

## **ANNEX 1**

### ***Vitamin and mineral intakes in Europe:***

#### **Intake of selected nutrients from foods, from fortification, and from supplements in various European countries** (Flynn A, Hiroven T, Mensink GB et al.)

**BACKGROUND:** Recent European Union regulation requires setting of maximum amount of micronutrients in dietary supplements or foods taking into account the tolerable upper intake level (ULs) established by scientific risk assessment and population reference intakes.

**OBJECTIVE:** To collect and evaluate recently available data on intakes of selected vitamins and minerals from conventional foods, food supplements and fortified foods in adults and children. Intake of calcium, copper, iodine, iron, magnesium, phosphorus, selenium, zinc, folic acid, niacin and total vitamin A/retinol, B(6), D and E was derived from nationally representative surveys in Denmark, Germany, Finland, Ireland, Italy, the Netherlands, Poland, Spain and the United Kingdom. Intake of high consumers, defined as the 95th percentile of each nutrient, was compared to the UL.

**RESULTS:** For most nutrients, adults and children generally consume considerably less than the UL with exceptions being retinol, zinc, iodine, copper and magnesium. The major contributor to intakes for all nutrients and in all countries is from foods in the base diet. The patterns of food supplements and voluntary fortification vary widely among countries with food supplements being responsible for the largest differences in total intakes. In the present study, for those countries with data on fortified foods, fortified foods do not significantly contribute to higher intakes for any nutrient. Total nutrient intake expressed as percentage of the UL is generally higher in children than in adults.

**CONCLUSION:** The risk of excessive intakes is relatively low for the majority of nutrients with a few exceptions. Children are the most vulnerable group as they are more likely to exhibit high intakes relative to the UL. There is a need to develop improved methods for estimating intakes of micronutrients from fortified foods and food supplements in future dietary surveys.

#### **Dietary surveys indicate vitamin intakes below recommendations are common in representative Western countries** (Troesch B, Hoefl B, McBurney M et al.)

Vitamins play a crucial role in health, but modern lifestyles may lead to suboptimal intakes even in affluent countries. The aim of the present study is to review vitamin intakes in Germany, the UK, The Netherlands and the USA and to compare them with respective national recommendations. Data on adults from the most recently published national dietary intake surveys for the first three countries and data for adults from the US National Health and Nutrition Examination Survey from 2003 to 2008 for the USA were used as a basis for the analysis. The proportions of the populations with intakes below recommendations were categorised as < 5, 5-25, >25-50, >50-75 and >75 % for each vitamin. The data generated are presented in a 'traffic light display', using colours from green to red to indicate degrees of sufficiency. The trends found were compared with the results from the European Nutrition and Health

Report 2009, even though in that report, only information on mean intakes in the different countries was available. We showed that, although inter-country differences exist, intakes of several vitamins are below recommendations in a significant part of the population in all these countries. The most critical vitamin appears to be vitamin D and the least critical niacin. The variation between the countries is most probably due to differences in recommendations, levels of fortification and local dietary habits. We show that a gap exists between vitamin intakes and requirements for a significant proportion of the population, even though diverse foods are available. Ways to correct this gap need to be investigated.

### **Projected Prevalence of Inadequate Nutrient Intakes in Europe** (Viñas BR, Barba LR, Ngo J et al.)

**BACKGROUND:** The purpose of this study was to analyze the prevalence of nutrient intake inadequacy in Europe, applying the Nordic Nutritional Recommendations in the context of the EURRECA Network of Excellence.

**METHODS:** Nutrient data was obtained from the European Nutrition and Health Report II. Those nutritional surveys using a validated food frequency questionnaire or diet history and a food diary/register with at least 7 days of registers or with an adjustment for intraindividual variability were included. The nutrients analyzed were: vitamin C, vitamin D, vitamin B(12), folic acid, calcium, iron, zinc, selenium, copper, and iodine. The estimated average requirement cut point was applied to estimate inadequacy. The Nordic and Institute of Medicine nutrient recommendations were used as references.

**RESULTS:** The mean prevalence of inadequacy was below 11% for zinc, iron, and vitamin B(12) (only in the elderly), and it was 11-20% for copper in adults and the elderly and for vitamin B(12) in adults and vitamin C in the elderly. The prevalence was above 20% for vitamin D, folic acid, calcium, selenium, and iodine in adults and the elderly and for vitamin C in adults.

**CONCLUSIONS:** Vitamin C, vitamin D, folic acid, calcium, selenium, and iodine were the nutrients showing a higher prevalence of inadequate intakes in Europe.

### **Comparison of Standardized dietary folate intake across ten countries participating in the European Prospective Investigation into Cancer and Nutrition** (Young Park J, Nicolas G, Freisling H et al.)

Folate plays an important role in the synthesis and methylation of DNA as a cofactor in one-carbon metabolism. Inadequate folate intake has been linked to adverse health events. However, comparable information on dietary folate intake across European countries has never been reported. The objective of the present study was to describe the dietary folate intake and its food sources in ten countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. A cross-sectional analysis was conducted in 36 034 participants (aged 35-74 years) who completed a single 24 h dietary recall using a computerised interview software program, EPIC-Soft® (International Agency for Research on Cancer, Lyon). Dietary folate intake was estimated using the standardised EPIC Nutrient DataBase, adjusted for

age, energy intake, weight and height and weighted by season and day of recall. Adjusted mean dietary folate intake in most centres ranged from 250 to 350 µg/d in men and 200 to 300 µg/d in women. Folate intake tended to be lower among current smokers and heavier alcohol drinkers and to increase with educational level, especially in women. Supplement users (any types) were likely to report higher dietary folate intake in most centres. Vegetables, cereals and fruits, nuts and seeds were the main contributors to folate intake. Nonetheless, the type and pattern of consumption of these main food items varied across the centres. These first comparisons of standardised dietary folate intakes across different European populations show moderate regional differences (except the UK health conscious group), and variation by sex, educational level, smoking and alcohol-drinking status, and supplement use.

### ***Folate status (serum/plasma folate and RBC folate)***

#### **Folate Status in Germany 1997-2000 (González-Gross M, Prinz-Langenohl R, Pietrzik K)**

Data about folate intake and blood values of the German population, published between 1997 and 2000, have been reviewed. Median folate intake is about 250 micrograms/day in the adult population, which indicates a high likelihood of inadequate intake when compared to the Estimated Average Requirement (EAR) of 320 micrograms/day. Only a few studies have evaluated serum and erythrocyte folate or plasma homocysteine as a marker of folate status. The most representative data show that 25% of German women of childbearing age have an inadequate recent folate intake. Only 13.3% of the women have red blood cell folate values above the critical value of 400 micrograms/day established by Daly et al (1995). Folic acid fortification of food is shown to be responsible for about 25% of folate intake in the German child and adolescent population in one study. If we extrapolate these data to the general population, folic acid fortification could be the explanation for the differences observed between folate intake and blood values. The discrepancy might also be explained by slight inaccuracies in food composition tables. Folate intake from fortified food or from supplements is not taken into account in most of the studies, which is a variable that can lead to confusion. Nutrition surveys should adapt official composition tables for local food patterns, and include fortified commercial foods, in order to make folate intake data more accurate. However, representative serum and erythrocyte folate values are lacking for most age groups. Before taking public health measures concerning folate fortification of food, the real folate status of the German population should be established.

#### **The prevalence of folic acid deficiency among adolescent girls living in Edirne, Turkey**

(Öner N, Vatansever U, Karasalioglu S et al.)

##### **PURPOSE:**

A high incidence of iron-deficiency is a common observation among adolescent girls, whereas only limited data are available regarding the folic acid status of this group. This study was designed to determine the prevalence of biochemical folic acid deficiency in a group of Turkish adolescent girls.

#### METHODS:

We surveyed the serum folic acid, complete blood count, and dietary folic acid intake of Turkish adolescent girls after using three-day self-reported food intakes in urban and rural areas of Edirne, Turkey.

#### RESULTS:

A sample population was composed of 704 adolescent girls; their serum folic acid levels were found to be adequate for 37.6% ( $\geq 6$  ng/mL), marginal for 46% (3 to 5.9 ng/mL), and at deficient levels for 16.3% ( $< 3$  ng/mL). Folic acid deficiencies were found in 20.1% (36 of 179) and 14.7% (61 of 416) of adolescent girls from rural and urban areas, respectively. Self-reported three-day folic acid intakes were correlated with the corresponding blood values for this nutrient. In the logistic regression analysis, three factors emerged as significant independent predictors of folic acid deficiency: low income (odds ratio [OR]: 2.4, 95% confidence interval [CI]: 1.3-4.2,  $p < .001$ ), low vitamin C (OR: 1.9, 95% CI: 1.1-3.5,  $p < .05$ ), and folic acid intake (OR: 4.8, 95% CI: 2.8-8.1,  $p < .001$ ).

#### CONCLUSION:

Data from the present study may indicate that serum folic acid is low in a group of Turkish adolescent girls. These low values appear to be associated with low income, and low dietary intakes of folic acid and vitamin C.

### **Determinants of folate status in pregnant women: results from a national cross-sectional survey in Belgium** (Vandevijvere S, Amsalkhir S, Oyen HV, Moreno-Reyes R.)

**BACKGROUND/OBJECTIVES:** Folic acid deficiency during pregnancy can lead to neural tube defects (NTD) in the fetus. Folate status was determined in a representative sample of Belgian pregnant women and determinants of folate status were assessed.

**SUBJECTS/METHODS:** The women were selected using a multi-stage proportionate-to-size sampling design. Blood samples were collected and a questionnaire was completed face-to-face with a study nurse. Erythrocyte (red blood cell (RBC)) folate concentration was measured by chemoluminescence.

**RESULTS:** In total, 1311 pregnant women participated and women with a lower socio-economic status were well represented. Median RBC folate concentration was 436 ng/ml (95% confidence interval=425-452 ng/ml) among first trimester and 496 ng/ml (95% confidence interval=474-515 ng/ml) among third trimester women. Few women had a RBC folate concentration below 140 ng/ml, indicating depletion of folate stores. In the first trimester, 39% of women had a RBC concentration below 400 ng/ml, whereas 15% of the first trimester women had a RBC concentration below 300 ng/ml. Among women in the first trimester, 69.1% reported taking folic acid-containing supplements of which 41.2% started taking them before pregnancy. For third trimester women, these percentages were 76.2% and 21.9%, respectively. In both trimesters, folate status increased

significantly with education level and was significantly higher among women who planned the pregnancy and who did not smoke.

**CONCLUSIONS:** It was found that 39% of the first trimester pregnant women had a folate status that might not be optimal to prevent NTD. Some groups of women need to be targeted as they are at higher risk of inadequate folate status.

### ***Folic acid can prevent NTDs:***

#### **Double-Blind Randomised Controlled Trial of Folate Treatment Before Conception to Prevent Recurrence of Neural Tube Defects** (Laurence KM, James N, Miller M et al.)

A randomized controlled double-blind trial was undertaken in south Wales to prevent the recurrence of neural-tube defects in women who had had one child with a neural-tube defect. Sixty women were allocated before conception to take 4 mg of folic acid a day before and during early pregnancy and 44 complied with these instructions. Fifty-one women were allocated to placebo treatment. There were no recurrences among the compliant mothers but two among the non-compliers and four among the women in the placebo group. Thus there were no recurrences among those who received supplementation and six among those who did not; this difference is significant ( $p = 0.04$ ). It is concluded that folic acid supplementation might be a cheap, safe, and effective method of primary prevention of neural-tube defects but that this must be confirmed in a large, multicentre trial.

#### **Prevention of neural tube defects: results of the Medical Research Council Vitamin Study** (MRC Vitamin Study Research Group)

A randomised double-blind prevention trial with a factorial design was conducted at 33 centres in seven countries to determine whether supplementation with folic acid (one of the vitamins in the B group) or a mixture of seven other vitamins (A,D,B1,B2,B6,C and nicotinamide) around the time of conception can prevent neural tube defects (anencephaly, spina bifida, encephalocele). A total of 1817 women at high risk of having a pregnancy with a neural tube defect, because of a previous affected pregnancy, were allocated at random to one of four groups--namely, folic acid, other vitamins, both, or neither. 1195 had a completed pregnancy in which the fetus or infant was known to have or not have a neural tube defect; 27 of these had a known neural tube defect, 6 in the folic acid groups and 21 in the two other groups, a 72% protective effect (relative risk 0.28, 95% confidence interval 0.12-0.71). The other vitamins showed no significant protective effect (relative risk 0.80, 95% CI 0.32-1.72). There was no demonstrable harm from the folic acid supplementation, though the ability of the study to detect rare or slight adverse effects was limited. Folic acid supplementation starting before pregnancy can now be firmly recommended for all women who have had an affected pregnancy, and public health measures should be taken to ensure that the diet of all women who may bear children contains an adequate amount of folic acid.

## **Possible prevention of neural-tube defects by periconceptional vitamin supplementation**

(Smithells RW, Shepard S, Schorah CJ et al.)

Women who had previously given birth to one or more infants with a neural tube defect (NTD) were recruited into a trial of periconceptional multivitamin supplementation. 1 of 178 infants/fetuses of fully supplemented mother (0.6%) had an NTD compared with 13 of 260 infants/fetuses of unsupplemented mothers (5.0%).

## ***Supplementation is underutilized***

### **Awareness, knowledge, and use of folic acid among women: a study from Turkey**

(Baykan Z, Oztürk A, Poyrazoğlu S et al.)

**PURPOSE:** To investigate the awareness, knowledge, and behaviors relevant to folic acid intake in women aged 15-49 years.

**MATERIALS AND METHODS:** A questionnaire designed by the researchers was administered to 1,083 women who attended to family health care centers for any reason, between 1 and 15 of December 2009.

**RESULTS:** Half of the women (53.7%) surveyed did not hear or read about folic acid. Women older than 35 and less-educated women were more unaware of folic acid. Out of 171 pregnant women, 81.3% (139 women) were taking/took vitamin/folic acid supplementation but only 12.2% of the users started to take supplements at least 1 month before conception. Out of 912 non-pregnant women 81 (8.9%) said they are taking any vitamin or mineral supplement. Out of the women who are not pregnant, not using a modern contraceptive method and planning to have a child at the time of the survey, only 9 (10%) were taking vitamin/folic acid. The most common information sources on folic acid were the doctors.

**CONCLUSION:** In order to improve the intake of folic acid during the recommended period, preconceptional counseling by the family doctors to inform women of childbearing age about the need to take folic acid to prevent NTDs seems to be important.

### **Women's awareness and periconceptional use of folic acid: data from a large European survey** (Bitzer J, von Stenglin A, Bannemerschult R.)

**OBJECTIVE:** To investigate the awareness and use of folic acid in European women of child-bearing age, particularly in the setting of pregnancy and pregnancy planning.

**METHODS:** Between November 2009 and December 2009, women aged 15–49 years old from 18

European countries completed a 30-minute structured questionnaire either online or via face-to-face interviews. To achieve nationally representative samples for each country quotas were set for age, education, income, and regional distribution.

**RESULTS:** A total of 22,925 women participated in the survey. Of the respondents, 58% had at least one biological child, and of these 38% reported that their first pregnancy was not planned. Nearly 60% of women who planned their pregnancy indicated that they had stopped using their method of contraception without first consulting a doctor or another health care professional. Overall, 70% reported that they had heard of folic acid and 40% stated that they knew the benefits of folic acid. However, when prompted to indicate which diseases and/or birth defects folic acid can protect against, only 17% knew that folic acid can reduce the risk of neural tube defects/spina bifida.

**CONCLUSIONS:** A large proportion of European women of child-bearing age in this survey were unaware that periconceptional folic acid supplementation reduces the risk of birth defects.

### **Social and ethnic differences in folic acid use during preconception and early pregnancy in the UK: effect on maternal folate status** (Brough L, Rees GA, Crawford MA et al.)

**BACKGROUND:** The role of folate supplementation in preventing neural tube defects is well known; however, preconception supplement use continues to be low, especially amongst the socially disadvantaged. The present study explored periconception folic acid supplement use in a socially deprived, ethnically diverse population.

**METHODS:** Pregnant women (n = 402) in the first trimester of pregnancy were recruited in East London. Using a researcher led questionnaire, details were obtained regarding social class, ethnicity and folic acid use. Red cell folate levels were determined for 367 participants during the first trimester.

**RESULTS:** Although 76% of participants reported using folic acid supplements during the first trimester, only 12% started preconception and a further 17% started before neural tube closure. Mothers from higher social groups or with higher levels of education were more likely to use folic acid and started taking it earlier. Ethnic differences were also seen in preconception usage (Africans, 5%; West Indians, 8%; Asians, 12%; Caucasians, 19%;  $P = 0.038$ ). Participants who took folic acid supplements had significantly higher mean (SD) red cell folate concentrations than those who took none [936 ( $\times 1.6$ ) and 579 ( $\times 1.6$ ) nmol L<sup>-1</sup>], respectively;  $P < 0.001$ ].

**CONCLUSIONS:** Folic acid supplement use preconception and prior to neural tube closure continues to be low, exhibiting both social and ethnic disparities.

### **Preconceptional and prenatal predictors of folic acid intake in Hungarian pregnant women** (Paulik E, Csasza J, Kozinszky Z et al.)

**OBJECTIVE:** The purpose of the study was to determine demographic, obstetric and pregnancy care related factors of folic acid intake during preconceptional and prenatal period of pregnancy.

**STUDY DESIGN:** A questionnaire-based retrospective study was delivered at the Department of Obstetrics and Gynecology and Pregnancy Care Centre. The frequency of folic acid intake was measured before and during pregnancy in 349 pregnant women.

**RESULTS:** Factors influencing preconceptional folic acid consumption were planning of pregnancy, previous infertility therapy, multivitamin intake before pregnancy, and folic acid intake during pregnancy. Probability of taking folic acid during pregnancy increased with age, and decreased with gestational age. Earlier detection of pregnancy corresponded to a higher chance of folic acid intake. Prenatal folic acid intake significantly related to the earlier intake of folic acid, and prenatal multivitamin medication.

**CONCLUSION:** It is important to target women who are less likely to take periconceptional folic acid as well as to increase awareness of women of childbearing age in general through an intensive campaign and improved education.

### **Dietary intake and nutritional adequacy prior to conception and during pregnancy: a follow-up study in the north of Portugal (Pinto E, Barros H, dos Santos Silva I)**

**OBJECTIVE:** To assess maternal diet and nutritional adequacy prior to conception and during pregnancy.

**DESIGN:** Follow-up of a cohort of pregnant women with collection of questionnaire data throughout pregnancy and after delivery.

**SETTING:** Antenatal clinics at two public hospitals in Porto, Portugal.

**SUBJECTS:** Two hundred and forty-nine pregnant women who reported a gestational age below 13 weeks at the time they attended their first antenatal visit.

**RESULTS:** Intakes of energy and macronutrients were within recommended levels for most women. Pregnancy was accompanied by increases in the dietary intake of vitamins A and E, riboflavin, folate, Ca and Mg, but declines in the intake of alcohol and caffeine. The micronutrients with higher inadequacy prevalences prior to pregnancy were vitamin E (83%), folate (58%) and Mg (19%). These three micronutrients, together with Fe, were also those with the highest inadequacy prevalences during pregnancy (91%, 88%, 73% and 21%, respectively, for folate, Fe, vitamin E and Mg). Ninety-seven per cent of the women reported taking supplements of folic acid during the first trimester, but the median gestational age at initiation was 6.5 (interquartile range 5, 9) weeks. Self-reported prevalences of Fe and Mg supplementation were high, and increased throughout pregnancy.

**CONCLUSION:** The study identified low dietary intakes of vitamin E, folate and Mg both in the preconceptional period and during pregnancy, and low intake of Fe during pregnancy only. The low



dietary intake of folate and the late initiation of supplementation indicate that current national guidelines are unlikely to be effective in preventing neural tube defects.

### ***Flour fortification reduces the prevalence of neural tube defects:***

#### **Folic acid to reduce neonatal mortality from neural tube disorders**

(Blencowe H, Cousens S, Modell B et al.)

**BACKGROUND:** Neural tube defects (NTDs) remain an important, preventable cause of mortality and morbidity. High-income countries have reported large reductions in NTDs associated with folic acid supplementation or fortification. The burden of NTDs in low-income countries and the effectiveness of folic acid fortification/supplementation are unclear.

**OBJECTIVE:** To review the evidence for, and estimate the effect of, folic acid fortification/supplementation on neonatal mortality due to NTDs, especially in low-income countries.

**METHODS:** We conducted systematic reviews, abstracted data meeting inclusion criteria and evaluated evidence quality using adapted Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. Where appropriate, meta-analyses were performed.

**RESULTS:** Meta-analysis of three randomized controlled trials (RCTs) of folic acid supplementation for women with a previous pregnancy with NTD indicates a 70% [95% confidence interval (CI): 35-86] reduction in recurrence (secondary prevention). For NTD primary prevention through folic acid supplementation, combining one RCT with three cohort studies which adjusted for confounding, suggested a reduction of 62% (95% CI: 49-71). A meta-analysis of eight population-based observational studies examining folic acid food fortification gave an estimated reduction in NTD incidence of 46% (95% CI: 37-54). In low-income countries an estimated 29% of neonatal deaths related to visible congenital abnormalities are attributed to NTD. Assuming that fortification reduces the incidence of NTDs, but does not alter severity or case-fatality rates, we estimate that folic acid fortification could prevent 13% of neonatal deaths currently attributed to congenital abnormalities in low-income countries.

**DISCUSSION:** Scale-up of periconceptional supplementation programmes is challenging. Our final effect estimate was therefore based on folic acid fortification data. If folic acid food fortification achieved 100% population coverage the number of NTDs in low-income countries could be approximately halved.

**CONCLUSION:** The evidence supports both folic acid supplementation and fortification as effective in reducing neonatal mortality from NTDs.

#### **Impact of fortification of flour on neural tube defects: a systematic review**

(Castillo-Lancelloti C, Tur JA, Uauy R.)

**OBJECTIVE:** To review the impact of folic acid fortification of flour on the prevalence of neural tube defects (NTD).

**DESIGN:** Systematic review of the literature on MEDLINE via PubMed, Scopus, OvidSP and LILACS (Latin American and Caribbean Health Sciences Literature) reporting the impact of folic acid fortification of flour on the prevalence of NTD in 2000-2011. Focusing on Santiago of Chile's birth defects registry (1999-2009) and the monitoring of flour fortification, we analysed the prevalence (NTD cases/10 000 births) pre and post flour fortification and the percentile distribution of folic acid content in flour (2005-2009). We explored the potential association between median folic acid in flour (mg/kg) and the prevalence of NTD.

**SETTING:** Chile, Argentina, Brazil, Canada, Costa Rica, Iran, Jordan, South Africa and the USA.

**SUBJECTS:** Live births and stillbirths.

**RESULTS:** Twenty-seven studies that met inclusion criteria were evaluated. Costa Rica showed a significant reduction in NTD (~60 %). Prevalence in Chile decreased from 18.6 to 7.3/10 000 births from 1999 to 2007 and showed a slight increase to 8.5 in 2008-2009, possibly due to changes in fortification limits. When we related the prevalence of NTD with levels of flour fortification, the lowest prevalence was observed at a folic acid level of 1.5 mg/kg.

**CONCLUSIONS:** Fortification of flour with folic acid has had a major impact on NTD in all countries where this has been reported. Chile showed a 55 % reduction in NTD prevalence between 1999 and 2009. There is a need to constantly monitor the levels of flour fortification to maximize benefits and prevent the potential risk of folic acid excess, moreover to be vigilant for any new adverse effects associated with excess.

## ***Encouraging flour fortification in Europe***

### **Preventing neural tube defects in Europe: A missed opportunity**

(Busby A, Armstrong B, Dolk H et al.)

Each year, more than 4500 pregnancies in the European Union are affected by neural tube defects (NTD). Unambiguous evidence of the effectiveness of periconceptual folic acid in preventing the majority of neural tube defects has been available since 1991. We report on trends in the total prevalence of neural tube defects up to 2002, in the context of a survey in 18 European countries of periconceptual folic acid supplementation (PFAS) policies and their implementation. EUROCAT is a network of population-based registries in Europe collaborating in the epidemiological surveillance of congenital anomalies. Representatives from 18 participating countries provided information about policy, health education campaigns and surveys of PFAS uptake. The yearly total prevalence of neural tube defects including livebirths, stillbirths and terminations of pregnancy was calculated from 1980 to 2002 for 34 registries, with UK and Ireland estimated separately from the rest of Europe. A meta-analysis of changes in NTD total prevalence between 1989-1991 and 2000-2002 according to PFAS

policy was undertaken for 24 registries. By 2005, 13 countries had a government recommendation that women planning a pregnancy should take 0.4mg folic acid supplement daily, accompanied in 7 countries by government-led health education initiatives. In the UK and Ireland, countries with PFAS policy, there was a 30% decline in NTD total prevalence (95% CI 16-42%) but it was difficult to distinguish this from the pre-existing strong decline. In other European countries with PFAS policy, there was virtually no decline in NTD total prevalence whether a policy was in place by 1999 (2%, 95% CI 28% reduction to 32% increase) or not (8%, 95% CI 26% reduction to 16% increase). The potential for preventing NTDs by periconceptual folic acid supplementation is still far from being fulfilled in Europe. Only a public health policy including folic acid fortification of staple foods is likely to result in large-scale prevention of NTDs.

### **Case for folic acid and vitamin B12 fortification in Europe**

(Cwernichow S, Noisette N, Blacher J et al.)

The number of pregnancies affected by neural tube defects has been estimated to be 4000/year in Europe, with a higher prevalence in Celtic populations and in women of low socioeconomic status. Since the 1980s, it has been shown that supplementation with folic acid during the periconceptual period reduces the risk of neural tube defects in the fetus. However, in view of the period during which supplementation should be taken (< 4 weeks before conception until 8-10 weeks after) and the fact that in some countries 30-50% of pregnancies are unplanned, a public health initiative based solely on increasing dietary folate intake or recommendations on use of folic acid supplements is likely to be insufficient. Mandatory fortification has been started in 38 countries throughout the world. Several European countries have advocated mandatory flour folic acid fortification over the last 6 years, but none has introduced it. A recent public health decision in Hungary stimulated flour fortification on a voluntary basis, but it remains the only European country to take this action. Many European countries have deferred a decision to introduce fortification because of concerns about possible masking of vitamin B (12) deficiency. This review advocates a proposal for combined fortification of folic acid and vitamin B (12) to address possible hazards of fortification with folic acid alone.

### **Folic acid fortification of wheat flour: A cost-effective public health intervention to prevent birth defects in Europe** (Pachón H, Kancherla V, Handforth B, Tyler V, Bauwens L.)

Neural tube defects (NTDs) annually affect an estimated 320 000 newborns worldwide. Folic acid (FA), provided through supplementation and fortification, is an effective primary-prevention strategy for NTDs if consumed in the periconceptual period. However, the potential impact of FA supplementation is tempered by low compliance. Countries that mandate FA fortification of wheat flour report an average reduction of 46% in NTD birth prevalence and favourable benefit : cost ratios of 12–48:1. Despite the well-documented benefits of fortification and the new evidence that provides a better understanding of purported risks associated with FA, European countries have yet to embrace this public health initiative. Viable primary-prevention strategies are needed given that an estimated 4500 NTDs occur in the 27 countries of the European Union annually, of which 72% end in terminations. Many existing factors will facilitate the success of FA flour fortification programs in the region: widespread consumption of wheat-based products, a technologically advanced milling industry,

experience adhering to and monitoring food safety measures, and familiarity with mandatory food fortification.

***Folic acid does not cause cancer-even when consumed in an amount greater than the UL for a sustained period of time:***

**Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality meta-analysis of 8 randomized trials involving 37,485 individuals**

(Clarke R, Halsey J, Lewington S.)

Elevated plasma homocysteine levels have been associated with higher risks of cardiovascular disease, but the effects on disease rates of supplementation with folic acid to lower plasma homocysteine levels are uncertain. Individual participant data were obtained for a meta-analysis of 8 large, randomized, placebo-controlled trials of folic acid supplementation involving 37 485 individuals at increased risk of cardiovascular disease. The analyses involved intention-to-treat comparisons of first events during the scheduled treatment period. There were 9326 major vascular events (3990 major coronary events, 1528 strokes, and 5068 revascularizations), 3010 cancers, and 5125 deaths. Folic acid allocation yielded an average 25% reduction in homocysteine levels. During a median follow-up of 5 years, folic acid allocation had no significant effects on vascular outcomes, with rate ratios (95% confidence intervals) of 1.01 (0.97-1.05) for major vascular events, 1.03 (0.97-1.10) for major coronary events, and 0.96 (0.87-1.06) for stroke. Likewise, there were no significant effects on vascular outcomes in any of the subgroups studied or on overall vascular mortality. There was no significant effect on the rate ratios (95% confidence intervals) for overall cancer incidence (1.05 [0.98-1.13]), cancer mortality (1.00 [0.85-1.18]) or all-cause mortality (1.02 [0.97-1.08]) during the whole scheduled treatment period or during the later years of it. Dietary supplementation with folic acid to lower homocysteine levels had no significant effects within 5 years on cardiovascular events or on overall cancer or mortality in the populations studied.

**Treatment with B vitamins and incidence of cancer in patients with previous stroke or transient ischemic attack results of a randomized placebo-controlled trial**

(Hankey GJ, Eikelboom JW, Lees KR et al.)

**BACKGROUND AND PURPOSE:** To determine the effect of B vitamin treatment on the incidence of cancer among patients with stroke or transient ischemic attack.

**METHODS:** A total of 8164 patients with recent stroke or transient ischemic attack were randomly allocated to double-blind treatment with 1 tablet daily of placebo or B vitamins (2 mg folic acid, 25 mg vitamin B(6), 500 µg vitamin B(12)) and followed for a median of 3.4 years for any cancer as an adverse event.

**RESULTS:** There was no significant difference in the incidence of any cancer among participants assigned B vitamins compared with placebo (4.04% versus 4.59%; risk ratio, 0.86; 95% CI, 0.70-1.07) and no difference in cancer mortality (2.35% versus 2.09%; risk ratio, 1.09; 0.81-1.46). Among 1899 patients with diabetes, the incidence of cancer was higher among participants assigned B vitamins compared with placebo (5.35% versus 3.28%; adjusted risk ratio, 2.21; 1.31-3.73), whereas among 6168 patients without diabetes, the incidence of cancer was lower among participants assigned B vitamins compared with placebo (3.66% versus 5.03%; adjusted risk ratio, 0.67; 0.51-0.87; P for interaction=0.0001).

**CONCLUSIONS:** Daily administration of folic acid, vitamin B(6), and vitamin B(12) to 8164 patients with recent stroke or transient ischemic attack for a median of 3.4 years had no significant effect, compared with placebo, on cancer incidence or mortality. However, a post hoc subgroup analysis raises the hypothesis that folic acid treatment may increase the incidence of cancer among diabetics and reduce the incidence of cancer among nondiabetics with a history of stroke or transient ischemic attack.

### **Effects of folic acid supplementation on overall and 621 site-specific cancer incidence during the randomised trials: meta-analyses of data on 50 000 622 individuals**

(Vollset SE, Clarke R, Lewington S et al.)

**BACKGROUND:** Some countries fortify flour with folic acid to prevent neural tube defects but others do not, partly because of concerns about possible cancer risks. We aimed to assess any effects on site-specific cancer rates in the randomised trials of folic acid supplementation, at doses higher than those from fortification.

**METHODS:** In these meta-analyses, we sought all trials completed before 2011 that compared folic acid versus placebo, had scheduled treatment duration at least 1 year, included at least 500 participants, and recorded data on cancer incidence. We obtained individual participant datasets that included 49 621 participants in all 13 such trials (ten trials of folic acid for prevention of cardiovascular disease [n=46 969] and three trials in patients with colorectal adenoma [n=2652]). All these trials were evenly randomised. The main outcome was incident cancer (ignoring non-melanoma skin cancer) during the scheduled treatment period (among participants who were still free of cancer). We compared those allocated folic acid with those allocated placebo, and used log-rank analyses to calculate the cancer incidence rate ratio (RR).

**FINDINGS:** During a weighted average scheduled treatment duration of 5.2 years, allocation to folic acid quadrupled plasma concentrations of folic acid (57.3 nmol/L for the folic acid groups vs 13.5 nmol/L for the placebo groups), but had no significant effect on overall cancer incidence (1904 cancers in the folic acid groups vs 1809 cancers in the placebo groups, RR 1.06, 95% CI 0.99-1.13, p=0.10). There was no trend towards greater effect with longer treatment. There was no significant heterogeneity between the results of the 13 individual trials (p=0.23), or between the two overall results in the cardiovascular prevention trials and the adenoma trials (p=0.13). Moreover, there was no significant effect of folic acid supplementation on the incidence of cancer of the large intestine, prostate, lung, breast, or any other specific site.

INTERPRETATION: Folic acid supplementation does not substantially increase or decrease incidence of site-specific cancer during the first 5 years of treatment. Fortification of flour and other cereal products involves doses of folic acid that are, on average, an order of magnitude smaller than the doses used in these trials.

### **Cancer risk with folic acid supplements: a systematic review and meta-analysis**

(Wein TN, Pike E, Wisløff T et al.)

OBJECTIVE: To explore if there is an increased cancer risk associated with folic acid supplements given orally.

DESIGN: Systematic review and meta-analysis of controlled studies of folic acid supplementation in humans reporting cancer incidence and/or cancer mortality. Studies on folic acid fortification of foods were not included. Data sources Cochrane Library, Medline, Embase and Centre of Reviews and Dissemination, clinical trial registries and hand-searching of key journals.

RESULTS: From 4104 potential references, 19 studies contributed data to our meta-analyses, including 12 randomised controlled trials (RCTs). Meta-analysis of the 10 RCTs reporting overall cancer incidence (N=38 233) gave an RR of developing cancer in patients randomised to folic acid supplements of 1.07 (95% CI 1.00 to 1.14) compared to controls. Overall cancer incidence was not reported in the seven observational studies. Meta-analyses of six RCTs reporting prostate cancer incidence showed an RR of prostate cancer of 1.24 (95% CI 1.03 to 1.49) for the men receiving folic acid compared to controls. No significant difference in cancer incidence was shown between groups receiving folic acid and placebo/control group, for any other cancer type. Total cancer mortality was reported in six RCTs, and a meta-analysis of these did not show any significant difference in cancer mortality in folic acid supplemented groups compared to controls (RR 1.09, 95% CI 0.90 to 1.30). None of the observational studies addressed mortality.

CONCLUSION: A meta-analysis of 10 RCTs showed a borderline significant increase in frequency of overall cancer in the folic acid group compared to controls. Overall cancer incidence was not reported in the seven observational studies. Prostate cancer was the only cancer type found to be increased after folic acid supplementation (meta-analyses of six RCTs). Prospective studies of cancer development in populations where food is fortified with folic acid could indicate whether fortification similar to supplementation moderately increases prostate cancer risk.

### ***Folic acid and B12 deficiency***

## **Does folic acid harm people with vitamin B12 deficiency? (Dickinson CJ.)**

Oral folic acid given before and during pregnancy can prevent about 75% of fetal neural tube defects. Even in large dose (20 mg daily) folic acid has never been shown to harm normal people, but it has acquired a bad reputation in pernicious anaemia. Before 1930, if untreated patients survived the anaemia, they succumbed to peripheral neuritis, subacute combined degeneration of the spinal cord, and death. The speed of this progression was extremely variable. From 1947 onwards, there were many reports of rapid neurological deterioration during administration of folic acid as sole therapy to people with pernicious anaemia. However, a review of clinical studies published before the introduction of liver and vitamin B12 therapy shows that neurological deterioration was often quite as rapid and severe in untreated patients. Oral folic acid can usually correct or prevent the anaemia of pernicious anaemia. Thus it could mask the underlying disease, and allow the development or progression of neurological deterioration, if diagnosis depended on the presence of anaemic symptoms. This possibility can readily be overcome by adequate education of doctors, so that a macrocytic anaemia is not regarded as a necessary accompanying sign of the neurological disorder. The hypothetical and avoidable side-effects of food fortification with folic acid have to be balanced against the certain benefit of preventing neural tube defects in unplanned pregnancies, and also against the probability that adults may be spared the neuropsychiatric and other ill-effects which result from inadequate dietary folic acid.

## **Do high blood folate concentrations exacerbate metabolic abnormalities in people with low vitamin B12 status? (Mills JL, Carter TC, Scott JM et al.)**

**BACKGROUND:** In elderly individuals with low serum vitamin B-12, those who have high serum folate have been reported to have greater abnormalities in the following biomarkers for vitamin B-12 deficiency: low hemoglobin and elevated total homocysteine (tHcy) and methylmalonic acid (MMA). This suggests that folate exacerbates vitamin B-12-related metabolic abnormalities.

**OBJECTIVE:** We determined whether high serum folate in individuals with low serum vitamin B-12 increases the deleterious effects of low vitamin B-12 on biomarkers of vitamin B-12 cellular function.

**DESIGN:** In this cross-sectional study, 2507 university students provided data on medical history and exposure to folic acid and vitamin B-12 supplements. Blood was collected to measure serum and red blood cell folate (RCF), hemoglobin, plasma tHcy, and MMA, holotranscobalamin, and ferritin in serum.

**RESULTS:** In subjects with low vitamin B-12 concentrations (<148 pmol/L), those who had high folate concentrations (>30 nmol/L; group 1) did not show greater abnormalities in vitamin B-12 cellular function in any area than did those with lower folate concentrations ( $\leq$ 30 nmol/L; group 2). Group 1 had significantly higher holotranscobalamin and RCF, significantly lower tHcy, and nonsignificantly lower ( $P = 0.057$ ) MMA concentrations than did group 2. The groups did not differ significantly in hemoglobin or

ferritin. Compared with group 2, group 1 had significantly higher mean intakes of folic acid and vitamin B-12 from supplements and fortified food.

**CONCLUSIONS:** In this young adult population, high folate concentrations did not exacerbate the biochemical abnormalities related to vitamin B-12 deficiency. These results provide reassurance that folic acid in fortified foods and supplements does not interfere with vitamin B-12 metabolism at the cellular level in a healthy population.

## ***Costing studies***

### **Reevaluating the Benefits of Folic acid Fortification in the United States: Economic Analysis, Regulation and Public Health** (Grosse SD, Waitzman NJ, Romano PS, et al.)

Before a 1996 US regulation requiring fortification of enriched cereal-grain products with folic acid, 3 economic evaluations projected net economic benefits or cost savings of folic acid fortification resulting from the prevention of pregnancies affected by a neural tube defect. Because the observed decline in neural tube defect rates is greater than was forecast before fortification, the economic gains are correspondingly larger. Applying both cost-benefit and cost-effectiveness analytic techniques, we estimated that folic acid fortification is associated with annual economic benefit of 312 million dollars to 425 million dollars. The cost savings (net reduction in direct costs) were estimated to be in the range of 88 million dollars to 145 million dollars per year.

### **Economic evaluation of folic acid food fortification in the Netherlands**

(Jentink J, van de Vrie-Hoekstra N, de Jong-van den Berg L, et al.)

**BACKGROUND:** Folic acid intake before and during pregnancy reduces neural tube defects (NTD). Therefore, several countries have enriched bulk food with folic acid resulting in a 26-48% decrease in the prevalence of NTDs. In 2000, the Dutch Health Council advised against folic acid enrichment based on literature research; yet formal cost-effectiveness information was absent. We designed our study to estimate cost-effectiveness of folic acid food fortification in the Netherlands.

**METHOD:** Prevalence of NTD at birth, life-time costs of care, and folic acid fortification costs were estimated using Dutch registrations, Dutch guidelines for costing, (inter)national literature and expert opinions. Both net cost per discounted life year gained and net cost per discounted quality adjusted life year (QALY) gained were estimated for the base case and sensitivity analyses.

**RESULTS:** In the base case and most sensitivity analyses, folic acid enrichment was estimated to be cost-saving. Bulk food fortification with folic acid remains cost-effective as long as enrichment costs do not exceed euro5.5 million (threshold at euro20 000 per QALY).



**CONCLUSION:** Our model suggests that folic acid fortification of bulk food to prevent cases of NTD in newborns might be a cost-saving intervention in the Netherlands. Additionally, besides the evidence that folic acid reduces the number of NTDs, there are indications that folic acid is associated with the prevention of other birth defects, cardiovascular diseases and cancer. Our model did not yet include these possibly beneficial effects.

### **Cost-effectiveness of a folic acid fortification program in Chile**

(Llanos A, Hertrampf E, Cortes F, et al.)

**OBJECTIVE:** Periconceptual intake of folic acid reduces the risk of neural tube defects (NTDs), a frequent birth defect that can cause significant infant mortality and disability. In Chile, fortification of wheat flour with folic acid has resulted in significant reduction in the risk of anencephaly and spina bifida. We investigated the cost-effectiveness implications of this policy.

**METHODS:** We conducted an ex-post economic analysis of this intervention. Estimates of the effect of fortification in decreasing NTDs and deaths were derived from a prospective evaluation. The costs of fortification and provision of medical care to children with spina bifida in Chile were based on primary data collection.

**FINDINGS:** The intervention costs per NTD case and infant death averted were I\$ 1200 and 11,000, respectively. The cost per DALY averted was I\$ 89, 0.8% of Chile's GDP per capita. Taking into account averted costs of care, fortification resulted in net cost savings of I\$ 2.3 million.

**CONCLUSION:** Fortification of wheat flour with folic acid is a cost-effective intervention in Chile, a middle income country in the post-epidemiological transition. This result supports the continuation of the Chile fortification program and constitutes valuable information for policy makers in other countries to consider.

### **Decline in the Prevalence of Neural Tube Defects Following Folic acid Fortification and Its Cost-Benefit in South Africa** (Sayed AR, Bourne D, Pattinson R, et al.)

**BACKGROUND:** In October 2003 South Africa embarked on a program of folic acid fortification of staple foods. We measured the change in prevalence of NTDs before and after fortification and assessed the cost benefit of this primary health care intervention.

**METHODS:** Since the beginning of 2002 an ecological study was conducted among 12 public hospitals in four provinces of South Africa. NTDs as well as other birth defect rates were reported before and after fortification. Mortality data were also collected from two independent sources.

**RESULTS:** This study shows a significant decline in the prevalence of NTDs following folic acid fortification in South Africa. A decline of 30.5% was observed, from 1.41 to 0.98 per 1,000 births (RR = 0.69; 95% CI: 0.49-0.98; p = .0379). The cost benefit ratio in averting NTDs was 46 to 1. Spina bifida showed a significant decline of 41.6% compared to 10.9% for anencephaly. Additionally, oro-facial clefts showed no significant decline (5.7%). An independent perinatal mortality surveillance system also shows a significant decline (65.9%) in NTD perinatal deaths, and in NTD infant mortality (38.8%).

**CONCLUSIONS:** The decrease in NTD rates postfortification is consistent with decreases observed in other countries that have fortified their food supplies. This is the first time this has been observed in a predominantly African population. The economic benefit flowing from the prevention of NTDs greatly exceeds the costs of implementing folic acid fortification.

### **Economic burden of neural tube defects and impact of prevention with folic acid: a literature review** (Yi Y, Lindemann M, Colligs A, et al.)

Neural tube defects (NTDs) are the second most common group of serious birth defects. Although folic acid has been shown to reduce effectively the risk of NTDs and measures have been taken to increase the awareness, knowledge, and consumption of folic acid, the full potential of folic acid to reduce the risk of NTDs has not been realized in most countries. To understand the economic burden of NTDs and the economic impact of preventing NTDs with folic acid, a systematic review was performed on relevant studies. A total of 14 cost of illness studies and 10 economic evaluations on prevention of NTDs with folic acid were identified. Consistent findings were reported across all of the cost of illness studies. The lifetime direct medical cost for patients with NTDs is significant, with the majority of cost being for inpatient care, for treatment at initial diagnosis in childhood, and for comorbidities in adult life. The lifetime indirect cost for patients with spina bifida is even greater due to increased morbidity and premature mortality. Caregiver time costs are also significant. The results from the economic evaluations demonstrate that folic acid fortification in food and preconception folic acid consumption are cost-effective ways to reduce the incidence and prevalence of NTDs. This review highlights the significant cost burden that NTDs pose to healthcare systems, various healthcare payers, and society and concludes that the benefits of prevention of NTDs with folic acid far outweigh the cost. Further intervention with folic acid is justified in countries where the full potential of folic acid to reduce the risk of NTDs has not been realized.

**\*Abstracts from <http://www.ncbi.nlm.nih.gov/pubmed/>\***