational study		Milunsky *et al*. (21) 1989	ca 400 µg	Recall by 22,776 women in the midtrimester of pregnancy: NTD = 0.9/1000 in supplemented and 3.5/1000 in unsupplemented women.				49	0.29	0.15-0.55
Observational study		Werler *et al.* (22) 1993	ca 400 µg	Recall of use of multivitamins by 436 women with a NTD pregnancy and 2615 controls with other foetal abnormalities				436	0.6	0.4-0.8
Observational study		Bower & Stanley (23) 1992	ca 400 µg	Recall of use of multivitamins by 77 women with an NTD pregnancy, 77 with other foetal abnormalities, and 154 with unaffected baby				77	0.11	0.01-1.33
Dietary folate		Bower & Stanley (28) 1989	Dietary					77	0.31	0.1-0.97
Dietary folate		Yates *et al*. (25) 1987	Dietary	Red cell folate in 20 women with 2 or more NTD pregnancies and 20 women with unaffected pregnancies				20	0.33	0.09-1.27
Dietary folate		Milunsky *et al*. (21) 1989	Dietary	Recall of dietary folate intake by 22,776 women in the midtrimester of pregnancy				39	0.42	0.16-1.15

O = study of prevention of first occurrence of NTD (Occurent NTD), **R** = study of recurrence of NTD (Recurrent NTD); **DD**: Daily Dose; **RR**: Relative Risk; **CI**: Confidence Interval; **Comm. Inter**.: Community Intervention; **RTC**: Randomized Clinical Trial.

The accumulated evidence of health benefits from folic acid supplementation is now so persuasive that several countries including the USA, Canada, Chile, Ireland and Israel have mandated folic acid fortification of essential foods. The WHO Office for the Eastern Mediterranean has recommended folic acid food fortification throughout the Region. In North America a significant decrease in the birth prevalence of neural tube defects has been documented following folic acid fortification of flour (39, 40).

NUTRITIONAL ASPECTS OF FOLATES

Dietary sources of folic acid and vitamin B12

The main sources of folate are fruit and vegetables (fresh when possible), and liver. About 50% of natural dietary folate is absorbed. The daily requirement, initially estimated to be about 50 μg, is now thought to be closer to 200 μg. Body stores are 5-10 mg, 50% in the liver, and folate is concentrated in the cerebrospinal fluid. When there is little or no folate in the diet average stores may last about 3 months.

Vitamin B12 is synthesised only by micro-organisms. Dietary sources are meat (particularly liver), shellfish, some cheeses, yeast extracts and the root nodules of legumes (peas, beans, etc.). Daily requirement is less than 1 μg. Average body stores are 2-5 mg (range 1-10 mg) mostly in the liver. Three to seven micrograms are excreted daily in the bile, but most is reabsorbed. Thus when there is little or no vitamin B12 in the diet, stores may normally last 2-3 years. In pernicious anaemia, where the fundamental problem is inability to absorb vitamin B12 from the intestine, intake is reduced and losses are increased.

Dietary deficiency of vitamin B12 is most likely in strict vegetarians. Folate deficiency is most likely in people with restricted access to fresh fruit and vegetables or liver.

Reduced absorption of both folic acid and vitamin B12 occurs in people with chronic malabsorption, including unrecognized forms of coeliac disease, which may affect 0.2-0.3% of the European population (9).

Relationship of folic acid to natural folate

Synthetic folic acid is stable, resistant to degradation during food processing and well absorbed, the efficiency of absorption increasing with age. There is therefore a predictable relationship between folic acid intake, plasma and red cell folate, homocysteine levels, and prevalence of neural tube defects (41).

Once absorbed, folic acid is reduced to the natural tetrahydrofolate form by the enzyme methyltetrahydrofolate reductase (MTHFR). This change generates a reactive site capable of binding and releasing single carbon (methyl) residues (see Figure 1). It also destabilises the molecule. As a result, natural folate is much more susceptible than synthetic folic acid to degradation (to pteridine and benzoylglutamic acid) during food preparation.

Folate with a single glutamic acid side chain as shown in Figure 1 is found in plasma and diffuses freely across cell membranes. The vitamin is retained inside cells by the addition of 5-7 additional glutamic acid residues, which prevent it escaping back across the cell membrane. Consequently, most dietary folate is in the polyglutamate form. The extra glutamic acid residues must be removed before it can be absorbed: as a result natural folate is absorbed much less efficiently than synthetic folic acid is.

These variables, plus age differences, confuse the interpretation of folate intake, especially when both natural folate and folic acid supplements are involved. The difficulty can be partly overcome by expressing folate intake in terms of *folic acid equivalents*, i.e. (folic acid) plus (dietary folate divided by two) (41-43).

The only reliable way to assess folate intake is by measuring blood folate levels (41). Plasma (monoglutamate) folate level reflects current folate intake, while red cell (polyglutamate) folate level reflects folate status over the previous months when the red cells now in circulation were developing in the bone marrow.

Recommended dietary intakes

The original estimates of dietary folate and vitamin B12 requirements and recommended dietary allowances (RDAs) were based on the amount needed to avoid manifest deficiency disorders (megaloblastic anaemia, with sub-acute combined degeneration of the cord in the case of vitamin B12 deficiency), and on levels observed in populations. However these levels do not necessarily represent necessary requirements. The growing evidence that they were generally too low, particularly for pregnant women, has led to the steady increase in recommended intakes shown in Table 2 (44).

Table 2. Evolution over time of recommended dietary intake of folates, µg/day

Organization/ Country	Year	Recommended daily Dietary Allowance (RDA)		
		Men	Women	Pregnant women
FAO	1988	200	170	
USA	1989	200	180	
UK	1991	200	200	
Germany	1991	300	300	
Netherlands	1992	200-300	200-300	
France	1992	300	300	
EC	1993	200	200	400 µg dietary folate, plus 400 µg folic acid supplement
FAO/WHO	1998	400	400	600 µg dietary folate, plus 400 µg folic acid supplement
USA	1998	400	400	400 µg dietary folate, plus 400 µg folic acid supplement
Eurodiet	2001	400	400	

FAO = Food and Agriculture Organisation. **EC** = European Community.
USA refers to US Institute of Medicine recommendations (45).

The recommendations are expressed in terms of both folate and folic acid intake. The US Institute of Medicine's recommendation for adults (400 µg dietary folate) represents a daily intake of 200 µg folic acid equivalents, while the recommendation for pregnant women (400 µg dietary folate plus 400 µg folic acid) represents a daily intake of 600 µg folic acid equivalents (45).

The average dietary natural folate intake in 17 recent surveys in Western Europe was by comparison only about 200 µg/day, with most women consuming less than 250 µg/day (44). There is an increasing trend of intake in many countries. For example in the UK dietary folate intake increased from 213 µg/day in 1980 to 273 µg/day in 1998 (46), but even so it is still well below the current recommended level. Most available studies relate to Western Europe: in much of Eastern Europe estimated folate intake is less than 170 µg/day, being particularly low in Winter.

To obtain adequate protection against risk of neural tube defects the mean plasma folate should be about 10 ng/ml (41). The mean plasma folate level in most populations is around

5 ng/ml. There is considerable variation within and between populations, but few have a mean plasma folate in the recommended range, and very few individuals could meet the recommendations of the US Institute of Medicine without food fortification or the use of folic acid supplements. The groups of greatest concern are those whose folate intake and plasma folate are at the lower end of the range for socioeconomic reasons, as this is the group least likely to be reached by targeted periconceptional folate supplementation: food fortification is the most efficient way to increase their intake.

In conclusion, there is a need to increase the intake of folate across the Region: the need is particularly urgent in Eastern Europe.

Recommended intake before and during pregnancy

The recommended periconceptional folic acid intake is based on achieving a high enough dose to have an appreciable effect in reducing risk of neural tube defects, with every indication that this is safe. Table 2 shows that recent recommended intakes indicate the importance of consuming additional folic acid over and above normal dietary folate. The source of additional folate could be from food fortification or from taking supplements in the form of vitamin pills, or a combination of both.

The US Institute of Medicine's recommendation of a basic dietary intake of 400 μg of folate plus an extra 400 μg of folic acid for women who may become pregnant should become a long-term target for fortification levels. The UK Committee on Medical Aspects of Food and Nutrition Policy (COMA) recommendation of 240 μg of folic acid per 100 g flour (46) is approximately equivalent to an additional folic acid intake of 200 μg a day – about half the 400 μg per day recommended by the Institute of Medicine (45). It is estimated that even the latter level would still achieve sub-optimal effects. It could approximately halve the risk of neural tube defects in many European countries compared to the 80% reduction shown with supplements of 4-5 mg. Thus even when basic foodstuffs are fortified with folic acid, women who may become pregnant still need to take folic acid supplements (47).

Current recommendations are 400 μg daily for women in the general population and 4-5 mg daily for women who have previously had a pregnancy affected by neural tube defect. However, there is no logical reason for this distinction. Women with no previous affected pregnancy have over 90% of affected conceptions, and are the group with the greatest potential for prevention.

In conclusion, food fortification is the most efficient way to increase folate levels and achieve the current recommended daily intake of 400 μg for women in the general population Folic acid supplements of 4-5 mg daily are recommended for all women who may become pregnant.

Appropriate, relevant information should be made available to health services and practitioners.

EFFECTIVENESS OF DIFFERENT METHODS OF INCREASING FOLIC ACID INTAKE

Dietary advice

There is some disagreement about the feasibility of achieving the recommended increase in intake of folate, particularly for women who may become pregnant, by increasing the proportion of fresh fruit and vegetables in the diet. It is doubtful if such a large dietary change could be widely adopted even in Western Europe: it is certainly out of reach in most of Eastern Europe at present, for economic reasons. It is highly desirable to achieve better dietary habits through well-planned nutritional education campaigns. Immediate implementation of dietary fortification with folic acid is an essential component of this long-term public health strategy.

Periconceptional supplementation

The confirmation of the role of folic acid in preventing neural tube defects was followed by public health campaigns promoting the use of folic acid supplements before and during pregnancy. Studies have consistently shown that though these campaigns increase awareness and lead to increased use of folic acid supplements in early pregnancy, relatively few women start supplementation prior to pregnancy (48, 49), and the quality and quantity of the information available on folic acid is variable (50). About 50% of pregnancies, though desired, are not precisely planned (a circumstance that is unlikely to change), and it is hard to maintain campaigns year on year. Furthermore, although folic acid tablets are relatively cheap few people in Eastern Europe can afford to pay for them.

Food fortification

Voluntary fortification of some breakfast cereals and some brands of bread has been implemented in several countries, and is likely to have contributed to the observed fall in prevalence of neural tube defects since 1980 in high-prevalence countries in Western Europe (33).

In 1996, the US Department of Health and Human Services mandated folic acid fortification of all cereal grain products at a level of 140 µg/100 g flour: the same policy was simultaneously adopted in Canada. The level is low in comparison with more recent recommendations, and in both the US and Canada the birth prevalence of neural tube defects (allowing for screening and selective abortion) has since fallen by about 20% (34, 40, 41). No adverse effects have been reported.

Studies of effects of dietary advice, providing a diet containing the recommended level of folates, and providing folic acid supplements have shown that only folic acid (taken either as supplements or in fortified food) reliably increases serum folate level (47, 48). It is concluded that food fortification is the only realistic option for providing the optimal folate intake equitably to the population.

Costs of folic acid

The cost of folic acid fortification has been put forward as a concern in some countries.

However, folic acid fortification of flour at the recommended levels is so cheap that it makes a negligible difference to the price of a loaf of bread. The cost of the folic acid required to fortify at 240 µg /100 g of flour is about USD 0.25 per metric ton of flour – i.e., an amount sufficient to feed one person for 30 years! (Erickson, personal communication). However, in some countries the additional one-off cost of modifying existing milling or mixing machinery may need to be taken into account.

In conclusion, intake of folate should be increased across the region through fortifying basic foodstuffs with folic acid, as well as encouraging a varied diet rich in folate as a long-range action.

CONGENITAL DISORDERS IN THE WHO EUROPEAN REGION

Demographic and economic background

Table 3 shows current demographic and economic indices for countries of the WHO European Region, grouped according to demographic, political, cultural and economic characteristics (for country details see in Annex Table A1).

Table 3. Demographic and economic statistics*

Sub-region	Population *millions*	Crude birth rate	Infant mortality rate	Annual births *thousands*	Annual infant deaths *thousands*	*Per capita* purchasing power parity $
Western Europe	269.8	11.2	4.9	3,029	14.8	21,665
Southern Europe	144.0	10.0	6.8	1,436	9.8	16,798
Turkey	64.4	21.1	37.9	1,359	51.5	6,594
Central Europe	102.6	9.7	11.7	996	11.6	7.596
Eastern Europe	210.2	8.4	15.8	1,772	28.0	5,732
Cent Asia & Caucasus	71.6	19.7	28.8	1,410	40.7	2,599
Israel *	6.1	21.8	5.7	134	0.76	16,861
WHO European Region	868.7	11.7	15.5	10,136	157	12,353

* Data from the UN Demographic Yearbook for 1999 (51) and the World Bank (52)

Broadly, the region includes a high-resource "western" grouping (western and southern Europe) with 48% of the population, excellent dietary opportunities and extensive medical facilities for treatment and prevention, and a lower-resource "eastern" grouping (Central and Eastern Europe, central Asia and the Caucasus, and Turkey) with 52% of the population and far more limited dietary opportunities and medical facilities. Per capita purchasing power parity in some countries in Eastern Europe is now close to that in Sub-Saharan Africa (see Figure B1 in Annex B). The 2002 report of the Pew Global Attitude Project (53) shows that from 35 to 64% of the population in the Eastern part of the Region are unable to afford food at times, compared with 5-11% in the Western European countries surveyed (see Table A2 in Annex A).

During the past 20 years, in western and southern Europe infant mortality has declined to the lowest level ever recorded (3.0-3.4 /1,000 in some countries); reduced infant mortality in these parts of Europe is also associated with increased survival of disabled children. A fall in Turkey from over 60 to under 40 /1,000 reflects improving medical services. The absence of a decline in eastern Europe (approximately 14/1,000) and Central Asia and the Caucasus (approximately 30/1,000) reflects both the economic problems of the region and the absence of services for prevention of congenital disorders.

Crude birth rate has also decreased throughout the Region. In Eastern Europe it has reached the lowest level ever recorded (8 /1000 in some countries), because many couples cannot afford to bring up children. In the absence of medical and social support systems, it is simply impossible for most parents to care successfully for a severely disabled child. Sadly, many affected babies are abandoned in the hospital of birth, and have no hope of surviving in an orphanage.

Any policy recommendations for the control of congenital disorders in the WHO European Region must take account of these economic and social realities.

Importance of registries of congenital anomalies

Baseline prevalence figures are needed to assess the importance of congenital malformations and the effects of preventive measures. National reporting systems cannot meet the need because of under-reporting, especially of terminations of pregnancy following prenatal diagnosis: dedicated registries of congenital and genetic disorders are required. Such registries can only be built up gradually, and it takes years before registration approaches completeness (54-56).

The 8th report of the European Surveillance of Congenital Anomalies (EUROCAT) system, which collects standardised results from 30 registries in 15 Western European countries, plus one in Croatia and one in Bulgaria, is a principal source of prevalence and outcome data for this report (34). Additional data has been provided from Belarus and Hungary. The Hungarian National Register of Congenital Anomalies, now over 40 years old, is one of very few national registries in existence. It covers a population of 10.5 million with an average of 135000 births /year (56). In the 1980s the Hungarian group used national outcome data to assess the burden of congenital disorders in terms of mortality, cure and chronic disability in a medium-developed country with a good health service, before the introduction of prenatal diagnosis and selective abortion (57). This data permits estimates of baseline mortality attributable to neural tube defects and other congenital malformations in the WHO European Region.

Table 4 shows the estimated prevalence of congenital and genetic disorders in the Region (see also Table A1 in Annex A for country details), and the proportion that cause death in the first few years, even when paediatric services are generally available. Congenital malformations are the largest group, and though they are the most treatable, they cause the most deaths.

Table 4. WHO European Region: estimated baseline rates of congenital and genetic disorders in the absence of prevention, their contribution to early mortality, and the contribution of neural tube defects. Calculations based on data of Cziezel *et al.* (57)

WHO European Region	Rate per 1,000 livebirths			NTD, per cent of	
	total congenital & genetic disorders	*congenital malformations*	*NTD*	*total congenital & genetic disorders*	*total congenital malformations*
Births	54.2	36.9	1.95	3.6	5.3
Deaths	14.2*	6.8	1.56	11.0	23.1

* About 50% of these deaths occur in the perinatal period or the first year of life., so the theoretical contribution to infant mortality is about 7/1,000.

In low-resource countries most affected infants die soon after birth, and their deaths are concealed in a generally high infant mortality – the present situation in much of Turkey, Central Asia and the Caucasus. As resources for diagnosis improve the contribution of congenital disorders to mortality is increasingly recognised – the present situation in much of Central and Eastern Europe. With improving facilities for treatment an increasing proportion of affected infants are cured (e.g., by paediatric surgery) or survive with long-term problems – the present situation in Western and Southern Europe.

In the absence of prevention, congenital and genetic disorders are responsible for an infant mortality of at least 7/1000. About 50% of this is attributable to congenital malformations. The estimate is confirmed from data on causes of death in the 1993 UN Demographic Yearbook (58) (see Figure B2). Clearly, infant mortality can fall below 10/1000 only when services for prevention of these disorders are in place. Food fortification with folic acid is an important primary prevention strategy for reducing this burden of individual suffering and social costs.

Approaches for prevention

Because of their diversity, prevention of congenital disorders requires multiple approaches (47, 48). *Primary prevention* strategies reduce the number of affected pregnancies. They include avoiding environmental risks during pregnancy (e.g., rubella immunisation, anti-D for Rhesus negative women, avoiding excess alcohol and smoking, appropriate use of drugs, control of workplace conditions), genetic counselling, and family planning (which reduces the number of older mothers and decreases the birth prevalence of infants with chromosomal disorders). *Secondary prevention* strategies reduce the number of affected births, but not the number of affected pregnancies. They include genetic counselling, routine foetal anomaly scanning, antenatal screening for Down syndrome, and screening for carriers of inherited disorders. In the high-resource countries of western and southern Europe these approaches, together with neonatal screening for malformations, deafness, congenital hypothyroidism and phenylketonuria, have been incorporated gradually into existing health services without being recognised as components of a single prevention strategy. Though their collective impact has not been formally assessed, they have played an important part in the continuing fall in infant mortality in these regions.

Fortification of basic foodstuffs and periconceptional folic acid (or multivitamin) supplementation must now be included as one of the simplest and most powerful approaches available for primary prevention of congenital disorders.

Prevalence of congenital malformations and neural tube defects

Table 5 lists the main groups of congenital malformations in decreasing order of prevalence. Malformations of the central nervous system (mainly neural tube defects), comprise about 7% of all congenital malformations but, because of their severity, they account for about 27% of deaths due to congenital malformations.

Table 5. Birth prevalence and outcomes of the main groups of severe congenital malformation in the absence of prevention

Group of congenital malformation	Prevalence /1,000 LB	% total	Early deaths /1,000 LB	Cure /1,000 LB	Chronic problems /1,000 LB	% early deaths
Cardiovascular system	7.9	27.0	2.7	3.9	1.4	41.2
Central nervous system	2.2	7.5	1.7	0.1	0.4	26.5
Alimentary system	2.8	9.6	0.6	2.0	0.1	9.9
Skeletal system	2.1	7.2	0.4	1.3	0.4	6.0
Urinary organs	1.6	5.5	0.3	0.7	0.6	4.6
Respiratory system	0.3	1.0	0.1	0.1	0.1	1.5
Eye	0.3	1.0	0.1	0.1	0.1	0.9
Cleft palate, +/- cleft lip	1.4	4.8	0.0	1.1	0.3	0.7
Ear, face, neck	0.5	1.7	0.0	0.3	0.1	0.0
Genital organs	7.5	25.6	0.0	6.5	1.0	0.0
Miscellaneous incl. multiple	2.7	9.2	0.6	1.6	0.6	9.6
Total	29.3	100	6.5	17.7	5.1	100

LB = live births. Prevalence figures are based on Czeizel *et al.* (59), with the exclusion of (a) musculoskeletal malformations because the high prevalence of congenital dislocation of the hip in Hungary distorts the figures, and (b) congenital malformations associated with chromosomal anomalies, as chromosomal disorders are included in Table 4. Estimates of outcome are from Czeizel and Sankanarayanan (57).

Table 6 shows the prevalence of pregnancies affected by neural tube defects in the Region (see Annex Tables A1 and A5 for country data). Over 70% of annual affected pregnancies occur in the eastern part of the Region, and this is where interventions aiming to reduce the prevalence of neural tube defects will have their greatest impact.

Table 6. Prevalence of neural tube defects (NTD) in the WHO European Region

Sub-region	Annual births, *thousands*	NTD /1000 pregnancies	Annual foetuses with NTD	% of affected foetuses in the Region
Western Europe	3,029	1.34	4,069	21.4
Southern Europe	1,436	0.85	1,217	6.4
Turkey	1,359	3.01	4,089	21.5
Central Europe	996	2.25	2,240	11.8
Eastern Europe	1,772	2.42	4,281	22.5
Cent Asia & Caucasus	1,410	2.09	2,948	15.5
Israel	133.5	1.4	187	1.0
WHO European Region	10,136	1.88	19,031	100

Outcomes of affected pregnancies

In Western and Southern Europe and neighbouring Eastern European countries where foetal anomaly scanning is available to all pregnant women, on average 20% of pregnancies where the foetus has a serious congenital malformation are aborted (33). As termination is usually requested only for the most severe disorders, foetal anomaly scanning selectively reduces the proportion of children born with lethal or incurable conditions, including neural tube defects.

Figure 3 shows the pattern of outcomes for neural tube defect pregnancies for countries included in the EUROCAT registries (33). In total, from 60-70% of affected pregnancies are terminated in Western Europe. By contrast, in the absence of facilities for prenatal diagnosis most affected pregnancies in Russia, Central Asia, the Caucasus and Turkey end in a live- or still birth.

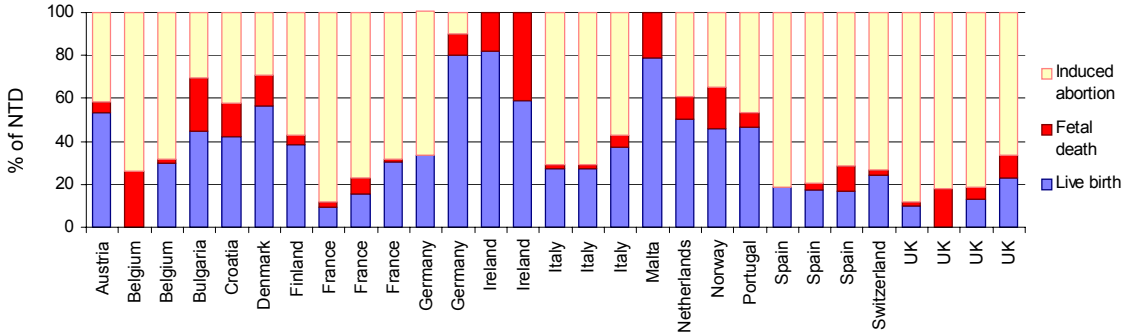


Figure 3. Outcome of neural tube defect pregnancies recorded in 29 registries in 16 countries (33). Registries with problems in ascertaining terminations of pregnancy are excluded. Registries are shown under the name of the country. From 50 to 80% of affected pregnancies are terminated in Belgium, France, Portugal, Spain, Switzerland and the UK: 30-40% are terminated in Croatia and Bulgaria, Netherlands and Norway. No affected pregnancies are terminated in Ireland and Malta

A proportion (yet to be determined) of pregnancies where the embryo is affected by neural tube defects or some other malformations ends in early miscarriage. Obviously, it is difficult to assess any impact of folic acid fortification on malformation-related early pregnancy loss. Low folate levels have been associated with significantly increased risk of recurrent miscarriage (60) and of miscarriage associated to foetal chromosomal abnormality (61). Also, lower folate levels induced by smoking may be associated with the higher rate of miscarriage, stillbirth, and other adverse pregnancy outcomes observed in women who smoke (64). Therefore, it is reasonable to expect a favourable effect of increased folate intake on the rate of successful pregnancies.

Predicting the effect of folic acid fortification of flour

Enough is now known about the relationships between dietary folic acid intake, serum folate levels and risk of neural tube defects to permit tentative predictions of the effect of different levels of folic acid supplementation/fortification on prevalence of neural tube defects. Figure 4 presents predictions for the WHO European Region based on the calculations of Wald *et al.* (42).

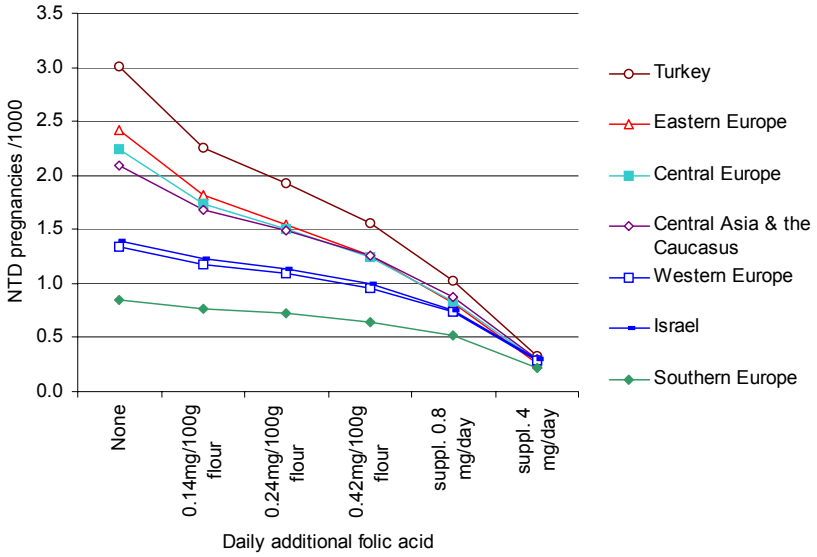


Figure 4. Estimated effect of different levels of folic acid fortification of basic foodstuffs. Predicted effect of periconceptional folic acid supplementation on prevalence of neural tube defects in the WHO European Region. The effect is greatest where prevalence is highest and least where it is already low. (Figures on which calculations are based are shown in Table A3)

The data permit the estimation that in the WHO European Region, folic acid food fortification at 240 micrograms per 100 g flour would lead to a minimum reduction of approximately 5,800 in the annual number of pregnancies affected by neural tube defect. Over 80% of the benefit would occur in Eastern Europe and Turkey. Currently about 1,300 of these pregnancies to end in abortion because of foetal abnormality and about 4,500 to end with the birth of an affected baby with little prospect of long-term survival.

Expressing the effects of interventions

All outcomes of a pregnancy affected by a neural tube defect – affected live birth, stillbirth, termination of pregnancy – are distressing, although to different degrees. Replacing an affected live-birth by abortion does not solve the problem. The abortion of a wanted pregnancy is simply the lesser of two evils, and must be counted as an unfavourable pregnancy outcome. Primary prevention is the only intervention not associated with distress: on the contrary, it increases the number of healthy wanted babies born and has a highly positive effect on the quality of life of parents and children. In evaluating the effects of folic acid fortification the appropriate index is therefore *gain in number of unaffected pregnancies*, rather than reduction in the number of affected live births. The latter index has been used in several publications. However this usage belittles the distress associated with abortion of a wanted pregnancy and leads to serious under-estimation of the benefits of primary prevention.

Figure 5 shows the predicted effects of folic acid fortification in the Region in terms of births of healthy children who would otherwise have had a neural tube defect. For example, fortification with 240 mg of folic acid per 100 g of flour would lead to a minimum annual gain of about 5,800 healthy liveborn babies who would otherwise have suffered from a neural tube defect, or be aborted because of foetal abnormality.

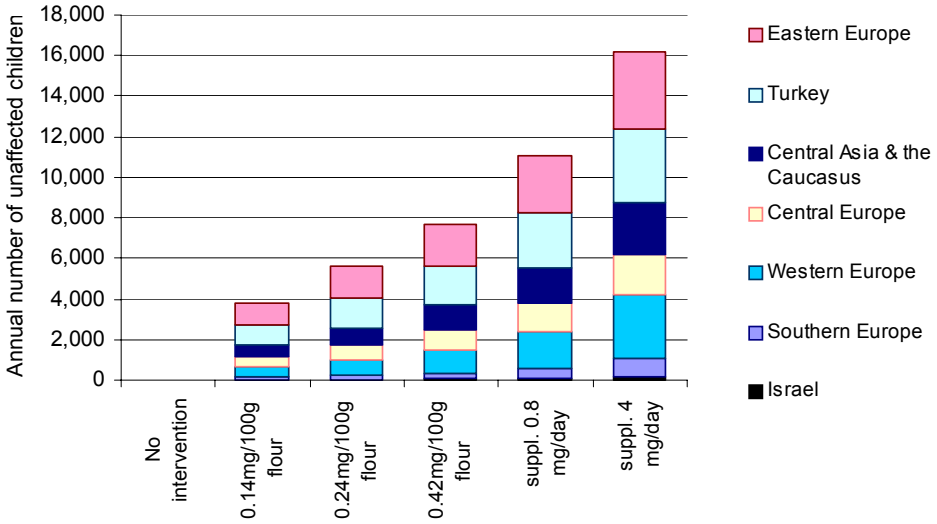


Figure 5. Estimated annual number of unaffected children born, who would otherwise have had a neural tube defect, with increased folic acid intake in the WHO European Region (Calculations shown in Table A4)

The approach can also be used to estimate the human cost of delaying food fortification with folic acid – for each year's delay in initiating fortification with 240 mg of folic acid per 100 g of flour, there are at least about 1,300 avoidable abortions for foetal abnormality and 4,500 avoidably affected liveborn children. This conservative estimate uses figures for NTD only, without taking into account possible effects on other malformations.

Possible effects on the prevalence of other congenital disorders

Since a general biological mechanism underlies the protective effect of folic acid against neural tube defects, it might be expected to protect against a wider range of malformations, and there is growing evidence to support this suggestion. Most of the studies listed in Table 1 focused exclusively on neural tube defects and would not have been able to observe any more general effect. Only an established congenital anomaly surveillance system with access to large-scale data on maternal folic acid or multivitamin intake could assess effects on the prevalence of all congenital malformations. These requirements are met by (a) the Hungarian Registry, which was used to record the effects of a prospective randomised trial of multivitamin supplementation, and (b) the National Centre on Birth Defects and Developmental Disabilities in the USA. Both groups observed a reduced prevalence of congenital malformations other than neural tube defects, among the offspring of women who took multivitamin preparations containing folic acid (28-30).

A recent review (32) summarised the present evidence for all major birth defects combined as follows: "The Hungarian randomised clinicians indicated, for preconceptional multivitamin use, a reduction in the risk of all birth defects (risk ratio, RR: 0.52; 95% Confidence Interval, CI: 0.36-0.71) even after excluding neural tube defects (RR: 0.54; 95% CI: 0.39-0.76). The Atlanta population-based case-control study, the only large observational study to date on all major birth defects, also found a significant risk reduction for all birth defects (odds ratio: 0.80; 95% CI: 0.69-0.93) even after excluding neural tube defects (odds ratio: 0.84; 95% CI: 0.72-0.97). The specific malformations whose risk was reduced in the two studies though not identical, were similar. These and other observational studies also provide data on specific anomalies, including heart, limb and urinary tract defects as well as orofacial clefts, omphalocele and imperforate anus".

This evidence, though suggestive rather than definitive, prompted an estimate of the potential overall effects in Europe if folic acid alone prevents the proportion of these major malformations specified by the Hungarian and North American studies. On a conservative estimate, the potential gain in infants born free of other serious malformations would be three to four times the gain in infants born free of neural tube defects. Though this estimate is highly tentative, it provides an indication of the possible additional benefit that might arise from increasing folic acid intake throughout the population

Because congenital malformations are so heterogeneous it is difficult to obtain diagnosis-specific evidence for preventive effects. At this stage in the evolution of public health policy on food fortification, the best evidence for or against such effects will be obtained through meticulous surveillance, oriented to detecting unexpected benefits as well as problems associated with widespread implementation of food fortification and periconceptional supplementation. It is essential to maintain the existing congenital malformation registers for this purpose.

Safety issues

No evidence of harm has ever been obtained in trials involving periconceptional supplementation with levels of folic acid ranging from about 400 μg to 4 mg /day. Equally, there is no evidence of harm to the high proportion of the North American population of all ages who already take supplements.

Specific concerns that have been raised include:

- A possible increase in the rate of dizygotic twinning (63), and a possible effect on miscarriage rate (64, 65): the very large population-based study in China has produced evidence that neither is an issue (66). The present weight of evidence does not support an increased twinning rate.
- Effect on the presentation of pernicious anaemia (vitamin B12 deficiency). Pernicious anaemia often presents as megaloblastic anaemia. This can be prevented by administration of folic acid, and there is a long-standing belief that folic acid administration can aggravate the neurological consequences of pernicious anaemia. It has been suggested that folic acid fortification of food might mask the anaemia and so lead to later presentation of affected people with neurological problems, and possibly more serious long-term consequences. Systematic review of the literature does not support this concern, and provides no good evidence that folic acid aggravates the neurological complications of pernicious anaemia (67). There has been no indication from North America of any such problem following folic acid fortification of flour. In addition, definitive diagnosis of pernicious anaemia by plasma vitamin B12 assay is now straightforward. Of course, regardless of fortification primary care physicians and neurologists need to be alert to the possibility of vitamin B12 deficiency and perform a B12 assay whenever the diagnosis is suspected.
- An increase in dietary folic acid could theoretically reduce the efficiency of some anticonvulsants, making it necessary to adjust established doses. Any such effect could readily be managed, but no evidence has arisen to support this concern in populations where food fortification is mandatory.

In conclusion, there is no evidence of any harmful effects of folic acid fortification of foods but vigilance is recommended.

Surveillance

Surveillance at the public health level is essential. It should include measures to monitor the amount of folic acid in foods, the level of fortification in flour and other basic foodstuffs, effective folate intake by the population using appropriate biomarkers, and effects on prevalence of congenital malformations. It would also be desirable to assess effects on other adverse pregnancy outcomes and twinning rates. However, lack of reliable recording mechanisms and concomitant change in other factors affecting these outcomes (e.g. increasing use of fertility treatments) complicate assessment and introduce a serious risk of spurious associations. Satisfactory surveillance requires reliable baseline (pre-fortification) values for the population and robust indicators. Sustainable systems should be in place for surveillance as follows:

- Monitoring the levels of folic acid in fortified foodstuffs.
- Measurement of population plasma or serum, and possibly red cell folate levels.
- Surveillance of the prevalence of neural tube defects. It is now clear that this is a simple and reliable indicator of sufficiency of folate (and possibly other essential vitamins) in a population. Consequently the prevalence of these defects may be seen as a "sentinel" for a broad range of health benefits now known to be associated with folate sufficiency.
- Surveillance of the prevalence of other congenital malformations.
- Identification of possible population subsets that need specific attention due, e.g., to specific dietary habits or metabolic problems.
- Comparisons of the effects of different policies for dietary supplementation.

What level of fortification should be recommended in the Region?

Various levels have been recommended for fortification of flour – for example the 140 µg/100 g recommended in North America and the 240 µg/100 g recommended in the UK would lead to an average additional daily folic acid intake of 0.1 and 0.2 mg/day respectively. Both values are well below the 0.8mg required for the near-full effect in preventing neural tube defects, especially in lower-prevalence areas. There are no valid scientific reasons against recommending fortification at a higher level which is known to be more effective –e.g., 500 µg/100 g of flour.

The public may be unwilling to accept a major fortification of food; moreover residual concerns (however hypothetical) exist about possible harm from increased long-term intake of folic acid to individuals who already have a high serum folate level. Therefore it seems wise to fortify at less than 500 µg/100 g flour at present, to maintain surveillance systems capable of detecting possible adverse effects, and to consider moving to higher levels in the future providing no adverse effects are observed and there is evidence that higher prevention can be achieved. Public perceptions must also be taken into account.

In view of the particular need for supplementation in many countries, especially in Eastern Europe, the UK recommendation of 240 µg of folic acid per 100 g of flour (46), which has already been accepted in the Ukraine, should be viewed as a *minimum* level. It may be appropriate to consider higher levels in parts of eastern and south-east Europe, where benefits are likely to be greatest and other options are severely limited.

It is also worth enquiring whether the effect of folic acid fortification can be maximised in any other way, for example by additional fortification with vitamin B12, which is affordable and can do no harm. Combined fortification has already been adopted on a voluntary basis in Hungary and could be the best strategy for Eastern Europe.

In conclusion, it must be emphasised that:

- Folic acid fortification of basic foodstuffs at the level recommended is essential, but it may not fully achieve the optimal folate intake.
- Promotion of periconceptional vitamin supplementation must not be relaxed, since there is a danger that the problem will be considered fully solved through food fortification.
- Women should be advised to take 5 mg folic acid while trying to become pregnant. Accordingly, health services and practitioners should receive and provide appropriate information on factors known to impair folate absorption or utilisation.
- The level of fortification should be set at least 240µg/100g flour; further modifications of the optimal level may take into account possible beneficial effects other than prevention of birth defects, e.g., cardiovascular diseases.
- The effects of fortification must be monitored at the population level.
- The level of fortification should be regularly reviewed, and adjusted in the light of emerging information on health benefits.
- Recommendations should be flexible and able to change in response to results of surveillance.
- Food fortification should be viewed as one component of a comprehensive strategy aiming to optimise pregnancy outcomes.

CONCLUSION AND RECOMMENDATIONS

Recognising the severity of neural tube defects and the distress they cause, as well as the fact that they can be largely prevented by increasing the intake of folic acid without any indication of harm, member countries should consider, as a matter of urgency, the fortification of flour with folic acid on a mandatory basis. This policy is reinforced by recognising the need to reduce social inequalities in disease and the responsibility of public health authorities to implement preventive measures in an equitable manner so that they can reach all who stand to benefit.

Therefore, the following recommendations are made:

1. Folic acid consumption should be increased in the populations of the WHO European Region, for the prevention of neural tube defects and to realise other health benefits.
2. The main strategy to accomplish this should be the universal mandatory fortification of flour with folic acid. In addition women should be advised to take folic acid supplements before and during pregnancy. This advice should be given against a background of generally recommending a folate rich diet.
3. Countries should consider adopting the folic acid fortification level recommended by the UK COMA Committee (240 μg folic acid per 100g flour). The level selected should be regularly reviewed, and increased or decreased as judged necessary on grounds of securing health benefits and safety.
4. Health Authorities should set up a standing expert committee to regularly review the effects of folic acid fortification on the health of the population.
5. The dose of folic acid for supplementation before and in the early stages of pregnancy is currently 400 μg a day for women in the general population and 4 or 5 mg per day in women who have previously had a pregnancy associated with a neural tube defect. There are no scientific grounds for this distinction. The same level of supplementation (5 mg/day) may be used by all women who may become pregnant.
6. It would desirable for health authorities to set up systems for monitoring blood folate levels and neural tube defects, in association with policies designed to increase folic acid intake in the population.
7. Further research should not delay the implementation of fortification but should be conducted at the same time, for example to determine the defects other than neural tube defects can be prevented by increasing folic acid intake, and to determine whether micro-nutrients other than folic acid (or folate) have a role in preventing birth defects.

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Annex A
WHO European Region: demographic data and prevalence of neural tube defects and congenital and genetic disorders

Table A1. Demographic data, prevelance of neural tube defects and congenital and genetic disorders in the WHO European Region

Country & Sub-region	Data from UNDY 1999							Reported CA deaths UNDY 1996			Birth prevalences			Annual affected births		
	Population millions	*Crude birth rate*	*Infant mortality*	*Calculated annual births 1999*	*Annual births, 1000s*	*Calculated annual infant deaths 1999*	*Annual infant deaths, 1000s*	*Reported annual deaths CAs*	*CA deaths /1000 livebirths*	*CA deaths, % of IMR*	*Total congen/ genetic /1000*	*Total malformations /1000*	*NTD pregnan-cies /1000*	*Annual congen/ genetic disorders*	*Annual congen malfns*	*Annual NTD pregnan-cies*
Armenia	3.8	10.4	14.7	39,468	39.5	580	0.6	209	5.3	36.0	51.9	34.9	2.0	2,048	1,376	79
Azerbaijan	8.0	14.7	16.2	117,350	117.4	1,901	1.9	327	2.8	17.2	61.5	34.9	3.1	7,222	4,092	364
Georgia	5.4	11.3	12.4	61,009	61.0	757	0.8	130	2.1	17.1	52.1	34.9	2.0	3,177	2,127	122
Kazakhstan	14.9	14.0	20.4	209,188	209.2	4,267	4.3	1,270	6.1	29.8	52.6	34.9	2.0	10,997	7,295	418
Kyrgyzstan	4.9	21.7	26.0	105,571	105.6	2,745	2.7	287	2.7	10.5	72.1	34.9	2.0	7,607	3,681	211
Tadjikistan	6.2	31.8	56.5	198,337	198.3	11,206	11.2	430	2.2	3.8	73.7	34.9	2.0	14,616	6,916	397
Turkmenistan	4.4	28.6	54.8	125,382	125.4	6,871	6.9	289	2.3	4.2	53.6	34.9	2.0	6,721	4,372	251
Uzbekistan	24.0	23.1	22.3	553,337	553.3	12,339	12.3	1,533	2.8	12.4	52.6	34.9	2.0	29,107	19,296	1,107
Central Asia & Caucasus	**71.6**	**19.7**	**28.8**	**1,409,642**	**1409.6**	**40,666**	**40.7**				**57.8**	**34.9**	**2.1**	**81,496**	**49,157**	**2,948**
Bulgaria	8.2	8.4	14.5	68,947	68.9	1,000	1.0	443	6.4	44.3	52.6	34.9	1.9	3,628	2,404	130
Czech Rep	10.3	8.7	4.6	89,462	89.5	412	0.4	0	0.0	0.0	50.5	31.7	0.8	4,514	2,838	72
Estonia	1.4	8.4	8.9	11,861	11.9	106	0.1	59	5.0	56.2	51.0	31.7	1.0	605	376	12
Hungary	10.1	9.4	8.9	94,639	94.6	842	0.8	493	5.2	58.6	52.6	31.9	2.8	4,979	3,015	263
Latvia	2.4	8.0	11.4	19,456	19.5	222	0.2	165	8.5	74.6	51.1	31.7	1.0	994	617	19
Lithuania	3.7	9.7	8.8	35,880	35.9	316	0.3	270	7.5	85.5	52.0	31.7	2.0	1,866	1,138	72
Poland	38.7	9.9	8.9	382,675	382.7	3,406	3.4	2,165	5.7	63.6	52.8	31.7	2.7	20,212	12,140	1,026
Romania	22.5	10.5	20.5	235,809	235.8	4,834	4.8	1,123	4.8	23.2	52.4	31.7	2.5	12,353	7,481	590
Slovakia	5.4	10.7	8.8	57,727	57.7	508	0.5	0	0.0	0.0	50.7	31.7	1.0	2,928	1,831	58
Central Europe	**102.6**	**9.7**	**11.7**	**996,456**	**996.5**	**11,645**	**11.6**				**52.3**	**31.7**	**2.2**	**52,078**	**31,611**	**2,240**
Belarus	10.2	9.2	11.4	93,463	93.5	1,065	1.1	640	6.8	60.1	52.3	31.7	2.6	4,892	2,965	243
Moldova	4.4	11.3	17.9	49,494	49.5	886	0.9	359	7.3	40.5	52.5	31.7	2.7	2,598	1,570	134
Russia	145.6	8.3	17.1	1,208,140	1208.1	20,659	20.7	8,588	7.1	41.6	52.3	31.7	2.5	63,131	38,327	3,020
Ukraine	50.1	8.4	12.9	420,890	420.9	5,429	5.4	3,357	8.0	61.8	51.8	31.7	2.1	21,797	13,352	884
Eastern Europe	**210.2**	**8.4**	**15.8**	**1,771,987**	**1772.0**	**28,040**	**28.0**				**52.2**	**31.5**	**2.4**	**92,416**	**55,896**	**4,281**
Israel	**6.1**	**21.8**	**5.7**	**133,525**	**133.5**	**761**	**0.8**				**52.5**	**36.2**	**1.4**	**7,016**	**4,836**	**187**
Albania	3.1	15.9	15.0	49,497	49.5	742	0.7	128	2.6	17.2	53.8	34.9	1.5	2,665	1,726	72
Andorra	0.1	10.8	6.4	810	0.8	5	0.0	0	0.0	0.0	51.5	34.9	1.0	42	28	1
Bosnia-Herz	3.8	10.5	15.4	40,310	40.3	621	0.6	0	0.0	0.0	51.1	36.2	1.0	2,060	1,460	40
Croatia	4.6	9.9	7.7	45,085	45.1	347	0.3	150	3.3	43.3	51.1	36.2	0.6	2,304	1,633	25
Gibralter	0.0	15.7	9.8	393	0.4	4	0.0	0	0.0	0.0	51.4	36.2	1.0	20	14	0
Greece	10.6	10.9	5.5	115,823	115.8	637	0.6	393	3.4	61.7	56.7	36.3	1.5	6,570	4,207	168
Italy	57.3	9.2	5.5	527,556	527.6	2,902	2.9	1,892	3.6	65.2	51.7	36.3	0.5	27,256	19,154	264
Macedonia	2.0	14.8	15.7	29,763	29.8	467	0.5	76	2.6	16.4	50.7	33.1	1.0	1,509	984	30
Malta	0.4	12.2	5.2	4,709	4.7	24	0.0	0	0.0	0.0	52.7	33.1	1.1	248	156	5
Portugal	10.0	11.8	5.6	117,870	117.9	660	0.7	330	2.8	49.9	51.4	33.1	0.6	6,061	3,898	71
S Marino	0.0	11.1	10.6	289	0.3	3	0.0	0	0.0	0.0	51.5	33.1	1.0	15	10	0
Slovenia	2.0	8.8	4.5	17,503	17.5	79	0.1	74	4.2	93.4	51.0	33.1	1.0	893	579	18
Spain	39.4	9.3	4.9	366,587	366.6	1,796	1.8	1,301	3.5	72.4	51.9	33.1	1.1	19,041	12,124	403
Yugoslavia	10.6	11.3	12.6	120,198	120.2	1,514	1.5	521	4.3	34.4	51.3	31.0	1.0	6,161	3,732	120
Southern Europe	**144.0**	**10.0**	**6.8**	**1,436,392**	**1436.4**	**9,802**	**9.8**				**52.1**	**33.1**	**0.8**	**74,845**	**47,506**	**1,217**
Turkey	**64.4**	**21.1**	**37.9**	**1,358,524**	**1358.5**	**51,488**	**51.5**				**60.4**	**34.0**	**3.0**	**82,028**	**46,152**	**4,089**

to be continued

continues

Country & Sub-region	Data from UNDY 1999							Reported CA deaths UNDY 1996			Birth prevalences			Annual affected births		
	Population millions	*Crude birth rate*	*Infant mortality*	*Calculated annual births 1999*	*Annual births, 1000s*	*Calculated annual infant deaths 1999*	*Annual infant deaths, 1000s*	*Reported annual deaths CAs*	*CA deaths /1000 livebirths*	*CA deaths, % of IMR*	*Total congen/ genetic /1000*	*Total malformations /1000*	*NTD pregnan-cies /1000*	*Annual congen/ genetic disorders*	*Annual congen malfns*	*Annual NTD pregnan-cies*
Channel Is	0.2	11.2	3.0	1,702	1.7	5	0.0	0	0.0	0.0	51.7	33.1	1.0	88	56	2
Denmark	5.3	12.4	4.2	66,055	66.1	277	0.3	0	0.0	0.0	52.0	33.1	1.2	3,436	2,185	77
Faroe Is	0.0	14.3	6.4	615	0.6	4	0.0	0	0.0	0.0	51.2	33.1	1.0	31	20	1
Finland	5.2	11.1	4.2	57,332	57.3	241	0.2	196	3.4	81.5	51.7	33.1	0.9	2,963	1,896	50
I of Man	0.1	18.8	2.4	1,466	1.5	4	0.0	0	0.0	0.0	51.3	33.1	1.0	75	48	1
Iceland	0.3	15.3	2.6	4,269	4.3	11	0.0	11	2.7	103.1	51.5	33.1	1.0	220	141	4
Ireland	3.7	14.2	5.5	53,179	53.2	292	0.3	213	4.0	73.0	53.0	33.1	2.0	2,819	1,759	106
Norway	4.5	13.2	4.0	58,898	58.9	236	0.2	178	3.0	75.8	51.8	32.9	0.8	3,050	1,939	48
Sweden	8.9	10.0	3.4	88,570	88.6	301	0.3	292	3.3	97.1	52.0	33.8	1.0	4,604	2,997	89
UK	58.7	11.9	5.8	699,054	699.1	4,055	4.1	2,526	3.6	62.3	53.5	33.8	1.7	37,388	23,654	1,188
Austria	8.2	9.5	4.4	77,682	77.7	342	0.3	245	3.2	71.8	51.2	33.8	0.8	3,976	2,629	62
Belgium	10.2	11.3	5.5	114,718	114.7	631	0.6	325	2.8	51.5	51.4	33.8	1.2	5,898	3,882	132
France	59.1	12.6	4.8	744,647	744.6	3,574	3.6	1,655	2.2	46.3	52.1	33.8	1.2	38,825	25,197	879
Germany	82.1	9.5	4.5	779,827	779.8	3,509	3.5	0	0.0	0.0	52.1	33.8	1.5	40,629	26,387	1,131
Liechtenstein	0.0	13.9	18.4	445	0.4	8	0.0	0	0.0	0.0	51.9	33.8	1.0	23	15	0
Luxembourg	0.4	13.0	4.7	5,577	5.6	26	0.0	0	0.0	0.0	51.7	33.8	1.0	288	189	6
Monaco	0.0	20.7	1.9	683	0.7	1	0.0	0	0.0	0.0	51.4	33.8	1.0	35	23	1
Netherlands	15.8	12.7	5.0	200,787	200.8	1,004	1.0	648	3.2	64.6	52.4	33.8	1.1	10,515	6,794	221
Switzerland	7.1	10.3	3.4	73,542	73.5	250	0.3	0	0.0	0.0	51.6	33.8	1.0	3,796	2,488	71
Western Europe	**269.8**	**11.2**	**4.9**	**3,029,047**	**3029.0**	**14,772**	**14.8**				**52.4**	**33.8**	**1.3**	**158,661**	**102,495**	**4,069**
WHO EUR Total	**868.7**	**11.7**	**15.5**	**10,135,571**	**10135.6**	**157,174**	**157.2**				**54.1**	**33.8**	**1.9**	**548,541**	**342,962**	**19,031**

Table A2. The Pew Global Attitudes Project. What the world thinks in 2002. The Pew Research Centre for the People and the Press. www.people-press.org

Country	% of those interviewed unable to afford food at times in 2002
Uzbekistan	64
Ukraine	55
Russia	50
Bulgaria	46
Turkey	45
Poland	35
Slovakia	16
Italy	11
UK	11
Czech Rep	8
France	8
Germany	5

Table A3. Relationship between intitial serum folate level, folic acid intake and risk of neural tube defects. Based on Wald *et al*. 2001 (reference 42)

Initial serum folate	2.5 ng/mL		5 ng/mL		7.5 ng/mL		10 ng/mL	
Corresponding prevalence of NTD	**2.5 /1,000**		**1.8 /1,000**		**1.2 /1,000**		**1 /1,000**	
Increase in folic acid intake, mg/day	*pl folate ng/mL*	*% risk reduction*	*pl folate ng/mL*	*% risk reduction*	*pl folate ng/mL*	*% risk reduction*	*pl folate ng/mL*	*% risk reduction*
0.1	3.4	23	5.9	13	8.4	9	10.9	7
0.2	4.4	36	6.9	23	9.4	16	11.9	13
0.3	5.3	45	7.8	30	10.3	23	12.8	18
0.4	6.3	52	8.8	36	11.3	28	13.8	23
0.5	7.2	57	9.7	41	12.2	32	14.7	27
0.8	9.6	66	12.1	51	14.6	41	17.1	35
1.0	11.9	71	14.4	57	16.9	48	19.4	41
2.0	21.3	82	23.8	71	26.3	63	28.8	57
3.0	30.7	87	33.2	78	35.7	71	38.2	66
4.0	40.1	89	42.6	82	45.1	76	47.6	71
5.0	49.5	91	52	85	54.4	80	57	75

Table A4. Predicted gain in infants born free of neural tube defect, with different levels of folic acid fortification or supplementation without intervention

Region	Fortification of flour			Periconceptional supplementation	
	0.14 mg/100 g	***0.24 mg/100 g***	***0.42 mg/100 g***	***0.8 mg/d***	***4mg/d***
Central Asia & Caucasus	582	855	1,183	1,713	2,521
Central Europe	492	771	1,156	1,841	3,191
E Europe	1,022	1,472	1,963	2,699	3,639
Turkey	1,070	1,541	2,055	2,825	3,810
S Europe	115	185	285	477	903
W Europe	515	747	1,004	1,403	1,953
Israel	22	36	54	86	148
WHO EUR	3,819	5,606	7,700	11,044	16,165

Table A5. Projected effects of different levels of folic acid food fortification and periconceptional supplementation in the WHO European Region

Country, abbreviation	Demographic data 1999				Annual NTD pregnancies and extra folic acid						Annual gain in births free of NTD					
	Population millions	*Calculated annual births 1999*	*Annual births 1000s*	*NTD pregnancies /1000*	*No inter-vention*	*0.14 mg/100 g flour*	*0.24 mg/100 g flour*	*0.42 mg/100 g flour*	*Pericon-ceptnl 0.8 mg/d*	*Pericon-ceptnl 4 mg/d*	*No inter-vention*	*0.14 mg/100 g flour*	*0.24 mg/100 g flour*	*0.42 mg/100 g flour*	*Pericon-ceptnl 0.8 mg/d*	*Pericon-ceptnl 4 mg/d*
Armenia	3.8	39,468	39.5	2.00	79	64	57	48	34	12	0	15	22	31	45	67
Azerbaijan	8.0	117,350	117.4	3.10	364	273	233	189	124	40	0	91	131	175	240	324
Georgia	5.4	61,009	61.0	2.00	122	99	88	74	52	18	0	23	34	48	70	104
Kazakhstan	14.9	209,188	209.2	2.00	418	339	301	255	180	63	0	79	117	163	238	356
Kyrgyzstan	4.9	105,571	105.6	2.00	211	171	152	129	91	32	0	40	59	82	120	179
Tadjikistan	6.2	198,337	198.3	2.00	397	321	286	242	171	60	0	75	111	155	226	337
Turkmenistan	4.4	125,382	125.4	2.00	251	203	181	153	108	38	0	48	70	98	143	213
Uzbekistan	24.0	553,337	553.3	2.00	1,107	896	797	675	476	166	0	210	310	432	631	941
Central Asia & Caucasus	**71.6**	**1,409,642**	**1,409.6**	**2.09**	**2,948**	**2,366**	**2,094**	**1,766**	**1,235**	**428**	**0**	**582**	**855**	**1,183**	**1,713**	**2,521**
Bulgaria	8.2	68,947	68.9	1.88	130	110	100	87	64	23	0	19	30	43	66	106
Czech Rep	10.3	89,462	89.5	0.80	72	66	62	57	47	21	0	6	9	14	25	51
Estonia	1.4	11,861	11.9	1.00	12	11	10	9	8	3	0	1	2	2	4	8
Hungary	10.1	94,639	94.6	2.78	263	197	168	137	89	29	0	66	95	126	174	234
Latvia	2.4	19,456	19.5	1.00	19	18	17	16	13	6	0	2	3	4	7	14
Lithuania	3.7	35,880	35.9	2.00	72	58	52	44	31	11	0	14	20	28	41	61
Poland	38.7	382,675	382.7	2.68	1,026	769	656	533	349	113	0	256	369	492	677	913
Romania	22.5	235,809	235.8	2.50	590	442	377	307	200	65	0	147	212	283	389	525
Slovakia	5.4	57,727	57.7	1.00	58	53	50	46	38	17	0	5	8	12	20	41
Central Europe	**102.6**	**996,456**	**996.5**	**2.25**	**2,240**	**1,725**	**1,493**	**1,236**	**837**	**287**	**0**	**515**	**747**	**1,004**	**1,403**	**1,953**
Belarus	10.2	93,463	93.5	2.60	243	182	156	126	83	27	0	61	87	117	160	216
Moldova	4.4	49,494	49.5	2.70	134	100	86	69	45	15	0	33	48	64	88	119
Russia	145.6	1,208,140	1,208.1	2.50	3,020	2,265	1,933	1,571	1,027	332	0	755	1,087	1,450	1,993	2,688
Ukraine	50.1	420,890	420.9	2.10	884	663	566	460	301	97	0	221	318	424	583	787
Eastern Europe	**210.2**	**1,771,987**	**1,772.0**	**2.42**	**4,281**	**3,211**	**2,740**	**2,226**	**1,455**	**471**	**0**	**1,070**	**1,541**	**2,055**	**2,825**	**3,810**
Israel	**6.1**	**133,525**	**133.5**	**1.40**	**187**	**165**	**151**	**133**	**101**	**39**	**0**	**22**	**36**	**54**	**86**	**148**
Albania	3.1	49,497	49.5	1.45	72	63	58	51	39	15	0	9	14	21	33	57
Andorra	0.1	810	0.8	1.00	1	1	1	1	1	0	0	0	0	0	0	1
Bosnia-Herz	3.8	40,310	40.3	1.00	40	37	35	32	26	12	0	3	5	8	14	29
Croatia	4.6	45,085	45.1	0.55	25	23	22	20	16	7	0	2	3	5	9	18
Gibralter	0.0	393	0.4	1.00	0	0	0	0	0	0	0	0	0	0	0	0
Greece	10.6	115,823	115.8	1.45	168	148	136	119	91	35	0	20	32	49	77	133
Italy	57.3	527,556	527.6	0.50	264	243	229	211	171	76	0	21	34	53	92	187
Macedonia	2.0	29,763	29.8	1.00	30	27	26	24	19	9	0	2	4	6	10	21
Malta	0.4	4,709	4.7	1.10	5	5	4	4	3	1	0	1	1	1	2	4
Portugal	10.0	117,870	117.9	0.60	71	65	62	57	46	21	0	6	9	14	25	50
S Marino	0.0	289	0.3	1.00	0	0	0	0	0	0	0	0	0	0	0	0
Slovenia	2.0	17,503	17.5	1.00	18	16	15	14	11	5	0	1	2	4	6	12
Spain	39.4	366,587	366.6	1.10	403	363	339	302	238	97	0	40	65	101	165	306
Yugoslavia	10.6	120,198	120.2	1.00	120	111	105	96	78	35	0	10	16	24	42	85
Southern Europe	**144.0**	**1,436,392**	**1,436.4**	**0.85**	**1,217**	**1,102**	**1,032**	**931**	**740**	**313**	**0**	**115**	**185**	**285**	**477**	**903**

to be continued

continues

Country, abbreviation	Demographic data 1999				Annual NTD pregnancies and extra folic acid						Annual gain in births free of NTD					
	Population millions	*Calculated annual births 1999*	*Annual births 1000s*	*NTD pregnancies /1000*	*No inter-vention*	*0.14 mg/100 g flour*	*0.24 mg/100 g flour*	*0.42 mg/100 g flour*	*Pericon-ceptnl 0.8 mg/d*	*Pericon-ceptnl 4 mg/d*	*No inter-vention*	*0.14 mg/100 g flour*	*0.24 mg/100 g flour*	*0.42 mg/100 g flour*	*Pericon-ceptnl 0.8 mg/d*	*Pericon-ceptnl 4 mg/d*
Turkey	**64.4**	**1,358,524**	**1,358.5**	**3.01**	**4,089**	**3,067**	**2,617**	**2,126**	**1,390**	**450**	**0**	**1,022**	**1,472**	**1,963**	**2,699**	**3,639**
Channel Is	0.2	1,702	1.7	1.00	2	2	1	1	1	0	0	0	0	0	1	1
Denmark	5.3	66,055	66.1	1.17	77	70	65	58	46	19	0	8	12	19	32	59
Faroe Is	0.0	615	0.6	1.00	1	1	1	0	0	0	0	0	0	0	0	0
Finland	5.2	57,332	57.3	0.88	50	46	44	40	33	15	0	4	7	10	18	36
I of Man	0.1	1,466	1.5	1.00	1	1	1	1	1	0	0	0	0	0	1	1
Iceland	0.3	4,269	4.3	1.00	4	4	4	3	3	1	0	0	1	1	1	3
Ireland	3.7	53,179	53.2	2.00	106	86	77	65	46	16	0	20	30	41	61	90
Norway	4.5	58,898	58.9	0.82	48	44	42	39	31	14	0	4	6	10	17	34
Svalbard and Jan Mayen Islands	0.0	0	0.0	1.00	0	0	0	0	0	0	0	0	0	0	0	0
Sweden	8.9	88,570	88.6	1.00	89	81	77	71	58	26	0	7	12	18	31	63
UK	58.7	699,054	699.1	1.70	1,188	1,010	915	796	582	214	0	178	273	392	606	974
Austria	8.2	77,682	77.7	0.80	62	57	54	50	40	18	0	5	8	12	22	44
Belgium	10.2	114,718	114.7	1.15	132	119	111	99	78	32	0	13	21	33	54	100
France	59.1	744,647	744.6	1.18	879	791	738	659	518	211	0	88	141	220	360	668
Germany	82.1	779,827	779.8	1.45	1,131	995	916	803	611	237	0	136	215	328	520	893
Liechtenstein	0.0	445	0.4	1.00	0	0	0	0	0	0	0	0	0	0	0	0
Luxembourg	0.4	5,577	5.6	1.00	6	5	5	4	4	2	0	0	1	1	2	4
Monaco	0.0	683	0.7	1.00	1	1	1	1	0	0	0	0	0	0	0	0
Netherlands	15.8	200,787	200.8	1.10	221	199	186	166	130	53	0	22	35	55	91	168
Switzerland	7.1	73,542	73.5	0.96	71	65	61	56	46	20	0	6	9	14	25	50
Western Europe	**269.8**	**3,029,047**	**3,029.0**	**1.34**	**4,069**	**3,577**	**3,298**	**2,913**	**2,228**	**879**	**0**	**492**	**771**	**1,156**	**1,841**	**3,191**
WHO EUR Total	**868.7**	**10,135,571**	**10,135.6**	**1.88**	**19,031**	**15,212**	**13,425**	**11,331**	**7,988**	**2,867**	**0**	**3,819**	**5,606**	**7,700**	**11,044**	**16,165**

Annex B
WHO European Region: figures on estimated patterns of reduction of birth defects following implementation of folic acid fortification

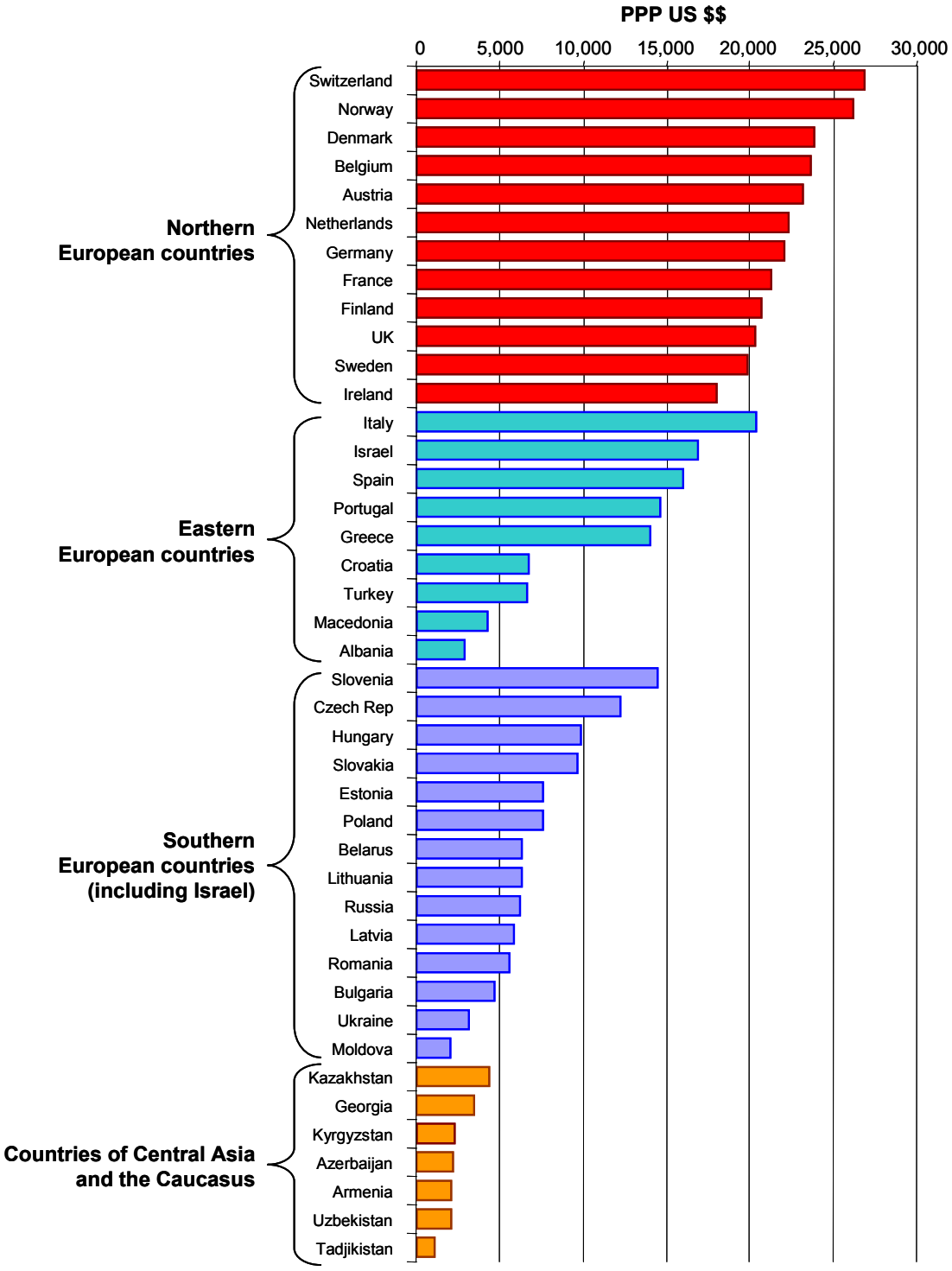

Figure B1. Relative *Per capita* Purchasing Power (PPP) (US $$ equivalent) in European countries (1998)

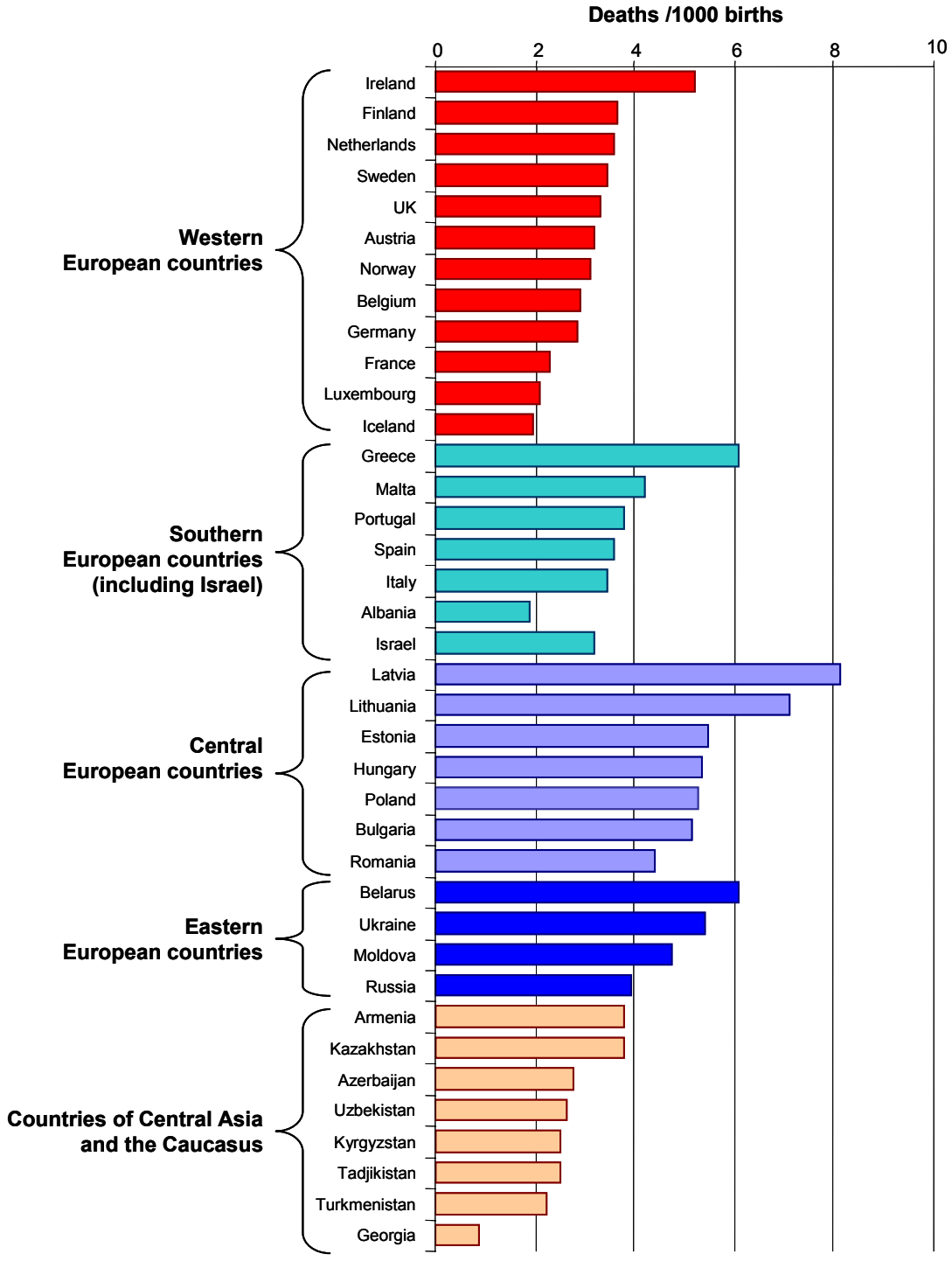

Figure B2. Rates of deaths in 1991 due to congenital malformations and chromosomal disorders in those countries of the WHO European Region with mortality data in the *1996 UN Demographic Yearbook*

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