Meeting of the Reproductive and Urologic Drug Products

FDA Advisory Committee
December 15, 2003

Discussion of the public health issues, including the safety and potential clinical benefit, associated with combining folic acid and an oral contraceptive into a single combination product

ADVISORY COMMITTEE BRIEFING BOOK

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PURPOSE OF THE MEETING

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The purpose of this Advisory Committee Meeting is to discuss the public health issues, including the safety and potential clinical benefit, associated with combining folic acid and an oral contraceptive into a single combination product. In addition, we are seeking support that our combination of folic acid with oral contraceptives is a rational concept.

PROPOSAL

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The US Public Health Service (PHS) recommends consumption of 400 μg of synthetic folic acid daily in addition to a diet rich in natural folates for all women of reproductive age who are capable of becoming pregnant to reduce neural tube defects.

Many women do not regularly take a synthetic folic acid supplement/vitamin or eat a diet rich in folates. Women seeking contraception are especially unlikely to be prepared for pregnancy, and therefore are not taking the recommended amount of synthetic folic acid every day. Women seeking hormonal contraception, who are also low consumers of folic acid, can be easily identified by clinicians through questions regarding vitamin/ supplement use and diet.

Our proposal is to develop combination oral contraceptive/folic acid (OC/folic acid) drug products in which active and inert tablets contain 400 μg of folic acid. These combination OC/folic acid drug products will help a subpopulation of women who are low consumers of folic acid to meet the PHS goals for folic acid intake.

EXECUTIVE SUMMARY

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- NTDs are the second most common group of serious congenital anomalies and are largely preventable -- by 50 to 70%, to a rate of about 6 NTDs per 10,000 pregnancies -- with adequate consumption of folic acid.
- The US PHS and IOM recommend that all women of reproductive age consume 400 μg folic acid daily in addition to a diet rich in natural folates, regardless of contraceptive use.
- The FDA's grain fortification program has been successful in increasing average daily consumption of folic acid; NTD rates have declined by 23% since this program was initiated.
- Additional NTDs could be prevented if there were additional initiatives to provide adequate folic acid to reproductive age women, particularly those who are low consumers.
- OCs are used by about 16 million women in the United States. Although highly effective when used correctly (i.e., 0.1% "perfect use" failure rate), typical use failure rates are reported to be 5-8%. About one million unplanned pregnancies occur each year in women using OCs. Another 600,000 women discontinue OCs each year to conceive.
- Many of these women do not consume 400 μg folic acid daily; those at particular risk can be identified with simple questions about folic acid supplement/multivitamin use and ready- to-eat cereal consumption.
- Folic acid is extremely safe and has a wide therapeutic index.
- Chronic supplementation will increase body stores.
- Combining folic acid with OCs is a novel and rational combination drug for women who choose OCs as a method of birth control. This OC/folic acid combination drug product would complement public health efforts to further decrease NTDs

RATIONALE FOR AN OC/FOLIC ACID COMBINATION PRODUCT

Neural tube defects (NTDs), the second most common group of serious birth defects, can have significant emotional and financial impact. It is well established that the periconceptual use of folic acid can reduce the incidence of neural tube defects by 50-70% to a rate of about 6 per 10,000 pregnancies. Since NTD formation has multiple etiologies, it would be impossible to totally eliminate all NTD affected births through adequate folic acid consumption alone.

Folic acid, the synthetic form of folate (Vitamin B_9), is considered to be relatively non-toxic and is so safe, that since 1998, the FDA has required that it be added to all "enriched" grain products to help lower the risk of folic acid-preventable birth defects. In addition, manufacturers of cold cereals have voluntarily fortified their products with folic acid. National educational campaigns have also been established to educate women of reproductive age on the importance of consuming folic acid. In fact, the US Public Health Service recommends consumption of 400 μg of folic acid daily in addition to a diet rich in natural folates for all women of reproductive age who are capable of becoming pregnant to reduce NTDs. This recommendation holds for all women of reproductive years, even those practicing contraception.

Fortification of cereal grains with folic acid and public awareness campaigns to increase folic acid supplementation have been successful in increasing national median blood folate levels. NTD rates have decreased, however, many women are still below national blood folate goals and further reduction is possible. A significant percentage of women do not take a folic acid supplement/vitamin or consume a diet rich in folate. These women can be easily identified by clinicians through simple questions regarding folic acid intake through vitamin/supplement use and diet. In particular, many women who are not intending pregnancy simply do not take folic acid supplements or multivitamins. Since many of the women in this group who are not intending pregnancy are motivated to take OC pills, adding folic acid to OCs would provide an effective means to increase consumption of folic acid and subsequently increase the blood folate levels of these women without changing prescribing or drug-taking behavior.

OCs are the most commonly used reversible form of contraception in the United States. A significant percentage of reproductive age women use oral

contraceptives (16.1 million) as their method to prevent pregnancy. These women may stop their OC and become pregnant soon after discontinuation. A significant number of these pregnancies will remain undetected during the first few weeks or months when adequate folate levels are necessary to prevent NTDs. If these women were to receive a folic acid containing OC prior to becoming pregnant, they may have the benefit of a preconception reservoir of blood folate because serum and RBC concentrations remain elevated above pre-supplementation levels and then gradually decline over months (on average, at least 3 months) after one stops taking folic acid.

OC users may also experience unintended pregnancies. Because these pregnancies are unplanned, the mother may not be consuming adequate dietary folate or taking folic acid supplements. Many of these women will not have the opportunity to see a healthcare professional or begin taking vitamins until after the fetal neural tube has closed (i.e., approximately day 30 after conception). If these women received folic acid with their OC, their risk of having low blood folate levels (and consequently, a folic acid-preventable NTD in their fetus) may be diminished. Women using these products at the time they become pregnant (i.e., unplanned/accidental pregnancy while taking OCs) will have increased serum and RBC folate concentrations in the early weeks of pregnancy (when folic acid prevents birth defects).

Targeting reproductive aged women, particularly those who consume sub-optimal amounts of folic acid, will help to minimize safety concerns, in particular those related to the elderly, a group for which the FDA seeks to limit folic acid exposure in order to minimize the risk of delaying the diagnosis of vitamin B_{12} deficiency.

Since women are more likely to consume supplemental folic acid if it is recommended by their healthcare professional, prescribing these products will also provide another point of contact where counseling regarding folic acid supplementation may take place, which would have intangible benefits to those women who may conceive in the future. Typically, women receive contraceptive counseling and preconception counseling by their health care professionals (HCPs) at separate times when one of these needs is identified. Prescribing an OC/folic acid product would potentially open a dialog between the patient and her HCP that encompassed both of these important issues in a single point of contact. This would provide many women with

critical health care information about the importance of folic acid long before they are contemplating becoming pregnant.

Overall, providing these combination OC/folic acid drug products to reproductive age women, particularly those who consume sub-optimal amounts of folic acid, would support the combined efforts of the FDA, CDC, the March of Dimes and other organizations with their goal of increasing consumption of folic acid to a level that could prevent all folic acid-preventable NTDs in as many women of reproductive age as possible.

OVERVIEW OF NEURAL TUBE DEFECTS

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The proper formation and closure of the neural tube, which later becomes the spinal cord, brain and bone surrounding the spinal cord and brain, normally takes place very early in pregnancy (approximately 6 weeks after the first day of a woman's last menstrual period). The closure of the neural tube often happens before a woman knows she is pregnant. Neural tube defects (NTDs) are birth defects that occur when the neural tube fails to close properly. They typically occur by the 30th day after conception, during the critical time of pregnancy when neural tube formation is complete.[1, 2, 3]

Figure 1: Images of the most common NTDs (Spina Bifida and Anencephaly)

Neural tube defects are the second most common serious group of fetal malformations in the United States. Approximately 90% of NTDs are comprised of spina bifida and anencephaly; however, they may also include other defects such as encephacele. Anencephaly accounts for about half of all cases of NTDs and is uniformly lethal. About 80-90% of infants with spina bifida survive with varying degrees of disability.[4] Each year in the United States, about 4,000 pregnancies are affected by a NTD. Of these pregnancies, about 1,500 result in a miscarriage or stillbirth. An estimated 2,500 infants (about 1 per 1000 pregnancies) in the US are born with a NTD each year.[5] Most NTDs lead to neonatal death or significant lifelong disabilities (e.g. inability to walk, incontinence, bowel dysfunction, hydrocephalus, developmental delays). The average total lifetime cost to society for each infant born with spina bifida is approximately $532,000 per child. For many children, the cost may be well above $1,000,000.[6]

FOLIC ACID METABOLISM

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Folate, a water soluble B-vitamin, is necessary for proper cell growth and development of the embryo. Folate is found in high concentrations in leafy green vegetables and many other foods. An important factor for a number of metabolic pathways in the cells that involve the transfer of one-carbon groups, folate plays a critical role in helping dividing cells appropriately form DNA and RNA.[7] This role makes folate indispensable to rapidly dividing cells, like those derived from bone marrow or the cells involved in fetal development. Folic acid, as the synthetic form of this compound used to supplement foods and multivitamins, is 1.7 times more bioavailable than folate from food. Expressed differently, 100 μg of dietary folate is considered equal to 60 μg of synthetic folic acid.[8, 9]

The body utilizes and stores folic acid in a more complex way than many other water-soluble vitamins. Radio-labeled pharmacokinetic folate studies by Gregory et al demonstrate that folic acid binds to specific liver and RBC proteins creating multiple folic acid compartments or "pools". [10, 11] Two primary pools exist - a fast turnover pool that is rapidly excreted and a slow turnover pool that is sequestered and slowly excreted (mean residence time of 100-200 days). This slow turnover pool is saturated by chronic folic acid administration. The elevated body stores of folate that are achieved after chronic supplementation decline slowly after supplementation is discontinued. Body stores remain elevated above baseline levels for 3-6 months depending on pre-supplemental body stores and supplement dose/duration of use.

In support of the rigorous radiolabeled studies are studies in both men and women in which subjects received chronic daily folic acid supplementation followed by evaluation of blood folate levels at varying time points after discontinuation of folic acid. These studies demonstrated that folate concentrations decrease slowly after folic acid supplementation is stopped, but remained above baseline levels (i.e., levels prior to supplementation) for the duration of follow-up, which ranged from 7-12 weeks.[12, 13, 14, 15] A summary of these studies is detailed in Table 1. These evaluations further demonstrate the slow decline in the body's folate stores after supplementation is stopped.

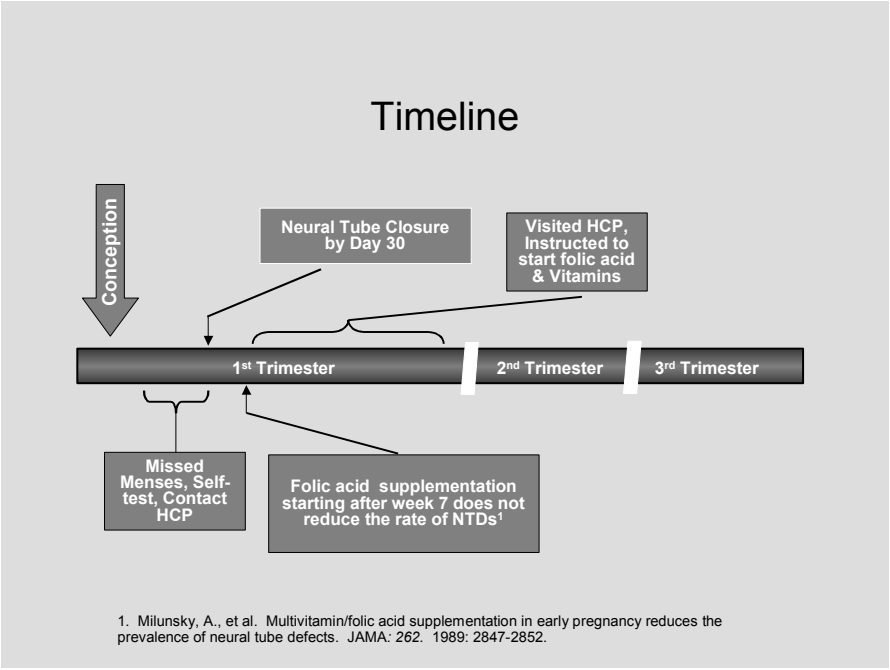
Table 1: Summary of selected publications demonstrating persistence of increased folate levels above baseline after folic acid supplementation is discontinued.

Authors	Hesekar et al.	Brouwer et al.	Wald et al.	Ward et al.
Citation	J Nutr Sci Vitaminol 1987;33:163-168.	Am J Clin Nutr 1999;69:99-104.	Arch Intern Med 2001;161:695-700.	Q J Med 1997;90:519-524.
Purpose	Effect of long-term supplementation of FA on folate levels in plasma and erythrocytes.	Effect of low dose FA administration for 4 wks on plasma total homocysteine and blood folate levels.	Effect of FA on serum homocysteine levels and serum folate levels in ischemic heart disease.	Effect of low dose FA on serum homocysteine and serum folate levels.
Number of Patients	6	144	151	30
Gender	2 women 4 men	Women (65-70% on OCs)	26 women 125 men	men
Dose of Folic Acid	1 mg (0.5 mg BID)	500 mcg QD 500 mcg QOD (250mcg /d) Placebo Mean dietary intake 280 mcg/d	200 mcg QD, 400 mcg QD 600 mcg QD, 800 mcg QD 1 mg QD, placebo	100 mcg x 6 wks 200 mcg x 6 wks 400 mcg x 14 wks Mean dietary intake 280 mcg/d
Duration of FA Supplementation	17 weeks	4 weeks	3 months	26 weeks
Dietary Modification	Not specified	Regular diet (~280 mcg/d) (no liver or marmito)	Not specified	Non consumers of FA fortified food or B-vitamins
Fortification Status	Not specified	Not specified	No fortification	No fortification
Study Location	1987, Germany	1999, Netherlands	2001, England	1997, Northern Ireland
Baseline Folate Levels	Plasma 5.5 ng/ml Eryth. 252 ng/ml	For 500 mcg QD Plasma 11.3 nmol/L (5.0 ng/ml) RBC 400 nmol/L (177 ng/ml)	Serum folate Median 15.4 nmol/L (6.8 ng/ml)	Serum 7.7 mcg/L or ng/ml RBC 467 mcg/L or ng/ml (mcg/L = ng/ml)
Peak Folate Levels (Varied based on study length)	Plasma 13 ng/ml Eryth (RBC) 596 ng/ml	For 500 mcg QD Plasma 27 nmol/L (11.9 ng/ml) RBC 508 nmol/L (224 ng/ml)	Not Available	Serum 17.2 mcg/L or ng/ml RBC 622 mcg/L or ng/ml (mcg/L = ng/ml)
Folate Levels after d/c Supplementation*	7 wks after d/c: Plasma 9.0 ng/ml Eryth. (RBC) 439 ng/ml	8 wks after d/c: For 500 mcg QD Plasma 9 ng/ml RBC 221 ng/ml	3 mos after d/c: 400 mcg: Serum 9 ng/ml 800 mcg: Serum 11 ng/ml 1 mg: Serum 12.3 ng/ml	10 wks after d/c: Serum 8.7 ng/ml RBC 609 ng/ml
Key Conclusions	Folate levels remained elevated above baseline levels even at 7 weeks after d/c FA.	Plasma and RBC folate levels remained elevated above baseline levels even at 8 weeks after d/c FA.	Serum folate levels remained elevated above baseline in all groups (except 200 mcg) at 3 months after d/c FA.	Serum and RBC folate levels elevated above baseline even at 10 weeks after d/c.

* All values have been converted to the traditional unit of ng/ml by using the conversion factor of 2.265518804 obtained from the IOM report on Dietary Reference Intakes (Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline. Washington, DC: National Academy Press, 2000).

Folic acid, when taken one month before conception and throughout the first trimester, has been shown to reduce the risk for an NTD-affected pregnancy by 50 % to 70 % to a rate of about 6 NTDs per 10,000 pregnancies. Figure 2 supports the importance of the timing of folic acid consumption and reduction in NTDs.

Figure 2: The relationships among conception, diagnosis of pregnancy, neural tube closure and when a patient would typically be instructed to take folic acid and vitamins are depicted.



Although it is not known exactly how folic acid works to prevent NTDs, its role in tissue formation is essential as it is required for the production of DNA, which is necessary for the rapid cell growth needed to form fetal tissues and organs early in pregnancy.

SAFETY OF FOLIC ACID

Both the safety and benefits of folic acid are well accepted based on the public health initiatives around grain fortification. Folic acid is cited to be relatively nontoxic to humans and has a wide therapeutic index.[16] A recent MEDLINE search of folic acid literature published in 2003 resulted in greater than 90% of retrieved articles reporting studies on the anti-toxic properties of folic acid with no studies reporting toxic effects. Additionally, the safety of folic acid has been supported by adverse event reports. Since 1986, when the USDA Center for Food Safety and Applied Nutrition established an adverse event reporting system for dietary supplements, no serious adverse events have been attributed to folic acid (source FDA).[17] Although under-reporting of such cases is expected in a voluntary reporting system, the absence of any reports cannot be explained by this alone. In the case of Vitamin A, the same reporting system includes numerous cases of serious adverse events since 1986. Moreover, the minimum toxic dose of folic acid is cited to be 400 mg, a dose that is 1000 times the RDA of 400 μg.[18]

One potential safety concern that has been cited with chronic high dose folic acid supplementation is masking of vitamin B_{12} deficiency by masking early signs of anemia.[19, 20] The potential consequence of this scenario is a delay in the diagnosis of vitamin B_{12} deficiency leading to delayed treatment which can result in irreversible neurologic sequelae. This is primarily a concern in the elderly population (between 5% and 15% of the elderly population in the United States suffer from vitamin B_{12} deficiency), but is rare in women of reproductive age.[21] The literature contains case reports suggesting this masking effect occurs primarily with high dose folic acid intake in the absence of concurrent vitamin B_{12} supplementation; there are rare cases of masking of vitamin B_{12} deficiency at doses of less than 1000 μg per day of folic acid. Because of a number of reports suggesting that 5,000 μg of folic acid a day may temporarily correct the anemia of vitamin B_{12} deficiency but would not prevent or correct the neurological sequelae, FDA set an upper threshold of 1,000 μg of "total" folate per day (known as Upper Tolerable Limit). The choice of the 1000 μg safe upper limit was not derived from any clinical or scientific data demonstrating toxicity, but rather was deemed to be a reasonable buffer covering all age groups inclusive of those with high probability for vitamin B_{12} deficiency (the elderly population). The concerns around masking of vitamin B_{12} deficiency would not be an issue if an individual receives supplemental vitamin B_{12} in addition to folic acid from

the same multivitamins or cereal. Given that vitamin B_{12} deficiency is rarely seen in women of reproductive age, the likelihood of this presenting a significant safety issue in the reproductive population is minimal.

Mills and colleagues explored this issue with a retrospective review of 18,106 patients in the Veterans Affairs Medical Center in Washington, D.C. between 1992 (i.e., before FDA-mandated fortification of cereal grains with folic acid) and 2000 (i.e., two years after fortification).[64] From this population, 1573 patients were identified with low serum vitamin B_{12} concentrations (i.e., <258 pmol/L) and known hematocrits and MCV measurements. The authors hypothesized that increased folic acid intake following fortification would lead to a *decrease* in the proportion of patients with anemia and low vitamin B_{12} levels. However, the authors found no changes in the proportion of subjects with low vitamin B_{12} levels and *without* anemia during the "prefortification phase", "optional fortification phase", and "mandatory fortification phase" (1992-1995: 39.2%; 1996-1997: 45.5%; 1998-2000: 37.6%; P=0.96). This study strongly suggests that increased folic acid intake following fortification of cereal grains has not caused a major increase in masking of vitamin B_{12} deficiency anemia.

The American College of Obstetrician-Gynecologists (ACOG) has addressed issues of the safety of folic acid in a recent ACOG Practice Bulletin, Neural Tube Defects: [4]

> "The risks of higher levels of folic acid supplementation [i.e., > 400 μg/day] are believed to be minimal. Folic acid is considered nontoxic even at very high doses and is rapidly excreted in the urine."

Supporting the contention that doses of folic acid up to 4000 μg per day are safe in reproductive age women, is a recommendation for "high risk" women stated in this ACOG Practice Bulletin:

> "For women at high risk of NTDs or who have had a previous pregnancy with an NTD, folic acid supplementation of 4 mg [4000 μg] per day is recommended."

Early studies reported that folic acid supplements could potentially interfere with intestinal zinc absorption. However, those reports have been refuted with direct measures of zinc metabolism in women who were administered large doses of folic acid (given as pteroylglutamic acid) daily.[22] This latter study is both noteworthy and relevant to the present application for several

reasons. First, the subject population of this study was women of reproductive age, who in this case had cervical dysplasia. Secondly, the folic acid dose used in the treatment arm was 10 mg/d, which is 10 times the limit described as the upper safety limit for this supplement. While folic acid supplementation at this level was shown to increase erythrocyte folate significantly above those of control subjects (given ascorbate) over the 4-month study ($P < 0.001$), "no untoward clinical effects were observed". The study is also significant in that folic acid levels in the subjects prior to the study were in the normal range and no anti-folate drugs were present.

Rare instances of allergic reactions to folic acid preparations have been reported and have included erythema, skin rash, itching, general malaise and respiratory difficulty due to bronchospasm. One patient experienced symptoms suggesting anaphylaxis following use of an injectable folic acid formulation. Many of these cases suggest an association between consumption of folic acid and the reported adverse event; however, documentation is limited and causation has not been firmly established. Overall, the safety profile of folic acid is quite reassuring.

FOLIC ACID REDUCES NTDs

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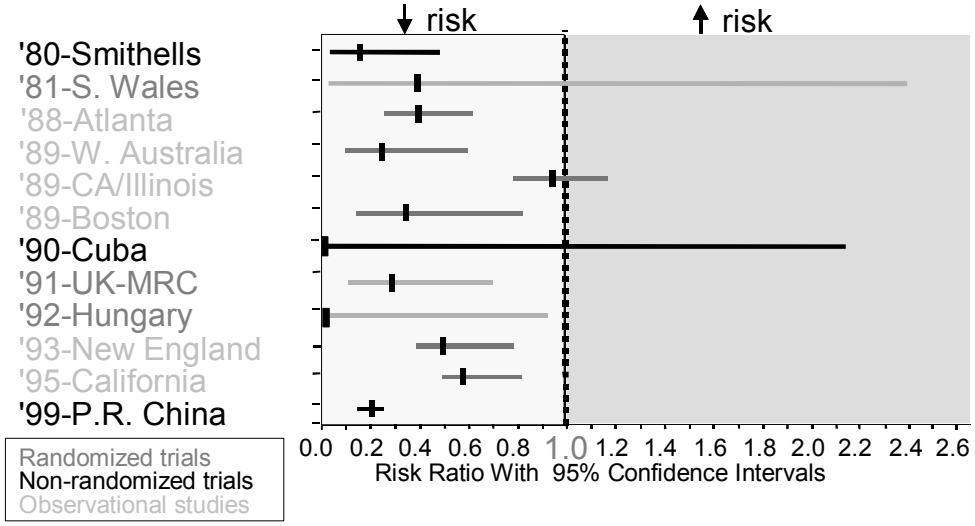
Randomized controlled trials and large, well-designed cohort studies demonstrate that folic acid supplementation can reduce the incidence of NTDs by 50-70% to a rate of about 6 NTDs per 10,000 pregnancies. The beneficial effects of folic acid in decreasing the rates of NTDs have been demonstrated in both high risk (i.e., women with a previous NTD-affected pregnancy) and low risk populations. Recent studies have also demonstrated an inverse relationship between maternal serum/RBC folate levels and NTD rates. Figure 3 below describes the results from several studies demonstrating the impact of folic acid on NTD rates.

Figure 3: Multivitamins with Folic Acid Neural Tube Defect Studies, 1980-1999



Data from some of the pivotal studies assessing this relationship are reviewed in the text below and are summarized in Table 2.

Table 2: Review of Pivotal Trials Demonstrating Folic Acid Reduces NTDs

Study/Author	Trial Design	Population	Intervention	Percent Reduction in NTDs	NTD Rate	Study Conclusions/Comments
Medical Research Council Vitamin Study	Randomized Controlled Trial	1,817 women with a prior NTD affected pregnancy (High Risk Population)	4 mg folic acid Vitamins Both Vitamins and 4 mg folic acid No Vitamins or folic acid	72% reduction in NTDs in folic acid arms	6 NTDs in two folic acid groups 21 NTDs in other groups	Synthetic folic acid is safe and effective at preventing NTDs in a high risk population
Czeizel and Dudas	Randomized Controlled Trial	~ 4000 women without a NTD affected pregnancy	800 μg folic acid Trace-element supplement (w/o folic acid)	NA	No NTDs in folic acid group 6 NTDs in trace element group	Synthetic folic acid is safe and effective at preventing NTDs in a low risk population
Berry et al	Cohort Study	> 200,000 women in the Northern and Southern regions of China	400 μg folic acid No Supplements	79% in Northern region 41% in Southern region	Reduction from 48/10,000 in Northern region to 10/10,000 Reduction from 10/10,000 in Southern region to 6/10,000	Reduction in NTD rates to a rate of 6/10,000 is achievable through large-scale supplementation programs
Milunsky et al	Cohort Study	> 22,000 women	400 μg folic acid containing multivitamin	> 65% reduction if folic acid taken prior to conception	Reduction from 35/10,000 to 12/10,000	Beginning folic acid supplementation prior to pregnancy is critical.

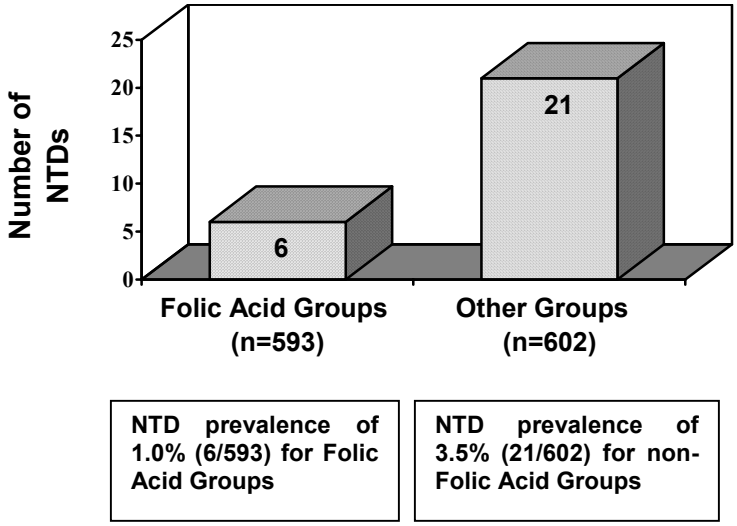
EFFICACY DATA

Randomized Controlled Trials - High Risk Populations

Medical Research Council Vitamin Study [23]

- The results of the most frequently cited study assessing the effect of folic acid supplementation on NTD rate, the Medical Research Council Vitamin Study (MRC), were published in 1991. This was a randomized, double blind study of high risk women with a prior NTD-affected pregnancy. Women were randomized into four groups: folic acid 4 mg, other vitamins, both, or neither. A total of 1,817 women were randomized, resulting in 1,195 pregnancies.
- Twenty-seven fetuses or infants had NTDs:
  - 6 occurred in the two folic acid groups
  - 21 occurred in the other groups

Figure 4: Prevalence of NTDs among the four groups in the Medical Research Council Study.



- The results demonstrated a 72% protective effect (RR 0.28, 95% CI 0.12, 0.71) with use of folic acid supplements. This study was terminated early, on the recommendations of the data safety monitoring committee, due to its positive results and the public health significance of the results.
- The authors noted that 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.
- The reviewers also concluded that the observed NTDs in the two folic acid groups likely occurred because of factors other than folate deficiency. There was no indication that multivitamins with folic acid had an enhanced effect over folic acid alone, indicating that folic acid can act as an independent protectant. This study firmly established synthetic

folic acid as safe and effective in preventing NTDs in a high risk patient population.

Randomized Controlled Trials - Low Risk Populations

Czeizel and Dudas [24]

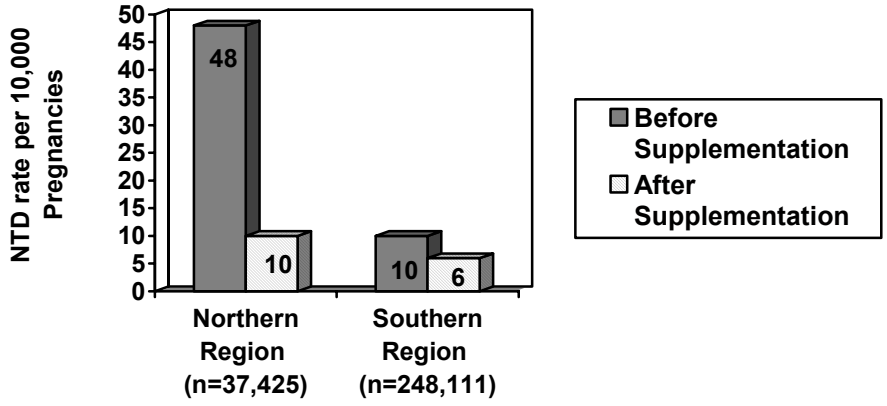
- The result of a randomized, controlled trial of low risk women who had not had a NTD-affected pregnancy was reported in 1992. Women were randomized to receive a prenatal vitamin with 800 μg of synthetic folic acid or a trace-element supplement (that did not contain folic acid) in addition to the natural folate in their food. There were over 2,000 women in each arm.
- The results revealed no cases of NTDs in the folic acid group versus 6 in the control group (P = 0.029).
- No comprehensive safety information was reported.
- This study was terminated early because of positive results. This study firmly established synthetic folic acid as safe and effective in preventing NTDs in low risk women in the general population.

Cohort Studies

Berry et al[25]

- These authors reported the results of periconceptional folic acid supplementation in a study conducted as part of a 1993-1995 public health campaign in China. There were four study groups – a test (400 μg/d folic acid) and control group (no supplementation) – in each of two different regions of China – northern region and southern region. The baseline incidence of NTDs was relatively higher in the northern region, presumably due to a lower dietary intake of folate, given a shorter growing season for fresh produce.
- Study numbers were large: 130,142 women took the folic acid supplement and 117,689 did not.
- Without supplementation, rates of NTDs were 48 per 10,000 pregnancies in the northern region and 10 per 10,000 pregnancies in the southern region. The greatest reduction in risk occurred among the fetuses or infants of a subgroup of women in the northern region with periconceptional use (79% reduction to a NTD rate of 10 per 10,000 pregnancies; Risk Ratio = 0.21, 95% CI 0.10 to 0.43). There was also a substantial reduction of risk in the southern region among the subgroup with periconceptional use (41% reduction to a NTD rate of 6 per 10,000 pregnancies; Risk Ratio = 0.59, 95% CI 0.36 to 0.97) among women taking any folic acid.

Figure 5: Number of NTDs among women in the Chinese Cohort Study.



- For women with high compliance (> 80% of folic acid pills consumed) and taking folic acid both before and after conception, the risk reduction was even greater: 85% in the northern region to a rate of 7 per 10,000 pregnancies. In the southern region, highly compliant women had a comparable reduction to that of the entire group (a rate of 6 NTDs per 10,000 pregnancies).
- This study established that a rate reduction to 6 NTDs per 10,000 pregnancies is achievable through large-scale fortification / supplementation programs.

Milunsky et al [26]

- This large prospective study of a cohort of >22,000 women evaluated the relation of folic acid intake and risk of NTDs. This study supported the need to begin supplementation prior to conception by demonstrating that the incidence of NTDs among mothers starting supplementation after week 7 of pregnancy was similar to that of non-users.
- Users beginning supplementation prior to conception and continuing through the first months of pregnancy showed >65% reduction in NTD occurrence (from 35 per 10,000 to 12 per 10,000, prevalence ratio 0.36, 95% CI 0.15 to 0.83). See previously discussed Figure 2, which supports the importance of timing folic acid supplementation.
- No comprehensive safety data was reported.

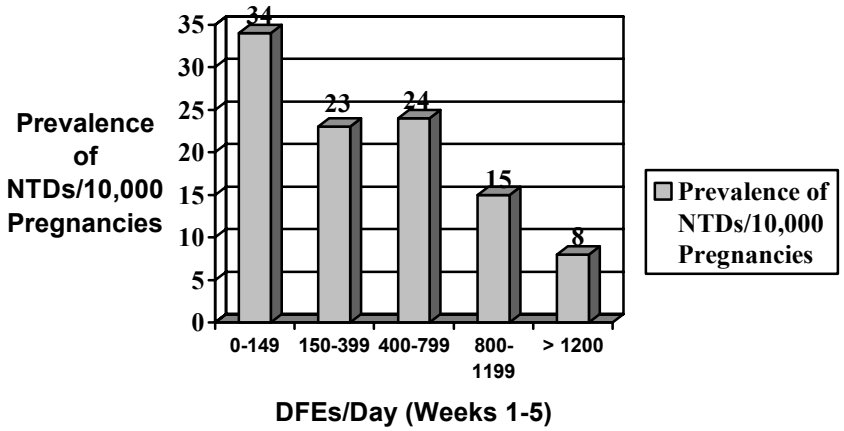
Moore et al [27]

- These authors used the data from the cohort of >22,000 women from Milunsky et al [26] to investigate the relationship between relative dose of supplemental folic acid or total folate intake and NTD risk.
- Folic acid intake was assessed from data gathered in the early second trimester. Patients were asked about use/intake of multivitamins, other vitamin supplements, folic acid supplements, and yeast. In addition, a 50-

item food frequency questionnaire was administered to each patient to estimate dietary intake of folic acid/folate. To account for the different sources of folic acid/folate, all reported intake was converted into dietary folate equivalents (DFE). For most analyses, folate intake was assessed during the first 5 weeks since a woman's last menstrual period.

- The results from this evaluation revealed that as intake of DFEs increased, the prevalence of NTDs decreased. The prevalence of NTDs decreased from 34 per 10,000 with intake of 0-149 DFEs per day to 8 per 10,000 pregnancies with the intake of >1200 DFEs per day. In fact, there was linear relationship between total DFE (from vitamins/supplements and food) intake and NTD risk.

Figure 6: Prevalence of NTDs according to daily folate intake during weeks 1-5 of pregnancy.

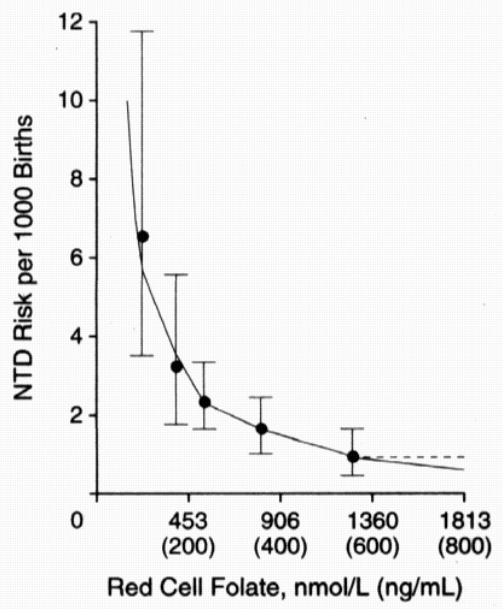


- These authors concluded that NTD risk declines steeply with increasing intake of total folate during early pregnancy.

Dose-Response Data

Recent studies have demonstrated an inverse relationship between maternal serum/RBC folate and NTD rate. Daly and colleagues published dose response relationships between plasma and RBC folate and the rate of NTDs.[28] Daly's analyses was based on 56,000 Irish women from whom blood was collected at the first prenatal visit and later assayed. Very few of these women, if any, consumed folic acid containing supplements or drugs, although some may have consumed breakfast cereals fortified with added folic acid. Daly's analyses demonstrated a high negative correlation between NTD rates and RBC folate concentrations. Over the range of RBC folate concentrations reported in this population, the rate of NTDs varied from about 65 per 10,000 to about 10 per 10,000 births (see Figure 7).

Figure 7: Inverse relationship between RBC folate and NTD risk. Adapted from Daly et al.



The study from China (Berry et al) suggested that, with folic acid supplementation, a NTD rate of about 6 per 10,000 pregnancies is achievable in both high risk and low risk populations. Daly's analyses suggest that the subgroup of Irish women with the highest levels of RBC folate could still benefit (i.e., have further reduction in NTD rates) with additional folic acid supplementation.

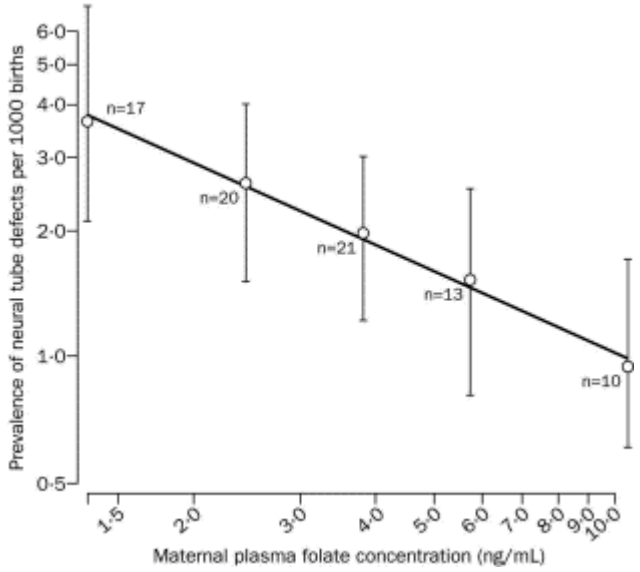
Wald and colleagues conducted analyses to quantify the effect of folic acid at preventing NTDs.[29] Their primary objective was to assess the relationship between folic acid supplementation and serum folate levels while a secondary objective was to model the association between maternal plasma folate and NTD prevalence. The primary objective was addressed by analyzing data from 13 studies of folic acid supplementation on serum folate concentrations. The 13 studies were required to meet the following criteria:

- ≤ 1mg folic acid administered per day
- Treatment duration of ≥ 3 weeks
- Serum folate measurements at baseline and final visits
- No dietary interventions
- No trials with subjects who had elevated homocysteine levels

Results of this analysis demonstrated a given absolute rise in intake of folic acid was associated with a predictable absolute rise in plasma folate from any starting concentration.

The second objective from the analyses conducted by Wald et al was to model the association between maternal serum folate and NTD prevalence. This was done by using data from Daly and colleagues' nested case-control analysis from a cohort study of 56,000 pregnant women, which included 84 cases of NTDs (the Irish population). The women were divided into five groups according to ranked measurements of maternal plasma folate, and for each group the mean plasma folate and the birth prevalence of NTDs were plotted, using logarithmic scales on both axes. The results demonstrated an inverse proportional relation between plasma folate and NTD risk, as seen in Figure 8.

Figure 8: Prevalence of births with neural tube defects according to maternal plasma folate concentration. Data taken from Daly and colleagues. n=pregnancies with neural tube defects. The slope of the regression line is the relative odds of neural tube defect pregnancy = (new serum folate÷old serum folate)$^{-0.59}$. Error bars are 95% CIs. Adapted from Wald et al.



Wald et al also modeled the expected effects of increases in folic acid intake on serum folate concentrations with estimates from the cohort study (Daly et al) of the proportional NTD reduction for a proportional increase in serum folate (see Table 3 below).

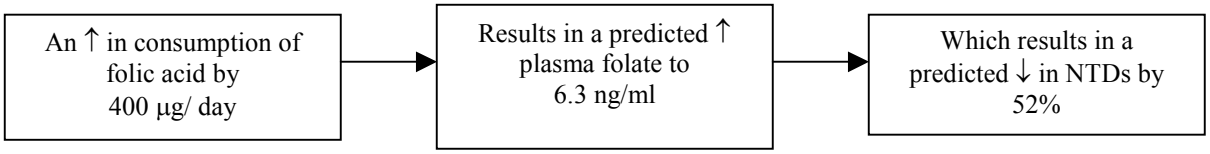
Table 3: Serum folate concentrations after increases in folic acid intake in younger women according to background serum folate and the predicted reduction in neural tube defect risk

	Serum folate (ng/ml) concentration (**and % risk reduction**) expected for given folic acid intake against baseline serum folate (ng/ml)			
Increase in folic acid intake (µg/day)	**Baseline serum folate levels (ng/ml)**			
	2.5	5.0	7.5	**10.0**
100 µg	3.4 (23 %)	5.9 (13 %)	8.4 (9 %)	10.9 (7 %)
400 µg	**6.3 (52 %)**	8.8 (36 %)	11.3 (28 %)	**13.8 (23 %)**
1000 µg	11.9 (71 %)	14.4 (57 %)	16.9 (48 %)	19.4 (41 %)
4000 µg	40.1 (89 %)	42.6 (82 %)	45.1 (76 %)	47.6 (71 %)
5000 µg	49.5 (91 %)	52.0 (85 %)	54.5 (80 %)	57.0 (75 %)

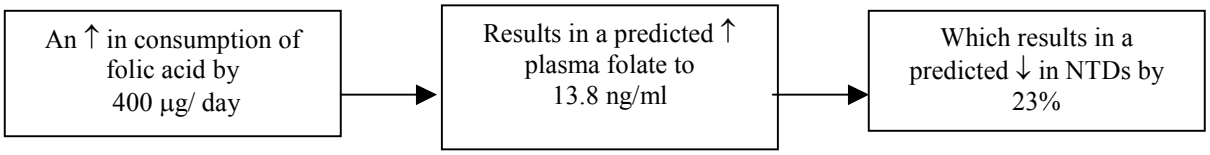
Values are baseline plasma folate (reduction in risk of neural tube defect). Table adapted from Wald et al.

According to this model (see bolded examples in table above):

- If the baseline maternal serum folate concentration is **2.5 ng/ml:**



- If the baseline maternal serum folate concentration is **10.0 ng/ml**:



Thus, the degree of NTD reduction depends upon both baseline serum folate and the amount of incremental folic acid consumed each day.

Wald et al conclude that their model:

- Is validated by direct observations of data assessing the impact of folic acid on NTDs (e.g. the MRC Vitamin Study).
- Predicts the relation between increased folic acid intake, increases in serum folate, and decrease in risk of NTDs.
- Demonstrates the importance of baseline serum folate levels in response to folic acid supplementation and change in NTD risk.

Based on their findings, the authors maintain that current folic acid fortification levels do not achieve maximum NTD risk reduction.

FOLIC ACID INTAKE RECOMMENDATIONS

FOLIC ACID INTAKE RECOMMENDATIONS

Proven efficacy coupled with minimal toxicity has allowed for public health policy actions and endorsement of folic acid supplementation. In 1998, the Institute of Medicine/Food and Nutrition Board published Dietary Reference Intakes for folate. This group set the current RDA for folic acid at 400 μg/day for adults, 600 μg/day for pregnant women, and 500 μg/day for lactating women.[8] Their report stated:

> "To reduce the risk of NTDs for women capable of becoming pregnant, the recommendation is to take 400 μg of folic acid daily from fortified foods, supplements or both in addition to consuming food folate from a varied diet."

Folic acid in fortified foods and in supplements is synthetic folic acid.

Continued Advocacy from Public Health and Professional Organizations

The results from the studies discussed previously have produced evidence sufficient to justify the recommendation from major public health and professional medical organizations that women of reproductive age should routinely supplement with folic acid. Table 4 below provides a summary of several organizations and their recommendations around folic acid.

Table 4: Summary of recommendations for Folic Acid Consumption

Public Health or Professional Organization	Dose of Folic Acid Recommended		
	Women of child bearing age	Pregnant women	Women with previous NTD affected pregnancy
US Public Health Service [30]	400 μg		
FDA [31]	400 μg	800μg	
American College of Obstetricians and Gynecologists [32]	400 μg		4000 μg
American Academy of Pediatrics Committee on Genetics [33]	400 μg		
American Academy of Neurology [34]	400 μg		
National Council on Folic Acid [35]	400 μg		
Council for Responsible Nutrition [36]	400 μg		
National Healthy Mothers, Healthy Babies Coalition [37]	400 μg	800 – 1000 μg	
The Teratology Society [38]	400 μg		
Spina Bifida Association of America [39]	400 μg		

The recommendation by ACOG for folic acid supplementation in women at low-risk for NTD-affected pregnancy is stated in the ACOG Practice Bulletin for Neural Tube Defects: [4]

> "For low-risk women, folic acid supplementation of 400 μg per day currently is recommended because nutritional sources alone are insufficient. Higher levels of supplementation should not be achieved by taking excess multivitamins because of the risk of vitamin A toxicity."

GRAIN FORTIFICATION PROGRAM

GRAIN FORTIFICATION PROGRAM

FDA Mandates Grain Fortification – 1996 - 1998 [40]

In 1996, the FDA permitted "enriched" cereal grains to contain synthetic folic acid and required, by January 1, 1998, that all enriched cereal grains be fortified at a concentration of 140 μg per 100 grams of flour. Pre-fortification modeling of consumption of synthetic folic acid suggested that fortification at this concentration would increase the average consumption by 100 μg among women of reproductive age. Various levels of fortification were posed before the 140 μg folic acid per 100 grams of flour was set. A fortification level of 70 μg folic acid per 100 grams of flour was proposed because this would replace the amount of folate lost through the milling process of grains. The Centers for Disease Control (CDC), the American Academy of Pediatrics and the March of Dimes argued for a concentration of 350 μg folic acid per 100 grams. This higher concentration would have enabled a larger proportion of women of reproductive age to consume the PHS recommended 400 μg of folic acid per day, potentially protecting more women from having pregnancies affected by folic acid-preventable NTDs. The FDA selected a level of 140 μg because models of consumption at this level were projected to keep the majority of consumers of "enriched" grain from consuming more than 1,000 μg of "total" folate (estimated post-fortification consumption of natural folates from food and synthetic folic acid from enriched foods and from voluntary consumption of vitamin supplements). Table 5 provides a rationale for the various proposed levels of grain fortification.

Table 5: Folic Acid Dose Considerations for FDA Mandate of Grain Fortification {Adapted from Federal Register discussions on March 6, 1996 (Volume 61, Number 44)}.

Proposed level of grain fortification (μg/100 g grain)	70	140	350
Estimates of daily intakes of folic acid based on level and type of fortification	< 1mg/day when limited to cereal/grain. Most "low consumers" would not consume 400 μg/day of folic acid.	< 1mg/day when limited to cereal/grain. ~ 90% of target group predicted to receive at least 400 μg/day.	> 1mg/day when limited to cereal/grain.
Estimated Benefit		~ 116 NTDS per year would be prevented.	.

IMPACT OF GRAIN FORTIFICATION PROGRAM ON NTDS

IMPACT OF GRAIN FORTIFICATION PROGRAM ON NTDS

Rates of NTDs have decreased both in the United States and in Canada post fortification. Although birth certificates underestimate the rate of NTD-affected pregnancies, they are a large data set from a national population and one may assume that the underreporting of NTDs has been relatively consistent over time.

United States Data

A report by Honein and colleagues indicates that the birth prevalence of NTDs has decreased from 37.8 per 100,000 live births (1995/1996) to 30.5 per 100,000 live births (1998/1999), representing a 19% decline.[41]

Additional data from the NCHS comes from Mathews and colleagues who recently reported that from 1996 through 2001 the rates of spina bifida reported on birth certificates in the U.S. has decreased by 24% and anencephaly has decreased by 21%.[42]

Williams and colleagues also report on data from 1995 through 1999 from 24 population based birth defects registries in the United States.[43] They found that spina bifida had decreased by 31% and anencephaly by 16%.

Thus, there has been a 20 to 30% reduction in spina bifida and anencephaly after grain fortification in the United States. The reduction is still below the predicted 50% to 70% decrease possible with additional fortification or supplementation. These results have led some experts to advocate increasing folic acid fortification of the food supply.[44] However, increasing folic acid fortification levels may not be the most prudent strategy to lower NTDs further. Food intake cannot be regulated, raising potential concerns about providing excessive amounts of folic acid to seniors and young children. A combination OC/folic acid product addresses the issues of low consumption and safety: such a product would only be used by reproductive age women and the daily use dose would be controlled by a healthcare professional (i.e., it would be available by prescription only).

North Carolina Birth Defects Monitoring Program

Meyers and Siega-Riz presented data from North Carolina Birth Defects Monitoring Program that suggest targeted populations could further lower their risk of an NTD pregnancy if they were to consume additional folic acid.[45] They reported that rates of spina bifida per 10,000 live births did not

decrease for women less than 25 years of age, while they decreased 47% (from 7.55 to 3.99 per 10,000) among women ≥ 30 years of age. Better-educated (more than a high school education) women had a post fortification rate of 2.62 per 10,000 while women with less education had a post fortification rate of 6.18 per 10,000 - more than double that of better educated women. In addition, women who received Medicaid services had higher post fortification rates of spina bifida than women who did not use Medicaid (5.83 versus 3.25 per 10,000 live births). These results indicate the fortification program in the US may not have benefited all segments of the population equally - most likely due to sociodemographic differences in food consumption patterns and vitamin use.

The authors concluded the following:

> "These present findings indicate that substantial potential still exists for further reductions in spina bifida, particularly among minority women of lower socioeconomic status. With the effects of the fortification program probably having already been realized, sustaining the decline will require more aggressive efforts to encourage minority women of reproductive age, as well as those from lower socioeconomic groups, to take daily multivitamins containing 400 μg of folic acid in addition to eating a well-balanced, folate-rich diet."

Canadian Data

Persad and colleagues reported on the incidence of open neural tube defects occurring in live births, stillbirths and terminated pregnancies, (collectively defined as births in this study), before and after folic acid fortification in Nova Scotia, Canada.[46] The Canadian fortification plan (150 μg of folic acid per 100 g of grain) was very similar to the United States fortification plan (140 μg of folic acid per 100 g of grain). They reported that the prevalence of open NTDs decreased from 25.8 per 10,000 births before fortification to 11.7 per 10,000 births after fortification – this represents more than a 50% decrease. These data confirmed the effectiveness of folic acid fortification in preventing birth defects.

Given that the Canadian and US fortification concentrations were similar, this study provides insight into whether further consumption of folic acid would likely prevent more birth defects. The prevalence of open NTDs in Nova Scotia post fortification was about 11.7 per 10,000 births compared to the reduction of NTD prevalence to approximately 6 per 10,000 pregnancies

achieved in the study from China (Berry et al), in which 400 μg of folic acid was given daily. Based on the results reported in the study from China, it is likely that consumption of additional folic acid among women in Nova Scotia, especially those who were low consumers, may have further reduced the NTD prevalence by approximately 50 percent to 6 per 10,000 pregnancies.

Summary of Impact of Grain Fortification

Although folic acid fortification efforts and public awareness campaigns for folic acid supplementation have been successful in increasing median national blood folate levels and reducing NTD rates in live births (decline of 20-30% in the US), many women are still below national blood folate goals. In addition, the fortification program in the US may not have benefited all segments of the population equally - most likely due to sociodemographic differences in food consumption patterns. The Canadian fortification program was successful in reducing NTDs by nearly 50% to a rate of 11.7 per 10,000 births. However, this rate still exceeds the folic acid preventable NTD threshold from the Chinese cohort study (approximately 6 per 10,000 pregnancies), indicating that further reduction in NTDs may be possible with consumption of additional folic acid, especially among low consumers.

EPIDEMIOLOGY OF FOLIC ACID INTAKE

National Estimates for Blood Folate Levels Point to a Group of Low Consumers

In 1999, one year post fortification implementation, the National Center for Health Statistics (NCHS) reported on the folate status of women of reproductive based on data from NHANES (National Health and Nutrition Examination Survey).[47] The NHANES study data (NHANES represents a stratified, multistage probability sample of the civilian, U.S., noninstitutionalized population) provides folate status of U.S. women before (1988-1994) and after (1999-2000) folic acid fortification. According to this data, the median serum folate for women of reproductive age increased from 4.8 ng/ml to 13.0 ng/ml and the median RBC folate increased from 159.9 ng/ml to 263.6 ng/ml.[48, 49] However, the 10th percentile has only increased from 2.3 ng/ml to 6.4 ng/ml for serum folate (RBC folate increased from 92.2 ng/ml to 166.2 ng/ml) and the 25th percentile has only increased from 3.1 ng/ml to 9.1 ng/ml for serum folate (RBC folate increased from 119.5 ng/ml to 204.7 ng/ml). See Tables 6 and 7 below.

Table 6: Selected percentiles of **serum folate concentrations (ng/ml)** for women aged 15-44 years – NHANES Surveys, United States, 1988-1994 and 1999-2000.

		Percentile				
		10th	**25th**	**50th**	**75th**	**90th**
Years	N	ng/ml (95% CI)	ng/ml (95% CI)	ng/ml (95% CI)	ng/ml (95% CI)	ng/ml (95% CI)
1988-1994	5616	2.3 (2.2-2.4)	3.1 (3.0-3.4)	4.8 (4.5-5.2)	7.8 (7.3-8.30)	11.7 (10.9-12.8)
1999-2000	1648	6.4 (5.8-7.0)	9.1 (8.7-9.5)	13.0 (12.1-13.8)	18.1 (16.6-19.5)	26.1 (22.5-29.8)

Table 7: Selected percentiles of RBC folate concentrations (ng/ml) for women aged 15-44 years – NHANES Surveys, United States, 1988-1994 and 1999-2000.

		Percentile				
		10th	**25th**	**50th**	**75th**	**90th**
Years	N	ng/ml (95% CI)	ng/ml (95% CI)	ng/ml (95% CI)	ng/ml (95% CI)	ng/ml (95% CI)
1988-1994	5254	92.2 (88.5-95.8)	119.5 (115.9-123.4)	159.9 (153.6-168.6)	222.3 (214.2-232.2)	296.6 (284.9-315.2)
1999-2000	1656	166.2 (157.8-174.7)	204.7 (198.6-210.8)	263.6 (248.3-278.9)	343.0 (324.9-361.1)	432.6 (411.9-453.3)

These statistics demonstrate that more than 25% of U.S. women are still below the RBC folate target of 220 ng/ml.[29] This RBC target of 220 ng/ml was set as a median target for women between the ages of 15 – 44 years as part of the Healthy People 2010 initiative.[50] However, based on data by Daly et al (see Figure 7), many experts believe that 400 ng/ml may be a better RBC target for women of reproductive age.[51, 52] The most recent NHANES data reported that the national folate goals have been met for Mexican-American and non-Hispanic white women, but not for non-Hispanic black women (increase in median serum folate from 4.0 ng/ml to 10.2 ng/ml, increase in median RBC folate from 123.6 ng/ml to 213.8 ng/ml).

Median serum and RBC folate concentrations, and reductions in NTDs, have remained relatively unchanged since 1999, suggesting that the magnitude of change in these parameters has been realized and no further changes are expected. These data suggest that a sizable subpopulation of women of reproductive age does not consume an adequate amount of folic acid.

Consumers with Lower Blood Folate Levels can be Identified

Than et al reported that the serum folate concentration of a sample of mostly young women (60% < 26 years of age) attending family planning clinics in Georgia in 2000 had a median serum folate level of 8.9 ng/ml. [53] The median serum folate level reported for women of reproductive age in the 1999-2000 NHANES study was 13.0 ng/ml. [49] The reason for this discrepancy is unclear, but may be related to different dietary and supplement use and habits. As the serum folate levels in NHANES and the Georgia Family Planning Clinics study were analyzed in the same laboratory at CDC, the differences observed in the median serum and RBC folate levels were not likely to be due to laboratory variations. What is likely is that the NHANES results are higher because the women in the Georgia Family Planning Clinics study sample were less likely to consume folic acid supplements and/or cold breakfast cereals with 400 μg of folic acid per serving.

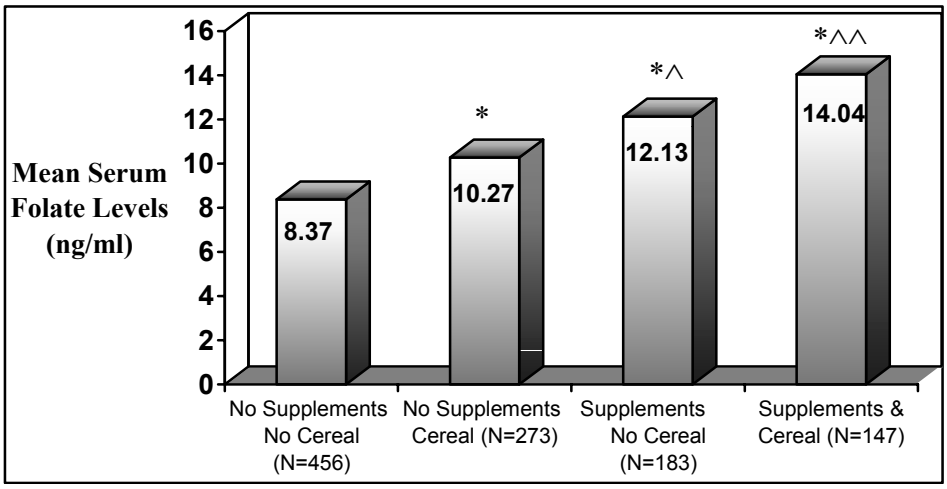
Than et al were able to stratify the population of reproductive age women based on responses to two questions:

1. In the last 2 days, did you take a folic acid pill or multivitamin?
2. In the last 2 days, how many servings of breakfast cereal have you eaten?

Women who regularly consumed folic acid supplements (OR 0.2, 95% CI 0.09, 0.30) or cereal (OR 0.4, 95% CI 0.26,0.62) were the least likely to be in the lowest quartile (≤ 6.2 ng/ml) of serum folate concentrations.

A more detailed analysis of these results did reveal that mean serum folate levels among women who did not consume multivitamin supplements (containing folic acid) or breakfast cereal were significantly lower ($P < 0.001$) than mean serum levels for women who consumed multivitamin supplements, breakfast cereal or both.[53] Figure 9 below provides mean serum folate levels based on use of multivitamin supplements and/or consumption of cereal.

Figure 9: Mean serum folate levels (ng/ml) based on use of multivitamin supplements or consumption of cereal in the past week.



* $P < 0.001$ for all groups vs. No Supplements/No Cereal group by two-sample t-test with unequal variances.

∧ P=0.002 vs. No Supplements/ Cereal group.

∧∧ P= 0.003 vs. No Supplements/Cereal group; P=0.15 vs. Supplements/No Cereal group.

These findings have several implications:

- Simple questioning about multivitamin supplement and cereal consumption can reliably differentiate subpopulations of reproductive age women relative to mean serum folate levels.
- Regular multivitamin supplement use leads to higher mean serum folate levels than regular cereal consumption or infrequent/no consumption of multivitamin supplements or cereal.
- Low consumers of folic acid can be identified using simple questions such as those used in the Georgia Family Planning Clinics Study.

It is of note that the Wald et al model predicts an increment of 3.8 ng/ml in serum folate with the intake 400 μg of folic acid. The data from the Georgia Family Planning Clinics Study precisely fits that model with an increase in serum folate from 8.37 ng/ml in the no supplements / no cereal group to 12.13 ng/ml in the supplements/no cereal group (a difference of 3.76) and from 10.27 ng/ml in the no supplements/cereal group to 14.04 in the supplements/cereal group (a difference of 3.77).

The Georgia Family Planning Clinics study demonstrates that, despite cereal grain fortification, availability of folic acid containing multivitamin supplements and widespread national eduction campaigns, many women of reproductive age fail to consume the recommended daily allowance (RDA) of folic acid. In this group of women who were actively receiving contraceptive services from the clinics (42% of these women were on OCs), only 17% were taking supplements/vitamins with at least 400 μg of folic acid. Based on the observed 8.9 ng/ml median serum folate concentration in the Georgia women, the Wald model suggests that increasing consumption by 400 μg would result in an approximately 25% drop in NTDs in this population. Women not taking multivitamin supplements had a median serum folate of 8.3 ng/ml. In these women, the Wald model predicts that an incremental daily dose of 400 μg of folic acid would result in a decrease of NTDs by 23% to 28%.

The authors of the Georgia Family Planning study conclude:

> "Although serum folate levels have increased in the aggregate national population, certain populations have lower folate levels. Because contraceptive methods are not 100% effective, all women capable of becoming pregnant, regardless of pregnancy intention or current birth control use, should consume adequate amounts of folic acid for preventing NTDs in their children. Targeting specific populations (e.g. women attending family planning clinics) who might be at higher risk for NTDs because of lower folic acid levels can be an effective strategy for continuing to reduce NTDs in the United States."

Survey Results Confirm that a Significant Percentage of Women are Low Consumers of Folic Acid

The March of Dimes, dedicated to reducing preventable birth defects, has implemented education campaigns to promote the use of folic acid in women of reproductive age. The programs were conducted in conjunction with the

Spina Bifida Association of America and promoted the use of multivitamins containing folic acid to reduce the incidence of NTDs.[54] They also performed serial studies on the impact of public education campaigns on folic acid awareness and behavior over time. In 1995, the March of Dimes funded a Gallup Survey of 2,010 women aged 18 to 45 years to benchmark knowledge and behaviors of reproductive age women relative to folic acid. The recently released 2003 survey (the sixth follow up to the initial survey) provides insight into changes in the awareness and behavior of 2,006 women aged 18-45 years relative to folic acid.[55]

Table 8: Selected Results from 2003 Gallup Survey

Awareness of	**1995 results**	**2003 results**
Folic acid	52%	79%
U.S. PHS RDA for folic acid (i.e., 400 μg)	15%	35%
Link between folic acid deficiency and birth defects	4%	21%
Importance of starting folic acid before pregnancy	2%	10%
Consumption of		
Folic acid-containing multivitamin	28%	32%

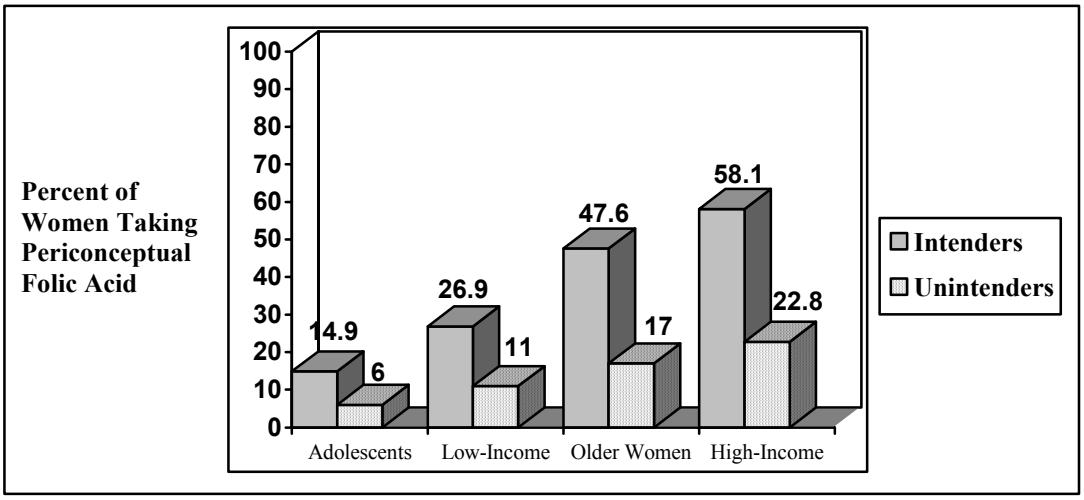
Of note, the 2003 survey indicates that only one-third (32%) of reproductive age women are consuming a folic-acid containing multivitamin. The 2003 survey also reported that, among women who do not take a vitamin or supplement, 33% would be more likely to take a vitamin or supplement if their healthcare professionals provide such a recommendation.

Women who are Not Intending Pregnancy Significantly Contribute to the Population of Low Consumers of Folic Acid

A retrospective analysis of the Oregon PRAMS (Pregnancy Risk Assessment Monitoring System) survey of 1,867 women explored the association between pregnancy intendedness and consumption of periconceptual folic acid.[56] The results revealed that women with intended pregnancies were 3.70 times more likely to have taken folic acid than those who had not (95% CI 2.38 to 5.56). Periconceptual folic acid was consumed by 45.3% of women with intended pregnancies (n=948) versus only 14.8% of women with unintended pregnancies (n=681). Stratification by patient type revealed very low rates of folic acid consumption among low-income and adolescent patients, regardless of pregnancy intention. The use of folic acid was even

low among high-income and older women who were not intending pregnancy. These results are summarized in below.

Figure 10: Periconceptual Use of Folic Acid by Pregnancy Intendedness: Stratified by Patient Type



Overall, these results demonstrate significantly lower consumption of periconceptual folic acid supplements among women who are not intending pregnancy. In particular, only 6% of adolescent women not intending pregnancy were taking folic acid periconceptually.

These results are particularly relevant to the proposal to develop OC/ folic acid products, as all women on OCs do not intend to conceive.

Despite cereal grain fortification and increased educational efforts, many reproductive age women continue to consume less than 400 μg of folic acid daily. Although counseling by healthcare providers and aggressive educational efforts should be continued, other strategies to improve folic acid intake must be considered. OC/folic acid combination drug products would provide the RDA of folic acid to many of these women without changing pill taking behavior. Such combination products may further reduce the number of NTDs with negligible incremental risk.

ORAL CONTRACEPTIVES (OCS) AS A VEHICLE FOR FOLIC ACID

ORAL CONTRACEPTIVES (OCS) AS A VEHICLE FOR FOLIC ACID

According to the 1998 U.S. Census, there are 70.1 million women between the ages of 15 and 50 in the United States. [57] Approximately 23% of these women (16.1 million) are taking OCs. Almost 8 out of 10 women (79%) take an OC at some point during their reproductive lifetime.

Nearly one-third of former OC users (31%) discontinue the pill to become pregnant. If women stop OCs with a goal of becoming pregnant, general estimates of fecundity rates during unprotected intercourse suggest that 50-60% of these women will become pregnant within the first months of attempting pregnancy.[58] Based on published evidence, it is well established that use of an OC does not adversely affect this fecundity rate.[59] Many women who discontinue OCs to conceive do not inform their healthcare provider and, as a result, may not be counseled about the importance of perinatal folic acid supplementation until their first prenatal visit. Unfortunately, this visit almost always occurs well after the neural tube has closed (See Figure 2).

OCs are among the most effective forms of reversible contraception. With perfect use (i.e. perfect or near perfect compliance), 0.1% to 0.5% of women taking OCs become pregnant each year.[60] However, many women become pregnant each year while taking OCs. The class labeling for combination OCs cites a 5% pregnancy rate with typical levels of compliance, while epidemiological reports cite rates as high as 8%.[61] In particular, the group of women under the age of 20 years may experience OC failure rates as high as 32%. The disparity between perfect use and typical use failure rates is attributable primarily to incorrect and inconsistent pill use. Population estimates indicate there are one million pregnancies per year due to incorrect or inconsistent use of OCs.[62] In general, about 50% of unintended pregnancy among OC users are carried to term.

Based on these estimates around the proportion of women who discontinue their OC to conceive as well as the estimates of pregnancies during OC use, it is possible to model the potential benefit of an OC/folic acid combination product in reducing the rate of NTDs. This model takes into consideration several assumptions reviewed earlier in this briefing document. These include the following:

- There are 16.1 million OC users in the United States, many who will discontinue their OC at some point to attempt pregnancy or some who will experience an unintended pregnancy while on their OC.
- Since OC users are not intending pregnancy, a significant percentage of these women are not consuming folic acid. Even those who are intending pregnancy may fail to consume a folic acid containing multivitamin.
- Recent studies have stratified women's serum folate concentrations based on their consumption of folic acid containing multivitamins, breakfast cereal, both, or neither.
- This stratification by consumption of multivitamins or breakfast cereal revealed distinct differences in serum folate levels based on these variables. These differences in serum folate levels can be linked to a potential NTD risk based on work done by Wald et al.
- Analyses by Wald et al have revealed distinct relationships between folic acid supplementation, serum folate levels, and a corresponding NTD risk.
- The relationships established by Wald allow us to predict the impact of an incremental consumption of 400 μg of folic acid (from the OC/folic acid product) on the increase in serum folate levels and the resulting potential reduction in NTD risk.

By modeling these assumptions, the number of NTDs that can be prevented by OC/folic acid combination products can be predicted. This is based on the following equation for which details can be found in Table 9A and Table 9B.

Note: this model assumes the use of an OC/ folic acid product by all OC users. Future proportion of users of an OC/ folic acid product to all OC users cannot be predicted with certainty.

Potential # of NTDs prevented by OC/folic acid **119**	=	Potential # of prevented in unplanned pregnancies while taking an OC/folic acid product **107**	+	Potential # of NTDs prevented in pregnancies occurring within 3 months of discontinuing an OC/folic acid product **12**

The models described in Tables 9A and 9B predict that an OC/folic acid combination product has the potential to prevent approximately 119 NTDs.

Table 9A: Model predicting the reduction in NTDs with OC/folic acid products among unintended pregnancies with OC use (assuming addition of 400 μg of folic acid to all OCs with ~16.1 Million OC users[A])

Usage Group	Consuming Cereal and a Multivitamin	Consuming Cereal but No Multivitamin	Consuming a Multivitamin but no Cereal	No Cereal or Multivitamin Consumption	Total
% of Population[B]	14%	26%	17%	43%	-
Number of Users[A] (Millions)	2.25	4.19	2.74	6.92	16.1
Unanticipated Pregnancies (5%)[C]	112,000	210,000	137,000	346,000	805,000
Live Births (~ 50% of Unanticipated Pregnancies)[D]	56,000	105,000	69,000	173,000	403,000
Mean Plasma Folate (ng/ml) [B]	14.04	10.27	12.13	8.37	-
Risk of NTD per 10,000 Births [E]	9.7	11.4	10.4	12.7	-
% Risk Reduction with OC/folic acid Product [E]	17%	22%	20%	26%	-
Expected # NTDs	54	120	72	220	466
Expected # NTD for OC/folic acid	44	94	58	183	359
Potential # NTDs Prevented	10	26	14	57	107

A Based on estimates from the Ortho Annual Birth Control Study [58]

B Based on Iuliano AD. Georgia Family Planning Clinics Study [54]

C Based on failure rates reported in class oral contraceptive labeling

D Based on Fu et al, estimates from NSFG [62]

E Based on Wald et al models that quantify the effect of folic acid [29]

Table 9B: Model predicting the reduction in NTDs due to delayed benefit with OC/folic acid products among women planning to conceive after discontinuing OC/ folic acid products

	Cycle 1	Cycle 2	Cycle 3	Total
Number of Women at start of Cycle[A]	408,000	294,000	244,000	-
Number of Pregnancies [B]	114,000	50,000	32,000	-
Live Births (~ 80% of Planned Pregnancies)	91,000	40,000	26,000	-
Live Births among women not taking multivitamin while attempting to conceive[C]	50,000	22,000	14,000	88,000
Mean Plasma Folate (ng/ml) if previously on OC/ folic acid product[D]	12.22	10.97	9.72	-
Risk of NTD per 10,000 Births if previously on OC/ folic acid product[E]	10.4	11.0	11.7	-
Risk Reduction if previously on OC/ folic acid Product (per 10,000 births) [F]	1.7	1.1	0.4	-
Potential # NTDs Prevented	9	2	1	12

A 16.1 million women on OCs, of which 3.7% (600,000 women) discontinue each year to attempt to become pregnant. An estimated 68% of these women (408,000) do not take a multivitamin, based on the March of Dimes Gallup Poll Survey.[56]

B 28% at cycle 1, 17% at cycle 2, 13% at cycle 3. [59]

C 55% of women intending to get pregnant do not take folic acid. [57]

D Based upon a linear decline over 3 cycles of folic acid in OC/ folic acid products.

E Based on Wald model.[29]

F Given that there would be 12.1 NTDs per 10,000 births if not previously on an OC/ folic acid product, based upon a mean plasma folate level of 9.09 ng/ml.[29]

SUMMARY AND CONCLUSIONS

- Ortho-McNeil Pharmaceutical, Inc. (OMP) and Johnson & Johnson PRD, L.L.C. (J&J PRD), propose to develop a combination oral contraceptive/folic acid (OC/folic acid) product to be used by women who elect to use OCs as a method of contraception and in whom supplemental folic acid intake is desirable.

- Each active and inert tablet would contain 400 μg of folic acid, providing hormonal contraception as well as the daily dose of folic acid recommended by the Institute of Medicine (IOM) and the United States Public Health Service (US PHS).

- NTDs are a devastating group of congenital anomalies that can be fatal or lead to serious lifelong disabilities. Prevention of NTDs is an important public health goal. Periconceptual folic acid supplementation can reduce the incidence of NTDs by 50-70% in most populations to a rate of about 6 NTDs/10,000 pregnancies. To be effective in preventing NTDs, supplementation with folic acid should precede pregnancy and continue until at least seven weeks' gestation.

- The IOM and US PHS both recommend that all women of reproductive age consume 400 μg of folic acid daily in addition to a diet rich in natural folates, regardless of contraceptive status in order to reduce the risk of neural tube defects (NTDs).

- In 1998, the Food and Drug Administration mandated cereal grain fortification with folic acid as a public health measure, in large part, to reduce NTDs. Since that time there have been significant increases in serum and red blood cell folate levels and a 23% reduction in the rate of NTDs. Further reduction in the rate of NTDs would be expected if more reproductive age women consumed the amount of folic acid recommended by the IOM and US PHS.

- Approximately 16.1 million women use OCs in the United States. Although the failure rate with perfect use is 0.1%, typical use failure rates are stated to be about 5% annually. The National Survey for Family Growth estimates an 8% annual failure rate, with higher rates of unintended pregnancy in certain subpopulations. Rosenberg et al estimated approximately 1,000,000 unplanned pregnancies in OC users each year. Another 600,000 women discontinue OCs each year to conceive.

- Folic acid is extremely safe and has a wide therapeutic index.

- Many women consume less than 400 μg of folic acid daily. More than two-thirds of reproductive age women do not take folic acid/vitamin supplements. The majority also do not eat ready-to-eat breakfast cereals or large amounts of processed flour products.

- These women can be identified with simple questions about cereal consumption and vitamin supplement use. Many of these women use combination OCs for the prevention of pregnancy. Women who use OCs are not intending to conceive and are less likely to use folic acid/vitamin supplements.

- OC users who experience an unplanned pregnancy could benefit from incremental folic acid consumption with an OC/folic acid product. Also, since folic acid is stored in the liver and red blood cells, chronic use of an OC/folic acid product could be beneficial to many women who conceive within three to six months after discontinuing OC/folic acid use, potentially preventing, a significant number of NTD-affected pregnancies.

- For these women, an OC/folic acid product would provide the amount of folic acid recommended by the IOM and US PHS, with negligible incremental risk and without requiring any change in pill-taking behavior.

- **In summary, the proposal by OMP/J&J PRD would address an unmet medical need (i.e., providing 400 μg folic acid daily to many reproductive age women) and would complement efforts by the FDA and US PHS to reduce the number of folic acid-preventable NTDs.**

REFERENCES