

**Food and Drug Administration**  
**Center for Drug Evaluation and Research (CDER)**

**Advisory Committee for Reproductive Health Drugs**

**December 15, 2003**

Hilton Grand Ballroom  
620 Perry Parkway, Gaithersburg, MD

Since 1998, the FDA has required the fortification of enriched cereal grain products with 140 mcg of folic acid per 100 g of cereal grain. The major impetus to this initiative was to reduce the incidence of neural tube defects (NTDs) by increasing folic acid intake among women of reproductive age.

The effect of the fortification program has been studied on a number of levels, from determination of the actual amount of folic acid present in fortified products, to changes in serum and plasma folate levels, to the effects on NTD incidence. The Center for Food Safety and Applied Nutrition at FDA has found that fortified cereals may contain anywhere from 100% to over 300% of the amount of folate noted on their labels. Several large studies comparing pre- and post-fortification blood levels of folic acid in various populations demonstrate increases ranging from about 50% to over 100%. Studies of the incidence of neural tube defects before and after the fortification program show a decrease in incidence by 19% to 54%, depending on the population studied and the specific study methodology.

There has been discussion in the literature as to whether the fortification program is optimal, or whether additional decreases in NTD rates, either nationally or in specific subpopulations, are possible through provision of additional folic acid to reproductive-age women.

The presentations and discussion will focus on the following issues:

1. Is there a need for additional population based interventions to increase further folic acid intake?
  - a. What percent of NTDs are potentially preventable by folic acid? Is there a difference between anencephaly and spina bifida in folate-responsiveness?
  - b. Will further increases in folic acid intake result in additional decreases in NTD incidence? If so, what level of increase would be required?
  - c. Will folic acid administered pre-conceptionally benefit a future pregnancy? If so, for how long will the benefit persist if the folic acid supplementation is stopped prior to conception?
2. Can we define and then identify a subpopulation among women of reproductive age that needs additional folic acid?
3. Are there any safety issues associated with folic acid supplementation targeted at reproductive-age women? If so, below what level of supplementation would safety not be a concern?
4. Is an oral contraceptive pill a reasonable delivery vehicle if additional folic acid supplementation is likely to reduce the risk of NTD? If so, what dose of folic acid should be provided?