UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

MEETING

MONDAY,
DECEMBER 15, 2003

The Advisory Committee met at 8:00 a.m. in the Grand Ballroom of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Lisa Guidice, Chair, presiding.

PRESENT:

LINDA C. GUIDICE, M.D., Ph.D.	Chair
SUSAN A. CROCKETT, M.D.	Member
PHILLIP DARNEY, M.D.	Consultant (Voting)
NANCY W. DICKEY, M.D.	Member
SCOTT S. EMERSON, M.D., Ph.D.	Member
RALPH GREEN, M.D.	Consultant (Voting)
MICHAEL F. GREENE, M.D.	Consultant (Voting)
W. DAVID HAGER, M.D.	Member
VIVIAN LEWIS, M.D.	Member
LARRY LIPSHULTZ, M.D.	Member
GEORGE A. MACONES, M.D., M.S.C.E.	Member
JAMES L. MILLS, M.D., M.S.	Discussant (Non-voting)
JOSEPH MULINARE, M.D., M.S.P.H.	Discussant (Non-voting)
VALERIE MONTGOMERY RICE, M.D.	Member
SONIA PATTEN, Ph.D.	Consumer Representative (Voting)
JEANNE I. RADER, Ph.D.	Discussant (Non-voting)
IRWIN ROSENBERG, M.D.	Consultant (Voting)
BARRY SHANE, Ph.D.	Consultant (Voting)
JOSEPH B. STANFORD, M.D., M.S.P.H.	Member
TSUNENOBU TAMURA, M.D.	Consultant (Voting)

JONATHAN A. TOBERT, M.D., Ph.D.	Acting Industry Representative
MICHIEL C. VAN den HOF, M.D., via phone	Guest Speaker
KATHERINE WENSTROM, M.D.	Consultant (Voting)
ELIZABETH YETLEY, Ph.D.	Discussant (Non-voting)
JAYNE E. PETERSON, R.Ph., J.D.	Acting Executive Secretary

SPONSOR REPRESENTATIVES AND CONSULTANTS:

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GODFREY P. OAKLEY, JR., M.D., MSPM
ANNA MARIA SIEGA-RIZ, Ph.D, R.D.

FDA/CDER REPRESENTATIVES:

DONNA GRIEBEL, M.D.
SCOTT MONROE, M.D.
DANIEL SHAMES, M.D.
LISA SOULE, M.D.

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

8:04 a.m.

DR. GUIDICE: Good morning. Would everyone take their seats, please. Good morning. I'm Linda Guidice and I would like to welcome everyone to the Advisory Committee for Reproductive Health Drugs. Today the issue will be the public health issues including safety and potential clinical benefits associated with combining folic acid with an oral contraceptive into a single combination product.

Before Jane Peterson reads the conflict of interest statement, I would like to go around the table and ask everyone to please introduce themselves and also their affiliation beginning on this end, please.

DR. TOBERT: I'm Jonathan Tobert. I'm the industry representative. I work for Merck.

DR. MULINARE: I'm Joe Mulinare from the Centers for Disease Control and Prevention.

DR. MILLS: I'm Jim Mills from the National Institute of Child Health and Human Development, Department of Health and Human Services.

DR. PATTEN: I'm Sonia Patten. I'm the consumer representative on this panel. I'm an

anthropologist on faculty at Macalester College in St. Paul, Minnesota.

DR. DARNEY: I'm Phillip Darney, Professor of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco.

DR. GREEN: Ralph Green, Professor of Pathology and Internal Medicine, University of California, Davis.

DR. CROCKETT: Hi. I'm Susan Crockett. I'm a general OB/GYN and I'm from Christus Santa Rosa Hospital in San Antonio, Texas.

DR. RICE: Valerie Montgomery Rice. I'm a Reproductive Endocrinologist and Infertility Specialist from Meharry Medical College.

DR. WENSTROM: Katherine Wenstrom, Maternal-Fetal Medicine and Reproductive Genetics from the University of Alabama.

DR. EMERSON: Scott Emerson from the Department of Biostatistics at the University of Washington.

DR. SHANE: Barry Shane from the Department of Nutritional Sciences and Toxicology, University of California, Berkeley.

DR. GUIDICE: I'm Linda Guidice. I'm a reproductive endocrinologist at Stanford University.

DR. PETERSON: I'm Jayne Peterson. I'm the Acting Executive Secretary of the Committee for today.

DR. GREENE: I'm Michael Greene. I'm a professor of Obstetric, Gynecology, and Reproductive Biology at Harvard Medical School.

DR. TAMURA: My name is Tamura from the Department of Nutrition Sciences, University of Alabama at Birmingham.

DR. ROSENBERG: Irwin Rosenberg, Professor of Medicine and Nutrition, Friedman School of Nutrition Science and Policy at Tuffs University.

DR. DICKEY: Nancy Dickey, Professor of Family and Community Medicine, Texas A&M University.

DR. LEWIS: Vivian Lewis. I'm Director of Reproductive Endocrinology at University of Rochester.

DR. LIPSHULTZ: I'm Larry Lipshultz, Professor of Urology, Baylor College of Medicine in Houston.

DR. MACONES: George Macones, Maternal Fetal Medicine and Epidemiology from the University of Pennsylvania.

DR. STANFORD: Joseph Stanford, Department of Family Preventive Medicine at the University of Utah.

DR. YETLEY: Beth Yetley, Center for Food

Safety and Applied Nutrition at FDA.

DR. RADER: Jeanne Rader, Center for Food Safety and Applied Nutrition, Food and Drug Administration.

DR. SOULE: Lisa Soule, Center for Drug Evaluation and Research at the FDA.

DR. MONROE: Scott Monroe, Clinical Team Leader, Reproductive Drugs, FDA.

DR. GRIEBEL: Donna Griebel, Deputy Director of Reproductive Drugs, FDA.

DR. SHAMES: Dan Shames, Director, Division of Reproductive and Urologic Drugs Products, FDA.

DR. GUIDICE: Thank you very much. We also have someone who is on the telephone, or will be on the telephone, and that is Dr. Michiel Van den Hof in Nova Scotia.

DR. VAN den HOF: Dr. Van den Hof here. I can hear you.

DR. GUIDICE: Wonderful. Welcome.

DR. VAN den HOF: Thank you.

DR. GUIDICE: I would like to introduce Jayne Peterson who will read the conflict of interest statement.

DR. PETERSON: The following announcement addresses the issue of conflict of interest with

respect to this meeting and is made as part of the record to preclude even the appearance of such at this meeting.

Based on the agenda it has been determined that the topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular company's product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All committee participants have been screened for their financial interest as they may apply to the general topic at hand. To determine if any conflicts of interest existed, the agency has reviewed the agenda and all relevant financial interest reported by the meeting participants.

The Food and Drug Administration has granted particular matter of general applicability matters waivers to those participants who require a wavier under Title 18, United States Code Section 208. A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office from 12A30 of the Parklawn Building.

Because general topics impact so many entities, it is not prudent to recite all potential

conflicts of interest as they apply to each member, consultant, and guest speaker. FDA acknowledges that there may be potential conflicts of interests but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jonathan Tobert is participating in this meeting as an acting industry representative acting on behalf of regulated industry. Dr. Tobert is employed by Merck and Company.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant's involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you.

DR. GUIDICE: Thank you. I would now like to ask Dr. Daniel Shames to give some opening remarks, please.

DR. SHAMES: Thank you. Good morning. Excuse my voice. I have a bit of the vocal virus. I would like to welcome everyone on behalf of the Division of Reproductive and Urologic Drug Products, today's meeting of the Advisory Committee for Reproductive Health Drugs. I would also like to thank the speakers, Dr. Guidice and our other advisors, for contributing their time and expertise.

The committee has been convened today to discuss an important public health issue, the impact of increasing the intake of folic acid by women of reproductive age on the incidence of neural tube defects.

We will be asking you if the fortification program that was put in place by the FDA Center for Food Safety and Applied nutrition can be enhanced by targeting specific subpopulations of women of reproductive age through supplementation of oral contraceptives with folic acid. I want to convey to the committee and other experts present today that we greatly value your opinions and appreciate your advice.

On that note, I would like to report that the division staff and myself are carefully reviewing your advice, the transcript and other materials

related to the Advisory Committee meeting that we convened in the fall related to drugs for female infertility.

We will be developing a guidance document on clinical evaluation of drugs for female infertility which we hope we will publish -- will have a draft publication sometime in 2004. There will then be a public comment period during which any interested party may communicate their comments to the division.

In addition, we will be meeting within a month with the sponsor whose NDA was the subject of the second day of the fall meeting to discuss scientific and regulatory approaches for moving forward with the drug product.

I will be here for the meetings today and tomorrow and will be happy to talk personally with any of the Advisory Committee members on issues specifically related to our last meeting or other topics related to the division's mission.

Finally, I would like to briefly describe today's agenda. We will hear from speakers this morning invited by the FDA and by Johnson and Johnson who will discuss the various aspects of folic supplementation. This afternoon the Advisory Committee will be asked to answer questions regarding

the need for additional interventions to further increase folic acid intake in reproductive age women.

Questions will also be posed about potential safety concerns with folic acid supplementation, the identification of specific populations that would benefit from additional supplementation, and finally the suitability of oral contraceptives as a delivery vehicle for folic acid supplementation.

We look forward to an interesting and important discussion. Thank you.

DR. GUIDICE: Thank you, Dr. Shames. Sorry for mispronouncing your name. I'm highly sensitive to that myself.

I would now like to invite Dr. Barry Shane to give his presentation on folate nutrition and metabolism and influence on neural tube defects. Dr. Shane.

DR. SHANE: Is this working? Yes. I was asked to give a general presentation on the roles of folate and how it's handled in the body with particular regard to its role in NTD prevention. I'll talk primarily about that but would like to point out that a very exciting area of folate research over the last few years has been the realization that common polymorphisms in folate dependent genes influence the

risk of a number of diseases, not just NTDs but also cancer and vascular disease.

The daily recommendations, or DRIs, for folate in the future when we have enough information may be different for various populations depending on their genetic profiles. By that I mean common polymorphisms, not individual subsets of the population.

For most people this will be very familiar. The bottom structure is a reduced folate, polyglutamate form, which is the coenzyme form of the vitamin. This is the form that functions inside tissues and it is also the form that is retained by tissues.

The top structure is folic acid which has a single glutamic acid on it and that is typical of a transport form of the vitamin. Folic acid is not found in nature. Folate is synthesized as a reduced derivative but folic acid itself is handled like other folates. It is rapidly reduced and incorporated into the folate pore.

Tissue folates are primarily polyglutamates so most of the folates in the diet are these coenzyme forms of polyglutamate derivatives and they are hydrolyzed in the gut to the monoglutamate before they

are absorbed into the body.

They are transported around the plasma and transported into tissues by two transport systems. The most common one is the transmembrane one but there is also a receptor-mediated system in some tissues such as the placenta and the blood-brain barrier that is responsible for taking folates into the tissue.

Once inside the tissue folate has to be converted to a polyglutamate form to be retained. Cellular forms of folate that are polyglutamates sometimes 500 fold higher than in the plasma because of this polyglutamalation.

Incomplete conversion to polyglutamate results in the release of the folate back into the circulation. When folate comes into the body or it goes into the tissues, any that is not converted to folate will be released usually by the liver. This is as a methylfolate form so it's partial metabolism and then released as methylfolates into plasma. Circulating folate is normally primarily methylfolate.

Tissue folates turn over quite slowly and whole body folate turnover has been estimated at between 100 and 200 days for half-life. This varies little bit depending on the folate intake. But even with high folate intakes the half-life has been

estimated to be about 100 days for overall body folate turnover.

When high levels of folates are given, plasma levels increase and there doesn't seem to be a limit to the level of folate one can achieve in plasma. But tissue folates saturate quite quickly so it's quite difficult to drive up tissue folate to very high levels.

This is not due to an inability to transport the folate into the tissue. It's a question of inability to convert enough of it to polyglutamate forms to be retained so the folate will go into the tissue and it will come out again as a mono- or diglutamate. Even if one has 1,000 times the RDA one would not expect tissue folates to go up more than about two or three fold. It's quite a narrow range for most tissues.

The folate that goes into the body when you have high levels of folate, you exceed the kidney threshold and so it would be excreted as intake folate. The folate and tissues that turn over the retain tissue is primarily turned over by catabolism. It's irreversible cleavage to other derivatives so that would not be reincorporated back into the body core.

As I mentioned before, the half-life of folate in the body, even with very high doses of folate, is still quite long so if someone is on a high folate diet, they are likely to retain a lot of that folate for a significant period of time.

This shows the RDAs. The RDAs which was set for folate a couple of years ago and for the adult woman or man it's 400 micrograms a day. This is as food folate. This does not take into account any requirement to prevent NTDs because by definition the RDA is supposed to meet the requirements of 97.5 percent of healthy individuals and NTDs of way out in the .1 percent at the top end of the scale for requirement possibly.

Now, because of this, the recommendation was made that women capable of becoming pregnant should receive an extra 400 micrograms of folic acid a day either as fortified food and/or as supplements. Because folic acid itself is more bioavailable than folate in food, this would be equivalent to about 700 micrograms of extra food folates a day.

With the fortification of the American food supply which was estimated initially to provide about 100 micrograms of folic acid a day, in fact, the average intake appears to have gone up by about 200

micrograms a day which would be equivalent to about 350 micrograms of food folate based on bioavailability. Essentially what fortification is done on average is supply people almost with an RDA extra of food folate a day in terms of folate content.

So why do we need folate? Well, this shows the three major cytosolic metabolic cycles that use folate. On the bottom left is the thymidylate cycle. On the bottom right is the purine cycle.

Folate provides one carbon for the synthesis of thymidylate and purines, precursors that are required for DNA synthesis and RNA synthesis. The reason why megaloblastic anemia is the classical symptom of folate deficiency is due to defective DNA synthesis in the erythropoietic cells.

The top cycle is methionine cycle where at the very top is the methionine synthase enzyme which is one of two B-12 enzymes that we have. If someone get pernicious anemia and becomes severely B-12 deficient, that enzyme is blocked and folate accumulate -- well, you can see the enzyme at the top is blocked and folate get trapped as methylfolate. The folate will be trapped as methylfolate here.

Because of that, there is no folate available for these other cycles so that's why if you

are B-12 deficient, you also display the same symptoms if you are folate deficient. If you trap folate in this cycle, it is no longer available for the other metabolic cycles.

I'm going to concentrate a little bit on this cycle because this has received a lot of interest for various chronic diseases as well as neural tube defects. I'll be talking a little bit later about a common polymorphism in this enzyme which produces methylfolate. That is a risk factor for a number of diseases.

So this is the methionine cycle and methionine itself is an essential amino acid. We need it in the diet. But it's a precursor for an activated form within adenosylmethionine which is the predominate methylating agent in biology.

Adenosylmethionine will methylate a large number of compounds. There has been a lot of interest in the last few years in DNA methylation and histomethylation which controls gene expression. Changes in methylation are very important during development. They are responsible for turning on and turning off a large number of genes including the X-chromosome in women.

When adenosylmethionine donates its

methylgroup in the methylation reaction, one ends up with adenocele homocysteine which is hydrolyzed to homocysteine. This can be exported into the plasma or it can be remethylated using folate.

In the folate cycle, one carbon comes from serine either directly here or by serine that is catabolized in the mitochondria and that is another pathway which I won't go into but it's an indirect pathway. One carbon form here is reduced to methylfolate by an enzyme known as methyltetrahydrofolate reductase. Then the methyl group is transferred to homocysteine to regenerate methionine. The methyl group that is used in methylation reaction is regenerated on the methionine or homocysteine backbone.

In NTDs there is an increased instance or polymorphism, which I'll refer to later, in this particular enzyme. Also there's been reports that homocysteine levels in the plasma of mothers of NTD babies is increased. So a lot of work has been going on on the genetics of this pathway.

I'll briefly mention that is what happens in most tissues. In the liver there is additional pathways, homocysteine is converted to cysteine in the transsulfuration pathway. There is also a second

enzyme which is folate-independent that can remethylate homocysteine back to methionine. This enzyme is present in humans in liver and kidney.

So if you have a deficiency or some sort of genetic change in the pathways for synthesis of methionine, homocysteine remethylation, and adenosylmethionine synthesis, what happens is the DNA is under-methylated. One ends up with elevated homocysteine and reduced methylation. This has been implicated to various degrees of certainty or uncertainty in cancer risk, vascular disease risk, possibly the demyelination that occurs in B-12 deficiency, and in NTD risk.

The thymidylate cycle if there is a deficiency in folate or a change in the cycle, there is increased uracil incorporation to DNA and this is implicated in cancer and anemia. Also there have been some studies showing or suggesting that this pathway is defective in NTDs.

The relationship between folate and NTDs, well, I am not sure but people in this room probably know better than me about whether it's the No. 1 cause of birth defects in the U.S. but an interesting aspect of NTDs is the neural tube closes in the fourth week of gestation post conception and during this period

the embryo is really dependent on the yoke sac for its nutrition.

It's very clear that peri-conceptual folic acid decreases the instance of NTDs and there have been a lot of studies over the last few years on disrupting mouse genes that are involved in folate metabolism. In a number of cases these produce the NTD phenotype and in some cases is preventable by folate. Unfortunately, these genes do not seem to be -- the defects in these genes do not seem to be the reason why humans get NTDs.

This will probably come up later this morning but this is a study from Daly, the Irish group, and Jim Mills' group. This shows the relationship of early pregnancy maternal red cell folate to risk of NTDs. There is a very clear relationship between lower red cell folate and increased risk for NTDs. I think Jim will probably discuss this later but this sort of data has been used to estimate what sort of reduction one might get in NTDs with various folate intakes.

So why does folate prevent NTDs? Well, the simplest answer is we really don't know why folate has an effect on NTDs but it is very clear that the etiology of NTDs is both environmental and genetic.

Of course, folate status being an important environmental aspect of it.

It's worth remembering not all NTDs are going to be preventable by additional folate. In the last few years common polymorphisms in various genes have been associated with NTD risk. I list two of them here, one in the MTHFR enzyme I mentioned before involved in the methionine cycle. This is a common polymorphism and it's a case risk for NTDs.

This is another enzyme involved in folate metabolism. It actually uses one carbon derived from mitochondria to incorporate into the cytosolic pore and this has been identified as a maternal risk for NTDs.

I have given a little bit of information on polymorphism in the MTHFR enzyme. It's a C to T transition which changes amino acid structure. In this country about one-third of the alleles are the variant. What we call the variant in this country and other countries is sometimes the wild-type allele.

Variant allele and the protein sequence of this particular enzyme leads to an unstable protein if folate and riboflavin levels are low. If someone has good folate and riboflavin status, then there is no phenotype associated with this polymorphism.

It's very interesting. There's a common polymorphism. In some cases over half the alleles in some populations have this variant. The effects of it are completely ameliorated by nutritional status. This is associated with elevated homocysteine, decreased cancer risk so sometimes it's good having a variant.

In the case of NTDs the Irish group have estimated that if you're TT for this variant, it could explain about 15 percent of the population risk for NTDs so it doesn't explain all NTDs but it could explain a significant portion of them. As I mentioned before, elevated homocysteine is a risk factor for vascular disease.

So as a nutritionalist we like this sort of data because when we start thinking about RDAs, we start thinking here is a classic RDI curve. At zero intake 100 percent of the population is at risk. As you increase to 50 percent of the population at risk you have the EAR for a nutrient and then at a high level you end up with an RDA for a nutrient where 97.5 percent have enough.

It's possible that with some of these common variants that the RDAs will be different for different subsets of the population which I'm sure is something

that is going to receive increased attention in the future. Thank you.

DR. GUIDICE: Thank you, Dr. Shane.

It appears that Dr. Stover is snowed in in Ithaca so fortunately in our electronic age his slides have been passed through the wires to Dr. Shane who will now present the next lecture on folic acid and safety.

DR. SHANE: Don't ask me any questions. "I'm Patrick Stover from Cornell University." The only reason why I'm giving this is because he refers to me in the talk.

Basically there are no toxicities associated with elevated folate intake. I made a sort of glib comment a few years ago that essentially there really is no data on safety. It's worth remembering that when folic acid was first isolated, it was thought to be the anti-pernicious anemia factor and it was used to treat people and it prevented -- it was effective treatment, at least it had some response with pernicious anemia patients in terms of anemia.

When B-12 was isolated a few years later, it became clear that, in fact, these people were B-12 deficient, not folate deficient. Since then you have not been able to go into a drug store and get mega

doses of folic acid and so when I say there is essentially no data on safety, for some of the water soluble vitamins we have only found out about toxicities.

Most of them are not toxic but some of them are toxic at high levels. We found out about it by people who have taken ridiculously high doses of these vitamins. There's no evidence that folate is unsafe but there have been very few cases of people taking very large doses.

We have gone through this. Patrick and I share slides. There have been three major concerns raised about increased folate intake and they are listed here. The first and probably the most important is masking vitamin B-12 deficiency.

Mask is not really a toxicity but it has unintended adverse consequences if you mask B-12 deficiency. The reason why, as I said before, increased folate will mask it because the anemia of B-12 deficiency essentially is the generation of a secondary folate deficiency.

There are many causes of B-12 deficiency. The classic one is pernicious anemia which is due to autoimmune disease. Many of the elderly have malabsorption problems for various reasons so 20 to 30

percent of the elderly may malabsorb B-12. Folic acid at intake about 1 milligram a day has a good probability of masking B-12 deficiency in the sense that it masks the symptoms of anemia.

The B-12 associated neurological symptoms are not related to folate and may be a methylation defect. It's really not known why the neurological symptoms develop. There's no evidence that folate itself will help in anyway or hinder the development of neurological symptoms.

One of the concerns about fortification or arguments about increased fortification was that the elderly were potentially a group that could be adversely affected in terms of their B-12 status. Of course, targeting to a younger population would reduce this concern significantly, although B-12 deficiency is not unheard of in the target population being considered today. Maybe about 10 or 11 percent of the cases of pernicious anemia or the early signs of pernicious anemia could be attributed to the age group of reproductively active women.

A second concern that occasionally comes up in the literature is impairment of zinc absorption by increased folate. I'm not going to go through these. I reviewed these a number of years ago. I haven't

followed the recent literature but as far as I can recall, there was really nothing to it. There was no real evidence. Tamura worked on this and there was no real evidence that increased folic intake would have any affect on the status.

There have been a number of reports that increased folate may reduce the effectiveness of some drug therapies. These are therapies involving cancer treatment or in anticonvulsants. Again, Tamura was involved in this. There's no direct evidence that folate does negate these things. In fact, the evidence on anticonvulsants is not very good that folate has an affect. The antiepileptic drugs, I think, any pregnant woman would be under the care of a physician if she was using antiepileptic drugs.

I think basically and, as I said, I'm not an expert in this area, but in terms of the toxicity of folate itself, there's really no evidence that folate is in anyway toxic. The only concern would be that it's really not been tested because no one has really looked for toxicity of folate or had the opportunity to serendipitiously observe the effect of a megadose over the last 50 years.

DR. GUIDICE: Does anyone have any questions for Dr. Shane or Dr. Stover? Maybe it's too early in

the morning. Thank you very much.

I would like to invite now Dr. Elizabeth Yetley to present on folic acid fortification in the United States, planning, implementation, and monitoring.

DR. YETLEY: Thank you. Let's see if I can figure out how to do this. Thank you very much. I am from the Center for Food Safety and Applied Nutrition. I along with Dr. Jeanne Rader, who is also on the panel, were the staff, I guess, that dealt with the mandatory fortification of certain types of food with folic acid several years ago.

This is a fairly rare event that we would have a nationally planned, nationally mandated fortification program. We've done it in a few cases with nutrients such as iron, niacin, thiamine, and whatnot, but it has not been commonly done. It is only done in response to a documented public health need. In this case, of course, the need to reduce the incidence of folate responsive NTDs by increasing the folate intakes of women of childbearing age.

In order to do this, we do not have legal authority to mandate fortification so what we do is work through our labeling authorities and we mandate that those products that were labeled as enriched,

specified products labeled as enriched, must contain specified amounts of folic acid.

We also allowed the continuation of fortification of breakfast cereals because that had been done for many years, as well as some of the meal replacements. We did not because of DSHEA put any limits on dietary supplements.

The last line has an error. We finalized our regulations in January of '96 and they became effective in January of '98 so there was a transition period between 1996 and 1998 as manufacturers geared up to meet the new requirements.

Just a brief overview of what are the characteristics of a fortification program. Once you mandate a particular nutrient to be fortified under specified conditions, it becomes ubiquitous in the food supply. That ubiquitous is an advantage in reaching the target population because you can increase their intakes without them having to do anything. It's a passive exposure on their part. It also has the disadvantage of reaching everyone who is not part of the target population.

Ubiquitous also means that because we eat about 20 to 25 different foods in a day, or at least different servings of foods in a day, very small

amounts, or relatively small amounts in a single food when added to all of the other sources from other foods can add up fairly rapidly.

Fortification is a lifetime exposure so one needs to be cautious when you extrapolate from short-term studies in terms of estimating effectiveness or safety. It is cumulative which means that the exposure is not of short term.

Our dilemma in doing fortification, as I've indicated, was that we had to make sure that the intakes were safe for all consumers because all consumers are exposed. While trying to improve to the extent possible the intakes of women of childbearing age, and as has always happened with every fortification program we've both ever done, we had considerable uncertainty surrounding every single decision that we did. We never have the luxury of a well-designed clinical trial to guide us in the process. We are always dealing with a considerable degree of uncertainty.

Just as an example, this concept of ubiquitous in the food supply, many, many foods will contain folic acid. If you had a bagel or a roll or a bun for breakfast you got folic acid. If you had orange juice you got folic acid. A serving of orange

juice will give you about 10 percent of the RDA.

I should not say McDonald's hamburger but a generic fast food hamburger according to USDA composition files will provide about 25 percent of the RDA for folic acid. It's in your pastas and casseroles which contain pastas or rices. It's in the breakfast bars and cereals. It's even in the so-called fun foods, cookies and cakes. It is ubiquitous. It is everywhere. You cannot get away from it.

This just as an illustration of the dilemma that we always have when we deal with a fortification program is that, first of all -- let me explain this. The vertical lines are the range of intakes of folate by the U.S. population. This was prefortification data. There's about a four-fold or five-fold difference between what is called the low consumer which is the 10th percentile intake of folate and the high consumer which was the 95th percentile of intake.

Our target population for increasing folate intake at the time we did this fortification program was women of childbearing age who had low intakes. This is our target population. As you can see there's nothing different about the target population than anyone else. These are other age gender groups. The

conflicting demands that we have to deal with is that as we increase the intake of our target group, it is going to increase concurrently the intakes of everyone else and shift the distribution of intakes for the entire population.

Just as a note of comment, and I don't know quite what to do with this except to give you background, is that intake distributions typically are very skewed and probably bimodal. This happens to be an old estimate of folate intake immediate post-fortification. I think the numbers are probably too low at this point in time.

The median intake for woman of childbearing age is right here so while half of the women seem to be in a group of women who have a normal distribution of intakes, half of the women have this tail that can be a very extended tail.

The fortification intervention shifted the entire curve so that one did achieve an increased intake in women at the low end of this distribution, but the high end of this distribution tends to move farther than the low end just as background and FYI for you.

This is the reverse of a graph that Barry Shane showed in terms of the nutrient function models

that we use. This one happens to have optimum health at the top, risk at the bottom. For a nutrient, when your nutrient intake is less than optimum you have increasing risk of adverse affects as your intakes go lower and lower. As a nutrient exceeds the optimum intake, higher and higher intakes are associated with higher and higher risk of adverse affects.

In this area between the optimal requirement in terms of meeting your basic requirements versus adverse affects, adding more nutrient within this range does not really give you added benefit. Keeping that model in mind, one can look at what we know about the relationship of folate intake to nutritional status, particularly relative to the NTDs as well as to upper limits. Barry Shane, again, commented on this briefly.

If you go to the Institute of Medicine's report of several years ago in which they looked at -- they established both an RDA and upper limit for folate. They in essence said, as Barry has indicated, 400 micrograms per day folate equivalents are enough to meet the folate status needs of virtually all of the population.

Then for NTDs the IOM went on to say that women should add 400 micrograms. In other words, get

to a total of 800 micrograms of folate a day in order to reduce the risk of NTDs. However, the report also notes that there is a paucity of dose response data.

In fact, there's just a little bit of dose response data from some observational studies where the reliability of those intake estimates would be of some question. There's a paucity of data. There's no dose response data between the 400 and 800. One of the significant uncertainties we have is whether or not the actual requirement for the NTDs is closer to 400 or closer to 800 or somewhere in the middle.

Also, as Barry Shane has noted, there is significant uncertainty as to what the upper limit should be. Basically there was a virtual absence of data for higher intakes, so part of the uncertainty.

Okay. Once we have done the fortification program we need to look at monitoring afterwards, particularly because of the uncertainties. We need to do post-fortification monitoring so that if we need to, we can make adjustments in the levels that we've added to the food supply.

We have always assumed, and I'll give you some data to support this, that using reports of consumers' intakes of folate will underestimate probably very significantly the actual amounts that

they are actually consuming which means that using dietary data alone we will underestimate effectiveness and we will underestimate the potential for safety. So FDA prefers to rely more in the post-fortification marketing on biomarkers of folate status and on the effectiveness as measured by changing incidence of NTDs.

Just as a little bit greater explanation on our concerns about the reliability of dietary intake data, since I think that this is one of the things that may be considered by the panel, is that we know from a number of studies, particularly intervention studies where they have actually looked at what people report they intake and then they have other measures, clinical measures of what they have actually consumed, that they significantly underestimate calorie intakes which means that since calories carry nutrients they will underestimate the intakes of other nutrients. This can be up to 30 to 40 percent depending on the situation.

We also know, and Jeanne Rader has done a lot of work with this, that the old analytical methods that have been used for food composition tables significantly under-reported the amount of folate in foods. We also know that because of FDA labeling

rules manufacturers under-report the amount of folate that are in their marketed foods.

At the same time when they are setting RDAs -- when the IOM is setting RDAs, they will err on the side of making sure that they protect everyone so prudence will have the RDA as high as possible so it protects everyone. You have the RDA that is going this way, you have the intakes with a bias that way, and the gap between the two tends to be more alarming than is actually there.

This just illustrates our concern with relying solely on dietary intake data. This happens to be data from NHANES in which we were evaluating the effectiveness of predicting iron status from dietary intake and from clinical and biochemical measures. If you look at dietary intake reports of women of childbearing age, 98 percent of the women appear to have diets inadequate in iron.

If you look at their clinical biochemical indices, hemoglobin, serum ferritins, serum transferrin saturations and whatnot, only about 4.5 percent actually had an impaired iron status. Once again, keep in mind that there is a large disconnect between what you see with dietary intake and what you see with clinical and biochemical measures.

This is not the slide I wanted so let me give you a little bit of background on this slide and then I'll give you some additional data that you can write down if you are interested. As I indicated, we like to use as much as possible clinical biochemical measures of folate status. This happens to be data from Kaiser Permanente in California in which they looked at the number of their patient samples that were analyzed for folate that went above their high cutoff for normal range and those that went below.

The time trend here is interesting. This is the date at which FDA published its regulation saying that we would require fortification of folic acid. This is the date at which it was fully effective so this is your transition period in which increasingly more and more manufacturers started to add folate to food.

What you can see from this slide is that they had an increasingly high number of their patient population with serum folate levels that were above their upper cutoff. They have data for 1999 that goes even higher.

What I intended to have on this slide but did not have was data from the National Health and Nutrition Examination Survey which is really a

nationally representative population survey in the U.S. that contains measures of nutrient status. They do have measures before fortification, of serum and red cell folate, and measures after.

If you compare pre- and post-fortification data from that NHANES survey, if you look at serum the median level went from 4.8 nanograms to 13 nanograms for women of childbearing age. Did this affect women all across the distribution? Yes. The 10th percentile folate for this survey went from 2.3 to 6.4.

What about women with higher folate status as determined by serum levels? The 90th percentile serum folates went from 11.7 to 26.1 so a doubling or a tripling of the serum folate levels. If you look at the red cell levels, the median went from 159.9 to 263.6 nanograms per mL. The 10th percentile consumer went from 92 to about 166. The 90th percentile went from 296 to 432. You can see that the serum and red cell folate levels show a very significant impact from the fortification program.

The bottom line in terms of food fortification, the advantages are passive exposure. Consumers take in larger amounts without having to take any extra -- make any changes on their part. The

disadvantages, passive exposure. You can't get away from it. As I indicated, it's a balancing act between safety and effectiveness.

In summary, these decisions are made with a great deal of uncertainty in terms of effective intakes and safety but they have made very significant impacts on folate status in terms of the U.S. population. Thank you.

DR. GUIDICE: Thank you very much.

Our next speaker is Dr. Joe Mulinare from the National Center on Birth Defects and Developmental Disabilities at the CDC. He will speak on assessing the impact of fortification on the epidemiology of neural tube defects.

DR. MULINARE: Good morning. My name is Joe Mulinare. I'm a pediatrician, medical epidemiologist. I'm the Chief of the Prevention, Research, and Health Communications Team at the National Center on Birth Defects and Development of Disabilities.

I've been asked to present an assessment of the impact of fortification on the epidemiology of neural tube defects this morning in the United States. I'm pleased to be able to give you some very good news. The facts are that pregnancies and births affected by spina bifida or anencephaly have declined

significantly since fortification started in 1998.

Hundreds of babies are being born who are now healthy and not affected by the physical and emotional toll resulting from these conditions which could have affected them and their families. As good as the news is, this decline is a fraction of what we can accomplish. Folic acid preventable pregnancies still occur and babies continue to be born with these deadly outcomes.

In my presentation today I'll focus on the following. First, I'll briefly review some of the history and you'll see some slides that you have already seen and you'll see some slides that you will be seeing.

Second, I'll review the ways to achieve adequate folate levels. I'll take Dr. Yetley's data and quickly put it into the computer and give you a figure that reflects the data that she showed about NHANES before and after fortification.

Third, I'll present data on the changing prevalence of neural tube defect in the U.S. which is the ultimate looking at how fortification and other attempts at increasing folic acid consumption have shown the decline in NTDs.

Finally, I'll make some comments on the

options for continuing our efforts to eliminate folic acid-preventable NTDs.

Spina bifida and anencephaly are severe central nervous system defects that result in serious disability and death. About one in every thousand pregnancies are affected with an NTD and we estimate that's about 4,000 NTD affected pregnancies and about 3,000 affected births per year in the United States. This was an estimate that we had prior to fortification.

There is also actually about 300,000 to 400,000 NTDs that occur worldwide. If you think about a possibility of preventing approximately 50 to 70 percent. That means that worldwide we might be able to effectively prevent 150,000 to 200,000 NTDs every year.

This is some of the history. Some of you have seen this slide before. Basically these are the studies that were done in the early '80s up until 1990 that were not randomized clinical trials with the exception of one that was conducted in Wales in 1981, that essentially show the reduction in risk from 40 percent to over 80 percent in decreased risk in having a baby with a birth defect.

In 1991 with the landmark study done in the

UK by the MRC that demonstrated that folic acid alone could reduce the risk of birth defects in women who had had a previously affected pregnancy. The recommended dose of folic acid that we used in the 1992 public health service recommendation actually recommended 400 micrograms. With the subsequent studies this dosage was confirmed in China in 1999.

This is the U.S. Public Health Service Recommendation. Many of you heard of it and know what the statements are but all women capable of becoming pregnant should consume 400 micrograms of folic acid daily to reduce their risk of a pregnancy affected by spina bifida or other neural tube defects.

Ways of achieving adequate folic acid intake included improving the diet, taking a daily supplement containing folic acid or consuming fortified foods. In many ways, achieving an adequate intake through improving diet by increasing the consumption of fruits and vegetables every day would be ideal.

It's apparent that this is difficult and expensive for most women, especially when attempting to get folate intakes up to 400 micrograms a day. The use of dietary supplements is also a very reasonable approach because folic acid pills are relatively inexpensive. I'll come back to fortification in a

moment.

Unfortunately, the education efforts in health messages by a number of federal, state, and local groups over the past 13 years have accomplished little to increase the use of supplements containing folic acid.

Here are the Gallup polls conducted through the March of Dimes. We have observed an increasing proportion of women who have heard of folic acid. In fact, it's gone from about half to almost three-quarters of the women in the United States that have heard about folic acid.

Attempts to increase knowledge about what folic acid does and when you should use it have not been too successful. In fact, only about 13 percent of women know that folic acid can prevent a birth defect. Only about 7 percent know that it should be taken prior to conception or before they attempt pregnancy.

The proportion of women who consume folic acid supplements has changed little. It's gone from about 28 percent to 32 percent over the last 10 years. Most disappointing is the fact that there is very little, if any, evidence that there is an increasing trend in use. Increases in blood folate levels or

decreases in NTD rates that we observed are very unlikely to have been influenced by women's behavior in the use of folic acid containing supplements.

Fortification, however, of cereal grain products, and increased amounts of folic acid in breakfast cereals, on the other hand, appear to have had a considerable impact on delivering folic acid to women of reproductive age.

The impact on blood folates in women of reproductive age is clear from the NHANES data that Dr. Yetley just talked about. As you can see, before fortification the serum folate levels before and after, a more than three-fold increase in the levels and a similar substantial increase in red blood cell folates from 160 to 260 nanograms per milliliter.

The ultimate measure of impact of folic acid lies in the results that we have observed in the changing prevalence of neural tube defects for the past three years. There are two birth defect surveillance programs in the U.S. that have monitored and reported changes in the NTD prevalence before and after fortification.

The first is from national birth certificate data from the National Center for Health Statistics. As you can see, spina bifida and anencephaly both have

seen a reduction or decline in the prevalence of NTDs. About 23 percent for spina bifida and about 11 percent for anencephaly. These are data taken before and after -- prevalence is taken before and after fortification for about a 19 percent overall decrease in NTDs.

The National Birth Defects Prevention Network state surveillance data base also improves on the NCHS data by actually including prenatally ascertained fetuses, fetal deaths, and some elective terminations. The results here show a 33 percent decline in spina bifida and a 14 percent decline in anencephaly for about a 25 to 27 percent decline overall.

These results demonstrate the folic acid food fortification has helped to prevent the occurrence of spina bifida or anencephaly in hundreds of babies. Because mothers of these babies consumed additional folic acid in their diet, their babies were born healthy without these birth defects and the devastating physical and emotional stresses attached to these conditions, they will not be experienced by these children, by their families, or in the community.

We estimate that there are about 4,000 NTD

affected pregnancies before fortification. Half are preventable. Approximately 1,000 babies each year are born without NTDs since fortification. We have only partially attained our goal for the complete elimination of folic acid-preventable NTDs.

Think about it. Since January 2001 if we have helped to save the lives of at least 3,000 babies, half of whom would have suffered with the complications of spina bifida costing somewhere around $300,000 to $350,000 in direct lifetime medical costs, our savings in health care costs would be about $500 million. We should be proud of that accomplishment.

We also have the opportunity to save more babies from developing these devastating conditions so that they can too live healthier lives. Our objective should be and is to do whatever is necessary to help all women of reproductive age to get 400 micrograms of folic acid each and every day.

In summary, we have seen blood folates increase substantially since fortification began in 1998 and NTD prevalence has decreased about 20 to 30 percent in the United States. Lower rates are consistent with the increase in folic acid content in fortified foods. There is little evidence available to demonstrate that dietary intake of folate rich

foods or reported use of vitamin supplements have increased appreciably.

There still exist a need to prevent the occurrence of an additional 1,000 NTD affected pregnancies, 1,000 additional babies who can be born healthy without the devastating affects caused by these serious birth defects.

More options are needed to provide additional folic acid to all reproductive age women at risk for having folic acid-preventable neural tube defect pregnancy. An esteemed colleague wrote some time ago that, "The opportunities to prevent birth defects are rare. Opportunities to prevent birth defects by an intervention as simple as taking folic acid are almost unheard of. Such an opportunity should not be missed."

We should be doing whatever is necessary to safely increase the amounts of folic acid that women of reproductive age need to prevent neural tube defects. Thank you.

DR. GUIDICE: Before going on to our next speaker, I would like to invite any questions for our previous two speakers, Dr. Yetley and Dr. Mulinare.

Dr. Rice.

DR. RICE: Have we seen any increase in any

of the vitamin B-12 deficiencies or any other potential complications while associated -- we have seen this associated decline and increase in the fortification process?

DR. SHANE: I really don't know but maybe Ralph would have more information on that.

DR. GREEN: I think the answer to the question is that there haven't been sufficient studies that have addressed the issue. Apart from the study that was published by Jim Mills and, perhaps, Jim, you can comment on that.

After your comment, I would like to have the opportunity to add something to that statement. Beyond Dr. Mills' study which examined prevalency rates of vitamin B-12 deficiency among anemic patients which, I believe, and, again, Jim, you should comment on this yourself, revealed no change. I'm not aware of any other studies. It has, of course, only been a relatively brief time that folate fortification has been in use.

DR. GUIDICE: Dr. Mills, would you like to comment?

DR. MILLS: I don't make any great claims for this study. What we did was to look at people who were having B-12 determinations done at the laboratory

in the Veteran's Hospital in Washington, D.C. Our hypothesis was that if there was a problem; that is, if they were masking, then we would be seeing more people who had B-12 deficiency but did not have anemia.

Essentially, as Ralph pointed out, the proportion of people who are identified as B-12 deficient but were not anemic has not changed since fortification occurred. I want to be the first to point out the limitations.

This population has so much neurologic disease that we were not able to determine who actually had neurological disease at the time that they were studied. That could be related to B-12 deficiency. What we can say is that we don't see more people who have B-12 deficiency coming in without anemia but what we can say is how that relates to the neurologic problems.

DR. GUIDICE: Dr. Darney.

DR. DARNEY: Philip Darney, UCSF. Do I understand correctly that there are no case reports of folate toxicity simply based on taking too much folate?

DR. SHANE: This is not my area but I'm not familiar with any case reports of folate toxicity.

DR. GUIDICE: Dr. Green.

DR. GREEN: I would just like to add one comment to Dr. Mills' comment about the limitations of his study and indicate that while I think this is a very important type of study that needs to be conducted, in my opinion a further limitation is that if you look at the overall prevalence rates of anemia in a population such as that, you would not anticipate that a large percentage of those anemias would be related to a B-12 problem but rather to many other problems.

Consequently, the background noise, so to speak, among a large group of patients who are anemic might obscure any apparent change in the prevalence rates of low B-12 levels in an anemic population.

DR. MILLS: May I clarify that? Our population was people with B-12 deficiency anemia. In other words, we looked at all people who had B-12 determinations done. Then we just studied those who had B-12 deficiencies so we're not diluting out the effects by looking at iron deficiency or folic deficiency or anything else.

DR. GUIDICE: Yes, Dr. Green.

DR. GREEN: I certainly don't wish to take too much time of the panel. Perhaps it's my

misunderstanding of the design of the study but the anemia, if I'm not mistaken, the group of patients with the anemia who were all comers regardless of whether they were macrocytic or not.

DR. MILLS: We started out with all people who had a B-12 determination done in the laboratory. From that group we identified the people who had low B-12s and that then was the population that we looked at over time to see if from 1992 to 2000 the proportion of people with B-12 deficiency who presented without anemia was the same.

Incidentally, this is a population that gets almost routine folate fortification if there is any suspicion that they had alcohol problems or anything else that would put them at risk.

DR. GUIDICE: So, Dr. Rice, was your question answered?

DR. RICE: Yes.

DR. GUIDICE: Okay. Before we go on, I just wanted to ask if anyone else had any additional information with regard to any reports of toxicity in response to Dr. Darney's question?

Yes, Dr. Tamura.

DR. TAMURA: I know only three things we should consider. One is the one case report of deep

reaction to folic acid supplementation which was published in 1960s, I believe. There have not been any other case report and we don't know exactly why it happened. That's No. 1.

No. 2 is in our department in 1970s IV injection of folic acid was done and abnormal EEG, electroencephalogram, was noticed and based on that data they suggested that it may be harmful to give folic acid to people with epilepsy.

No. 3, this is very controversial but in the 1960s and 1970s from British research groups published contradicting data on the supplementation of folic acid may cause irritability or difficulty falling asleep at night. One group said yes and one group said no so I don't think there is clear cut side effect in terms of that. In talking about the possibility of disturbance of zinc absorption by folic, I think it's settled. I don't think that is, no longer, an issue.

DR. GUIDICE: Thank you. I would like to just remind the speakers around the table after you have made your comments please turn your microphones off because it can interfere with background noise.

Yes, Dr. Greene.

DR. GREENE: I do have one further comment.

Not to belabor the point. Jim, I do apologize for extending this but I first would like to say that the points that you raised about the study as designed and I do this for clarification because, first of all, I want to state that my prior statements did have an inaccuracy clearly since this is not taking all comers with anemia.

However, I think that a substantive point still is that if you take a population with low B-12, it's generally acknowledged that with current assays there are serious limitations with respect to specificity of such an assay for B-12 deficiency. Consequently, and this is an estimate and an estimate only, between 50 percent and perhaps two-thirds of subjects who would have a serum B-12 level that is regarded in the deficient range would not, per se, be vitamin B-12 deficient but rather have a low level that is attributable to perhaps the entity known as food B-12 malabsorption prevalent among the elderly who have a chronic atrophic gastritis. Whether this is clinically significant or not remains to be determined.

Be that as it may, among that group there would also be a substantial number of individuals among the elderly in particular who would have anemia

of other cause. And if the assumption is made that low B-12 level, low by virtue of being in the low range below the normal cutoff, represented an anemia attributable to B-12 deficiency, I think that would constitute a background noise.

So perhaps in my initial statement, in fact, indeed in my initial statement there was a misrepresentation about the background noise but I think that this one is still a substantive one.

DR. GUIDICE: Yes, Dr. Mills.

DR. MILLS: I think that's a good point that B-12 deficiency is not quite as simple as a number of other deficiencies in terms of how one identifies it and the implications physiologically of having it. We were sensitive to this in terms of using two different cutoffs for B-12 deficiency based on different B-12 levels and also on where it was available looking at MMA as a confirmatory test. However, it is not a simple diagnosis and I don't want anyone to think that it is.

DR. GUIDICE: Dr. Rosenberg.

DR. ROSENBERG: I think perhaps the limitation of the Mills study for our purposes is not so much a question of whether the diagnosis of B-12 deficiency or anemia. But I remind you that the

Institute of Medicine DRIs identified as a potential adverse effect of too much folate above 1 milligram was not anemia. It was not the lack of diagnosis of anemia but the fact that there might be progression of neurologic problems.

Obviously I think the information which we would like to have with respect to the safety of fortification would be -- is not available from any of the studies that I know of which would be a change either in the prevalence or severity of neurologic problems in the populations at risk.

DR. GUIDICE: Thank you for your comments.

Yes, Dr. Greene. The other Dr. Greene.

DR. GREENE: Dr. Mulinare, I have a question for you. Assessing the impact of folic acid supplementation of the food supply on the incidence of neural tube defects is complicated by a couple of things. One is that the incidence of neural tube defects has been falling since 1960 which was obviously well before we thought about folic acid. And also the incidence of prenatal diagnosis and use of ultrasound has been increasing tending to diagnose these things and frequently the diagnosed cases don't make it to birth certificates. The question I have is to what degree can we be confident that the fall in

neural tube defects that we've seen in recent years is really due to the supplementation of food source with folic acid and not manifestation of these other trends.

DR. MULINARE: I would like to say to the folks that are running my program, please put up slide No. 32. Then I can show you some of the data that we have that would help to answer that question. Yes, the rates -- the prevalence NTDs have been decreasing since the 1960s and 1970s and a number of things have happened over those years that are logically associated with that.

One reflects in 1973 putting folic acid, 400 micrograms, or allowing folic acid 400 micrograms to be put into multivitamins. Dr. Rosenberg could talk about that because he was a member of those committees. In fact, he may have been the chair. I don't remember. That would have -- oh, it's not there. I'm sorry. Don't hunt for it.

In the 1980s and in the early '90s we appreciated the fact that prenatal diagnosis and the use of maternal alpha sera protein would actually diagnose cases prenatally. Systems were put into place. First in a couple of states and then in eight or nine states.

Some of those data I put up there reflect the use of getting information from prenatally ascertained cases of NTDs. You can see a leveling off of -- you can see a decrease in NTDs throughout the middle '80s and throughout the '90s.

When you look at data that we've gotten from prenatally ascertained cases, about anywhere from 25 to 50 percent of NTDs may have been prenatally diagnosed. We added those in to the declining rates. You could see that maybe from 1990 on the rate was relatively stable, about .8 to one per 1,000.

That has gone on since the '90s. After fortification even when you include information on prenatally ascertained cases, we have seen that 20 to 30 percent drop. We can't say that's the whole answer but we feel fairly confident that there is a contribution that has been made.

DR. GUIDICE: Thank you. Yes.

DR. RADER: May I go back a minute about the lack of toxicity data -- I'm sorry, the toxicity data that you had asked about? When we were doing our development of the documents that preceded the fortification proposal and then the final rule, we, of course, went back and tried to dig out every bit of toxicity information that we could find.

There is a surprising apparently lack of that kind of data. As Dr. Tamura mentioned, there is a few incidents of allergic reactions and some episodes were under a clinical situation. Too much folate was given and adverse things came about but usually there was an underlying B-12 problem.

When you actually go back and look at the possibility of overdosing during those years, the FDA did have a drug regulation that regulated how much folic acid would be used in a clinical setting and in the food supply in general. Since folic acid was a food additive it couldn't be added willy nilly to food so the chances of taking in high doses on your own initiative were very low.

We tried to find old data for breakfast cereals. Sometimes the cereals would have neither folate or B-12. Sometimes they would have both. The levels vary all over the place so it was a very spotty situation. You didn't have tablets and bottles where you could take huge amounts during that time.

The apparent lack of toxicity was probably as much due to the lack of being able to get it as a true lack of toxicity. I think that is an important point because it was different than some of the other B vitamins which were much more freely available and

much more freely added to foods before this fortification.

DR. GUIDICE: Thank you.

Dr. Rice.

DR. RICE: This is bringing up something that Dr. Greene sort of implied. Is there a decrease on the reporting of NTDs because of our increase in prenatal diagnosis?

DR. GREENE: If you only ascertain them for birth certificates, absolutely yes.

DR. RICE: To what extent do you think?

DR. MULINARE: The under-ascertainment from birth certificates is about 40 to 50 percent. You will not detect 50 percent of them and that is why we use in our National Birth Defects Prevention Network programs that are actually looking for prenatally ascertained cases. Depending on the program it could be anywhere from 30 to 50 percent of the NTDs that we are now finding that are related to fetal death or elective termination or still births.

I might say I was asked to talk about information from the United States but there are other places around the world that have been doing some very interesting work including in Chile where there is essentially not as much need for looking for prenatal

ascertainment.

In a recently published study they show that comparing pre-fortification and post-fortification data they actually saw about a 30 percent reduction in the prevalence of NTDs. These are among women in Chile who don't usually use multivitamins or take folic acid. The rates of NTDs have been apparently very stable up until recently.

DR. GUIDICE: Thank you. If there are no further questions, I think we can go on then. I hope Dr. Van den Hof is still on the phone. Are you there?

DR. VAN den HOF: Hello.

DR. GUIDICE: Yes. I would like to introduce you. He is the head of Maternal Fetal Medicine at Dalhousie University in Halifax, Nova Scotia and will talk to us through the wires on folic acid supplementation and fortification in Nova Scotia. Thank you.

Dr. Van den Hof.

DR. VAN den HOF: Yes. Hello. I'm just waiting for my first slide to come on. There is a little bit of a delay. Here we go. There is about a 30 second delay so if there is a mix-up in the slides, I won't know for about 30 seconds so just bear with me.

Thank you very much for inviting me to speak on our experience in folic acid. This is Canadian experience. I'm from Nova Scotia and if you don't know -- if you are not familiar with Canadian geography, Nova Scotia is on the eastern seaboard close to Maine. We have a population of just over a million people.

The next slide please. The history of folic acid has been reviewed already but, to summarize it, there were numerous studies from 1976 to 1991 suggesting the benefit of folic acid supplementation. But it wasn't really until the 1991 MRC vitamin study that someone has previously alluded to that finalized the benefit of at least high dose folic acid supplementation to reduce open neural tube defects in women with a prior history of this event.

Next slide, please. The following year Czeizel, et al. published a study in the New England Journal of Medicine that confirmed the benefit of supplementation to reduce open neural tube defects in low risk women. That folic acid was given in a multivitamin preparation. For both studies folic acid was used prior to conception.

Next slide, please. Despite the good news associated with these findings there was a

considerable lag by at least Canadian health authorities to increase public awareness about folic acid with eventual recommendations coming from Health Canada, the Society of Obstetricians and Gynecologists of Canada, and the Canadian Task Force on the Periodic Health Exam which is a forum we have to do these things. These initiatives took place between 1991 and 1994.

Next slide, please. Public health officials during this time were encouraged by the reduction in birth affected by open neural tube defects. This is a slide demonstrating the changes that occurred during that time and alludes to a point that was raised by one of the members earlier on.

Next slide. However, the reduction was due to an increase in prenatal diagnosis and women undergoing pregnancy termination. This highlighted, for us, at least, the importance of doing a very accurate population based study to define these important outcomes.

As we can see in this slide, when we took into account the increasing number of prenatal diagnostic cases with pregnancy termination, the incidence have actually not changed at all.

Next slide. The problem, of course, was

that despite the known benefit of folic acid supplementation studies including our own audits of our population, that the majority of women were actually not taking preconception folic acid supplements despite the fact that this recommendation was actually for all women capable of becoming pregnant.

Next slide, please. This eventually led to the folic acid fortification in grain products and your date to have these products fortified was January 1, 1998.

Next slide, please. In Canada fortification was actually mandated to start no later than November 1, 1998 so about eight or nine months later. It's interesting that the main driving force for Canadian fortification was not the potential health benefit but probably more related to the North America Free Trade Agreement and the free movement of products across the border.

Next slide. The question we wanted to answer was whether the recommendations for supplementation was effective. Then, more importantly was the relatively small amount of fortification also effective.

Next slide, please. This is an important

slide because in Nova Scotia we have a very stable population. As you know, in Canada we have a publicly funded health care system. In particular, for Nova Scotia there is a reproductive care program for the province. Part of their function is to maintain and run an extensive perinatal database.

In Nova Scotia we encode information on all births in the province with data being abstracted by trained registry personnel. This includes a maternal antenatal intrapartum and post-partum variables, as well as numerous neonatal data. There are up to 1,200 variables available for any case. Standardized forms that are used throughout the province help us to get consistent information and validation studies have shown the information to be reliable.

In addition, there is a provincial fetal anomaly database which captures information on all antenatally diagnosed anomalies including those that undergo pregnancy termination. All the pregnancy terminations for fetal anomalies in our province occur in one tertiary care center.

By combining these two data bases we can gather information on all births and birth defects that occur in this province allowing us to do a true population-based study.

Next slide. Open neural tube defects are described in our study, as alluded to before, as those involving spina bifida and anencephaly and those including other, the rarer forms, including encephalocele.

Next slide, please. Based upon the timing of government and institutional directives for folic acid supplementation, 1991 to 1994 were considered by us to be presupplementation because it just wasn't being used and there were not enough initiatives yet. Really, by 1994 the initiatives had been completed so we considered 1994 to 1997 the years when supplementation initiatives had been maximized but fortification had not yet begun.

Post-fortification was considered to be the years following 1998 with the understanding that there probably was a year of transition between 1997 and 1998. In our publication the post-fortification was until 2002, the publication that came out of the Canadian Medical Association Journal. Today I have also been able to include our data until 2002 and, in fact, really right through to the end of June 2003 we have data available.

Next slide. This is just again to acknowledge the debate that has gone on about the risk

of folic acid fortification with the potential to delay diagnosis of vitamin B-12 deficiency, particularly in the elderly.

Next slide. This slide shows the lack of affect from folic acid supplementation initiative in our province. There was essentially no change from 1991 to 1997 as supplementation initiatives were put in place.

Next slide. This slide shows graphically the same lack of change in the incidence of open neural tube defects during those years. Although here I have shown, again, that birth rate for open neural tube defects did drop as pregnancy terminations for antenatally diagnosed cases increased.

Next slide. With fortification there was a dramatic drop in the incidence of open neural tube defects in Nova Scotia from 2.58 per 1,000 births. We have a fairly high prevalence of open neural tube defects between 1991 to 1997 to 1.17 cases per 1,000 births from 1998 onward. The affect was seen for both anencephaly and spina bifida and was highly significant both clinically and statistically.

Next slide, please. This slides shows that the decline has been maintained through 2002 and, again, emphasizes that the majority of affected

pregnancies are being antenatally diagnosed and that women in this circumstance are often choosing pregnancy termination.

Next slide, please. Our calculations show that with the introduction of fortification there was a 59 percent reduction in both anencephaly and spina bifida with a 54 percent reduction in all open neural tube defects. This is much higher and we are obviously delighted than the reduction of 20 percent that had been calculated through theoretical model.

Next slide, please. The question is can prevention be further reduced. The study by Barry, et al. involving provinces in China had suggested that in both high and low-risk populations there was the potential to have reductions as low as .6 for 1,000 births. If this figure and this number were correct, then there is the theoretical potential for another 40 percent reduction in our population.

Next slide. Finally, this slide summarizes the affect of folic acid fortification and supplementation in Nova Scotia between 1991 and 2002. No affect from supplementation initiative but a fairly dramatic drop with fortification as a temporal relationship. That affect was with anencephaly and spina bifida but not necessarily for rarer forms of

open neural tube defects including anencephaly. Thank you.

DR. GUIDICE: Thank you very much. Are there any questions for Dr. Van den Hof?

Yes, Dr. Rosenberg.

DR. ROSENBERG: Dr. Van den Hof, I'm not sure if you can hear me but maybe we can transmit this. Is there any evidence from your interesting and promising study that there is an increasing affect over time since 1998, or does it appear as though the affect of fortification was achieved within the first year or two and now has stabilized at a new level, or is there any reason to expect that over time there will even be greater affect of the intervention?

DR. VAN den HOF: Well, our hope had been with the original description of numbers up to 2,000 that, in fact, the 54 percent reduction was perhaps minimal. But it seems that as we analyze the data going in through 2000 and even through to the first half of 2003 that, in fact, it appears to be stabilizing.

Of course, it's going to take a number of years further because there are natural variations in incidence for neural tube defects beyond the influence of folic acid that have to be taken into account. It

appears that the incidence is stabilized as was originally described.

DR. GUIDICE: Dr. Macones.

DR. MACONES: Hi. George Macones from Penn. Just a quick question. It seems to me that there are really two levels of recommendations for folic acid supplementation, if you will. One is for women who have had a prior affected child where we talk about the 4 milligrams, and then there is obviously the goal of the fortification program which is more focused on women who have not had a child with a neural tube defect in the past.

It seems to me that the data that you present really aggregate both of those. I was wondering if you could separate out the affect of the supplementation which, again, I believe is focused more on women who have not had a child with a neural tube defect in the past.

DR. VAN den HOF: Well, the vast majority of cases of open neural tube defects, despite the high risk for recurrence, the vast majority of cases for open neural tube defects continues to be in the low-risk population. That is the case for our population as well even though our background risk for open neural tube defects had always been higher than the

world population.

I think the recommendations for supplementation certainly within our population had been directed not -- had been directed most strongly in the area of patients who had previously affected pregnancies, but there was also a major public initiative for the low-risk population because this is where the majority of open neural tube defects occur. I don't think that is any different really.

DR. GUIDICE: Okay. There are two questions over here. Dr. Emerson and then Dr. Wenstrom.

DR. EMERSON: I was sort of interested in your -- I think this follows up on Dr. Macones' question. Your data seems to show a much -- I'm extrapolating wildly here -- a larger decrease for the live births rather than the terminated pregnancies.

Is there a tendency for the screening for neural tube defects that might lead to the terminated pregnancies to be at a higher risk population and is that perhaps evidence that what you're asking is that we're seeing a more dramatic affect in just a subset of the population rather than in the entire population which, I guess, goes with the idea of the genetic component and that there is some neural tube defects that can't be addressed with folate supplementation,

and is there a lot of room for a lot more improvement?

DR. VAN den HOF: No. Again, I think my own personal feeling is from our population the majority of the affected pregnancies are not coming from patients who have had previously affected pregnancies or babies.

The majority of our population are still coming from patients who don't have a prior history, either personal history or family history, and the patients who undergo pregnancy termination aren't necessarily those who have had previously affected pregnancies either.

I think it does highlight the importance, though, of antenatal screening and the importance of prenatal diagnosis. The vast majority of antenatally diagnosed neural tube defects, in fact, is through routine screening at 18 to 20 weeks. A very small number are further supplemented with the alpha fetal protein screening but that is actually a much less favorable way to screen.

DR. GUIDICE: And there was a second part of Dr. Emerson's question and that was whether or not there was a --

DR. VAN den HOF: Sorry. You'll have to repeat that.

DR. EMERSON: The question I had was how much more room do you think there is for improvement?

DR. VAN den HOF: I think that we probably have more room to improve. I mean, I think one of the questions that we had when we finished as we do our ongoing analysis for our population is the fact that perhaps we are going to see a larger drop in risk because we, in fact, had a higher background prevalence to start with.

The fact is that perhaps we may have an ability to have a further reduction of theoretically as high as, I believe, 40 percent. Certainly my own personal bias has been that, you know, I would like to see us try to increase the folic acid exposure to our entire pregnant population so that I can maximize the reduction in risk.

I think certainly for our population there may be room for further reduction and I think that is the goal we should go for.

DR. GUIDICE: Thank you.

Dr. Wenstrom.

DR. WENSTROM: You've seen both a greater reduction and prevalence after fortification and before fortification you had a greater prevalence of NTDs than we have here. I'm wondering if that's

because the MTHFR mutation is more prevalent in your population. Do you know what that is compared to its prevalence in the United States?

DR. VAN den HOF: Yes, we have studied that. That actually is probably the case. I'm certain there are areas within the U.S. where there are probably areas of higher prevalence. Part of it probably relates to the ethnic background for the population, so that in Nova Scotia the population basically comes from Wales and Scotland and Ireland, all areas that are known to have perhaps a slightly higher background risk for the gene mutations, and also over the years have been known to have a high prevalence of neural tube defect. I think the observation is correct.

DR. GUIDICE: Thank you. Thank you very much, Dr. Van den Hof.

DR. VAN den HOF: Thank you.

DR. GUIDICE: Our next speaker is Dr. James Mills and he is the Chief of Pediatric Epidemiology at the Division of Epidemiology, Statistics, and Prevention Research at NICHD at NIH. He will be speaking on what is the minimum effective dose of folic acid for preventing neural tube defects.

DR. MILLS: Thank you. As you can see, I was asked to talk about the minimum effective dose and

I would like to start out by acknowledging my college Dr. Caroline Signore who is sitting by the door there who contributed a tremendous amount to this talk.

I will cover basically four areas. One of the charms of going last is you get to edit your talk as you go along because of all the things people have already said. Given that, I'm going to talk about why this is a difficult question to answer and what we can do to estimate how much folic acid is needed to prevent neural tube defects. I'll talk about some of the actual experience with fortification and then summarize.

First, why is it a difficult question to answer? Well, it actually could be a very easy question. That is, you could simply take a very large group of women who are planning a pregnancy and give them doses until you got down to a dose where they started to have a lot of children with neural tube defect.

Of course, there is only one problem with that approach and that is that it's highly unethical. I don't think anyone is ever going to do that kind of study which leaves us with trying to answer the question in an indirect way.

Now, we know something about effective dose.

We know from the clinical trials that there are some doses which absolutely work. From the MRC trial 4 milligrams works. From the Hungarian trial 800 micrograms works. The problem is I think most people would agree that those are too high to use as a target dose for the general population.

We then move to a slightly lower quality level of evidence, case control studies. There are a number conducted in the United States. Women were taking the standard multivitamin which had 400 micrograms. These all showed that 400 micrograms could effectively prevent neural tube defects as well. The question I think is more are lower doses than 400 micrograms also going to be effective.

Now, before we even try to address that, I want to mention one other complication, and that is as Dr. Shane discussed earlier, the MTHFR 677 T variant has a major affect on folate metabolism. As you can see from our work in Ireland, those people who have the wild-type CC will have on the average a much higher red cell folate than people who have the homozygous mutant TT type. This is just one other complication we have to deal with.

Now, how can we estimate how much folic acid is needed? Well, the first attempt to do this was

also mentioned by Dr. Shane and this was Dr. Leslie Daly's work in Ireland where he used a cohort of 56,000 pregnant women in Dublin who were used then to do a nested case control study of neural tube defects.

The 84 women who produced children with neural tube defects were compared with 266 normal control women to see how their red cell folate levels compared. Dr. Daly constructed a logistic regression equation to look at the relationship between your level of red cell folate and your risk for having a child with a neural tube defect.

You've already seen this graph which essentially shows that your risk for having a child with a neural tube defect decreases very dramatically as your red cell folate level increases going from people who were essentially in the deficiency range of red cell folate with a risk of 6.6 per thousand pregnancies of having neural tube defect offspring to 0.8 NTD pregnancies per thousand when your red cell folate is greater than 400.

Now, you notice in this slide there's a little piece missing here. The problem is that there were not sufficient data to look at the most interesting part of the curve for our purposes and that is how much more decrease in neural tube defect

risk do you get as you increase red cell folate. One possibility is that the curve continues down and that you can get a risk as low as 0.2 NTD pregnancies per thousand.

The other possibility is that this levels off. We do know that the curve has to flatten out at some point because there are things like trisomies and other Mendelian defects which are simply not going to be folate preventable. Perhaps the optimal situation is 0.5 per thousand. However, we do know for certain from this analysis that 400 nanograms per mL, the red cell folate level is highly protective against neural tube defects.

So how much folate acid then would a woman need to be exposed to to raise the red cell folate to these levels that would be protective? Well, this is a study we did in Dublin at the Coombe Maternity Hospital with Dr. Sean Daly, another Daly. This was a randomized double-blind placebo-controlled trial with different doses of folic acid to see how much it took to raise women's levels to what would be considered a protective level. 121 women who worked at the Coombe hospital received either a placebo, 100 micrograms, 200 micrograms, or 400 micrograms of folic acid a day.

One of the advantages to the study design is that the women could come into the cafeteria, take the vitamin, sign a sheet indicating that they had taken it. For at least five days a week we had pretty good data on compliance.

Now, the results looking at red cell folate showed, luckily for us, that if you took a placebo you didn't change your red cell folate significantly. We would have been a little nervous if that had shown a change. But then as you increased your dose of folic acid, you had a significant increase in your median red cell folate, 100 micrograms producing an increase of 67 median, 200 micrograms per day an increase of 130, and 400 micrograms per day an increase of 200. Again, highly statistically significant.

So we were able then to use these data and plug those into the equation that the other Daly, Dr. Leslie Daly, had calculated to drive an estimated change in neural tube defect risk. In other words, how much would this increase in red cell folate drop your risk for having a child with a neural tube defect.

Once again, a placebo, of course, had no affect but a 100 microgram dose per day reduced the risk for NTDs by approximately 22 percent. 200

micrograms reduced the risk by 41 percent and 400 by about 47 percent.

Now, one of the important points to make here is this is a minimum estimate because, don't forget, this depended on the women's compliance. Unlike the fortification situation where you couldn't avoid getting folic acid if you wanted to, these women had to take the pills. Our estimate then would be that if you receive approximately 200 micrograms per day of folic acid, you would decrease your risk for having a child with a neural tube defect by about 40 percent.

Now, another approach to this was published by Dr. Nick Wald who reviewed all the literature on studies of folic acid supplementation and reporting on serum folate levels. He essentially constructed a mathematical model based on these trials to calculate a dose response relationship. This is essentially what Dr. Wald came up with. It's interesting that the people who were between age 20 and 35 had a smaller increase in serum folate for a given dose of folic acid than the people who were age 40 to 65.

Now, there are some problems, I think, with this study and one of them was that if you look at the predicted plasma folate levels from this study, they

were far lower than what was actually seen in the NHANES study that Dr. Yetley and some of the other speakers alluded to where it was estimated that women were getting about 200 micrograms per day of folic acid by food fortification.

The other, as you can see, is the effects were rather different, I would say probably inconsistent, by age. Why would this be? Well, first of all, the obvious differences in these studies that Dr. Wald used also depended on compliance so that compared to fortification you would probably see a lower increase in serum folate where the women had to take the tablets than you would in a fortification situation.

But I think the more interesting issue is that the studies that Dr. Wald selected for the model probably had an insufficient duration of exposure to reach a stable folate level. That is to say, if you don't wait long enough, you don't see the maximum affect on serum folate.

This is shown on the slide which comes from a report by Quinlivan and Gregory summarizing the literature on how long it takes to reach a stable level. You'll note that if you take a lower dose of folic acid per day, that's 200 micrograms or less, it

takes you about six weeks to get a stable blood level. If you take a higher dose, 400 or more, it can take 12 to 14 weeks so that has to be taken into account.

Now, if you translate this into the studies that were used in the Wald analysis, in the younger age group interestingly only two of the six studies, or one third, were of adequate duration to reach the stable folate level that you would need. In the older population half of the studies were long enough to reach the stable level. Over all fewer than half of the studies were of sufficient duration.

Now, that would explain the findings here. That is to say, the lower response of the younger age group could be because the studies didn't wait long enough to see what the total affect of the folic acid would be. In summary, the studies used in this model would lead to a systematic underestimation of the affect of folic acid on serum folate.

Now, what do the current exposure levels contribute to this? Well, this has been discussed somewhat before so I'll just show some summary slides. The FDA originally estimated that food fortification would increase the women of childbearing ages exposure to folate acid by about 100 micrograms per day.

A number of other people have used clinical

data and laboratory information to create their own estimate. These have shown, I would say, on the average about a 200 microgram per day or greater estimated effect.

So how has fortification actually affected levels? Since Dr. Shane was Dr. Stover, I'll be Dr. Yetley for a minute. This is the slide that you didn't have today which shows that in the best study, which is women of childbearing age and a representative sample of women, that the level was 4.8 before fortification. Fortification added an additional 8.2 to serum folate levels for a total of 13. I note that's 171 percent increase.

Just to amplify that a little, this was the data from Kaiser Permanente which was essentially just specimens that went to their laboratory and from Dr. Rosenberg's group from Framingham, all of which showed a dramatic increase.

The same is true of red cell folate levels and this, again, is a representative sample and shows a 65 percent increase in red cell folate following fortification. These data, I think, are of relevance because this is Canadian. Dr. Joel Ray in Canada showed a very similar increase which suggests that their exposure seemed to be somewhere to ours.

So to summarize this portion of the talk, fortification probably increases folic acid exposure by 200 micrograms a day or more in women of childbearing age and red cell folate levels by the best measures through the HANES have shown that serum and red cell folate have increased by 171 percent and 65 percent respectively. A very significant increase.

Now, how does this work in terms of actual experience with fortification? The gold standard is obviously how much would this additional 200 micrograms per day decrease neural tube defect rates because that's what it's really all about. If this is decreasing the rates to where we want, then that pretty much answers the question as to what the minimum effective dose is.

Now, to amplify what was discussed a little while ago by Dr. Green and others, one of the big problems that we face, and this is from South Carolina data from Roger Stevenson, is that very few neural tube defects first come to attention at delivery. If you notice, in their population 17 percent, which means that 83 percent were detected prenatally.

If you don't have a very good system in effect and didn't have a very good system in effect prior to fortification, you are going to miss a lot of

these cases and you are going to get rates that may not be quite accurate.

That's why I think that the last talk was so important because in Nova Scotia they had all of these. They had the live births. They had the still births. They had the terminations. Nova Scotia is a very insular, in the positive sense of the term, area so that it's possible to identify cases, not to have people go to the next state or the next county or elsewhere for diagnosis and to get a very good picture of the total experience.

As was also mentioned, their fortification is very similar to the U.S., 150 versus 140 micrograms. As noted, their incidence fell by 54 percent. I would say this suggest that 200 micrograms, or somewhat more than that, is capable of decreasing the NTD risk by over half so that the estimated effect in the Canadian population would be a 50 percent reduction given their current fortification levels. There are other data from Ontario to back up the Nova Scotia experience.

I would also argue that if we had U.S. data with comparably ascertained cases that we might very well see the same thing. One of the problems that we have in the U.S. is that we don't have the kind of

system that enables us to do that kind of a thorough investigation.

So, in conclusion, it's difficult to pinpoint the lowest effective dose of folic acid. However, our study from Ireland indicates 200 micrograms a day would prevent, or should prevent at least 40 percent of NTDs in that population. Now we know that actual experience in Canada indicates that 200 micrograms a day plus will probably prevent 50 percent or more of neural tube defects.

Now, one of the key questions for this group, I think, is that in the U.S. approximately 50 percent prevention may be the maximum. However, it may be possible that 70 percent are preventable. We don't know if the current level of fortification would mean that we have maxed out on our ability to prevent neural tube defects or if it would be possible to prevent more.

To focus the conclusions on our current discussion, given food fortification and supplement use in the U.S., many women are already at a level where they will not need fortified oral contraceptives. For women who are using supplements, fortified oral contraceptives might actually put them over the Institute of Medicine's recommended limit.

However, for other women who do not take supplements and who less fortified food, fortified oral contraceptives could be very beneficial. Thank you.

DR. GUIDICE: Thank you, Dr. Mills.

Yes, Dr. Crockett.

DR. CROCKETT: Thank you, Dr. Mills. I have a couple questions for you. I want you to go back to the study that you alluded to by Dr. Wald, the meta-analysis of the changes in the folate levels in the age groups and supplementation. You had showed a graph that showed that the age group of 20 to 35-year-olds had less of a change over time with supplementation than the older age group. I was wondering how much of that was due to their levels being higher to begin with compared to the older age group.

DR. MILLS: I don't recall whether that's in Dr. Wald's paper. That could be answered by going back to the original studies that he included. Does anyone know that?

DR. CROCKETT: Okay. I think that is particularly fascinating since the topic of our conversation is targeting that age group of 20 to 35 years.

The second question I had, and it may seem kind of like an obvious thing but it doesn't seem obvious to me, is at the very beginning of your talk you said that the higher doses, the 4 milligram or the 800 microgram cases definitely work but they are too high. In light of the discussion that we've had about the lack of toxicity of this drug to either the mother or the unborn child, I was wondering how we determine that those doses are too high?

DR. MILLS: First of all, I don't think that lack of evidence on toxicity is the same as evidence on lack of toxicity. That is the first issue there. The second is that in order to get the general population of childbearing age women up to 800 micrograms a day, you would have to put an enormous amount of folic acid into food because, as Dr. Yetley pointed out, people eat varying amounts of fortified food.

It would require an enormous quantity of folic acid and it would clearly put a number of people, a very large number of people in the elderly age group above the Institute of Medicine's safe upper limit so that you put a lot of people at risk for masking B-12 deficiency if you were to do that.

DR. CROCKETT: Yes, but if we're talking

about specifically putting it in oral contraceptives which are not going to be affecting that older population, how do we then apply the upper limit of the dosing to that population?

DR. MILLS: That reduces the risk for masking B-12 deficiency substantially. As Dr. Shane mentioned, about 10 percent of the people who have pernicious anemia are in the age group of interest to us so it doesn't eliminate that risk. Then I guess you just have to decide if the number of people in that risk group is sufficiently high that you would hesitate to fortify oral contraceptives with that larger dose.

At some point, by the way, this might be a good time to introduce this, I want to mention that there is an abstract that was just recently published from the Society for Reproductive Medicine reporting on use of methotrexate to terminate ectopic pregnancies medically. They found that people with higher blood folate levels were more likely to fail on the course of methotrexate.

Although it's just an abstract and I haven't seen the paper on it, it is something that we have to keep in the back of our minds in terms of the potential problems that we could create by raising

folate exposure very high.

DR. GUIDICE: Yes, Dr. Wenstrom.

DR. WENSTROM: My question involves how alcohol affects how much folate we absorb from fortification. When I saw that -- when I read Nick Wald's study, it occurred to me that maybe young people aren't seeing the effect because of alcohol use.

Other studies in which folic acid is given to reduce the levels of homocysteine have shown that when you use alcohol the resulting acid aldehyde breaks down folic acid in the gut and you absorb a lot less. But I'm not aware of any studies that have looked at that in terms of prevention of neural tube defects. Do you have any data about that?

DR. MILLS: I don't know of any published data whatsoever on alcohol in relation to folic acid and neural tube defects. Does anyone else?

DR. SHANE: There is some data on alcohol affecting the retention of folate in the body. I believe kidney retention. I'm not aware of any information that alcohol affects folate absorption per se.

DR. WENSTROM: Well, there is one big study looking at the folate supplementation and the

incidence of colon cancer, for example, that show that folate was protective in people who did not use alcohol but it was not protective if you used at least 15 grams of alcohol because that broke down folate.

Then I have also seen it, as I said, in relation to homocysteine levels. I have always wondered if we should be recommending more of supplementation for reproductive age women who use alcohol but I haven't seen any data on it.

DR. SHANE: It's complicated because that's an epidemiological study and it's interpreted by epidemiologists in terms of mechanism. There is no direct evidence that alcohol does any of these things. Alcohol in those studies influenced some of the outcomes. For some of those epidemiological studies looking at folate and vascular disease alcohol obviously has an affect on that. There might have been some affect of folate.

In terms of the colon cancer, it is interesting that the MTHFR phenotype, the so-called mutant allele, is protective. It is also protective at high folate, the affect, so it's not a question of low folate where you would expect to see the phenotypic effect.

There was some effect of alcohol in that

study but I think it's a stretch to interpret then when you are looking at the effect of alcohol and looking at the folate on colon cancer incidence risk to interpret the interaction between those two from the epidemiological studies.

DR. GUIDICE: Dr. Rice and then Dr. Green.

DR. RICE: Nobody has really spoke about this but I have a question on the Daly study. When you all looked at -- when it was looked at the subgroup that had the maximum levels of folate and RBCs in the serum, what was the outcome of those infants? Have there been any fetal affects that we've seen in patients who do have those higher levels in their serum or on the RBC folate? That's my first part.

DR. MILLS: The Leslie Daly study looked at an NTD rates as a function of red cell folate level. They did not go back and look at the individual infants to see if the ones who had NTDs despite the mother having a high red cell folate level were in any way different from the ones whose mothers had low red cell folate.

DR. RICE: How about any other fetal effects? Has any studies looked at that? Nobody has really looked at that?

DR. MULINARE: With the community intervention trial that was done with 400 micrograms of folic acid in China. They followed somewhere between 5,000 and 10,000 children of mothers who received 400 micrograms of folic acid. They have only looked at the early years and haven't seen any differences in development between those children that were exposed to folic acid in utero versus who were not.

DR. RICE: And then my second question, and maybe I should know this back from medical school, but I'm assuming that folate gets into the red blood cell by binding to some receptors, etc. Don't you end up saturating? Don't you get to a point where you can't raise the level any higher?

DR. SHANE: Well, it gets in by transporter but it gets in not as folic acid but as a reduced folate just like any other folate. A lot of folate binds hemoglobin so it sort of sops up folate so you can get very high levels in the red cell because of that.

It's difficult to saturate the red cell with very many things. This is like albumin and plasma. The hemoglobin in the red cell tends to bind lots of different things.

DR. RICE: In some studies where they have given patients injections, do you get to a point where you plateau out the serum level? When you measure the serum level don't you get to a point where it plateaus?

DR. SHANE: This has been done primarily in human studies primarily in terms of using leucovorin as a rescue therapy or in cancer treatment also to help FU treatment. A lot of experimental models have been looked at. It's very difficult to raise folate levels, say, in an experimental tumor but the folate levels in plasma will go through the roof if you give high levels of folate. There is almost no limit to how high you can get plasma folate if you give very huge doses of folate or any kind of folate to a person.

Red cell folates can go to very high levels but as you saw in the studies here, they do not go up in these studies of fortification to the same degree that plasma levels go up. I believe there is a theoretical limit to how much folate can be stored in the red cell. In tissues primarily you can't get it up as high as the red cell.

The reason why red cell is a very popular way of looking at folate status is from looking at the

history of folate status over a period of time. That is why people tend to think red cell folate is more accurate if someone is long-term status than measuring a single plasma level.

DR. RICE: Is the red cell also the most important in determining toxicity if we would be able to determine that or has that been determined based on serum?

DR. SHANE: I think it's dangerous looking for red cell because you are looking at a cell that is in various states of dying however long it's been there. In people with the TT, the double modified allele of MTHFR, their folate distribution of red cell is very different usually than in people with the so-called normal. They have a different folate distribution.

This does not seem to be that clear cut that you have this difference in tissues but you do find in the red cell. That may just reflect that whatever enzymes are in the red cell during this period in circulation is gradually dying and you are losing enzyme activities, cytosolic enzyme activities. I don't think the red cell is a particularly good indicator of toxicity. Others may have a specific example where they think it might be but I can't think

of any.

DR. RICE: So you would use the serum level?

DR. SHANE: I would not use those as measures of toxicity. I don't think a high level of folate is an indication of toxicity. The only concern I've really had about toxicity per se was that it's just never been looked at. As I think Jim mentioned before, people have not been exposed chronically to very high levels of folate in the past. You would have to take every pill in a bottle of vitamin pills to achieve megadoses of folate.

DR. GUIDICE: Thank you.

Dr. Green.

DR. GREEN: I have two comments. First of all, in relation to the question that Dr. Crockett raised and was addressed by Dr. Mills with respect to the at-risk population in terms of B-12 deficiency among women of reproductive age and that is merely to point out in addition to that number which is in the order of about 10 percent of all patients with pernicious anemia that there is a distribution among those that is different according to ethnic group according to several studies, most notably that of Carmel and Johnson who demonstrated that the occurrence of pernicious anemia among the Hispanic

population and the black population tends to affect older and, in particular, female patients.

Then just a brief addition to Dr. Shane's comment. This is actually contained in the information that was distributed as preparatory information for this hearing with respect to the protective effect of the common MTHFR polymorphism.

It has been demonstrated not only for colon cancer but also for acute lymphoblastic leukemia in children that the common TT homozygous mutation or polymorphism confers some protective effect with respect to the occurrence of acute lymphoblastic leukemia. To my knowledge, there has been no demonstration similar to the one that Dr. Shane referred to with respect to the protective effect of folate in those individuals who are TT.

In other words -- no, I'm sorry. Let me change that and say the protective effect of folate in those individuals who are CC who would appear otherwise to be at increased risk.

In other words, to clarify this, as long as the TT individuals have adequate folate nutrition since, as we heard from Dr. Shane, their folate levels are generally lower, as long as they have adequate folate, then they have the additional conferred

protection against colon cancer. I'm not aware of a similar study with acute lymphoblastic leukemia.

DR. GUIDICE: Thank you.

Dr. Tobert.

DR. TOBERT: With regard to Dr. Shane's point about the lack of clinical trial data with high doses of folate beyond the U.K. MRC trial, I just want to make the committee aware there is an ongoing trial being conducted in Oxford, the so-called SEARCH trial. That trial is designed to test the homocysteine-lowering hypothesis.

It started in 1998, 12,000 patients being randomized to a two-by-two factorial, but the arm of interest here is to two milligrams of folic acid but it's with one milligram of B-12. Still, it's 6,000 middle aged people who are getting 2 milligrams of B-12. Those data should be reported in 2005.

DR. GUIDICE: Thank you. We have time just for a couple of comments. I think Dr. Rader had a question or a comment but I think Dr. Shane has a direct response to the comment that was just made so please go ahead.

DR. SHANE: I would just like to add that the VISP trial, which was concluded which was on a more elderly population, stroke recurrence rate. I'm

not sure if it's published its data but it will have data on 3,600 people, I believe, who have been exposed to similar levels of folic acid. As far as I'm aware, they have not found any toxicities associated with the administration of folate.

DR. GUIDICE: Dr. Rader.

DR. RADER: I had a very short question for Dr. Mills. I was interested in your comments about the Wald paper. When you recognized the inadequate length of duration of some of the studies, when you took those out were you able to recalculate the data that was left that was adequate to see if those two lines were going to be possibly super imposable or, at least, more parallel?

DR. MILLS: No, but I would be happy to have you do that if you would be interested.

DR. RADER: I may take you up on that. Thank you.

DR. GUIDICE: Thank you. I'd like to thank all of the speakers for the very informative talks this morning. We'll take a 10 minute break so that we can then hear from the sponsor. Thank you.

(Whereupon, at 10:25 a.m. off the record until 10:37 a.m.)

DR. GUIDICE: Would everyone take their

seats, please. We would like to go on with the rest of the morning session. Please take your seats so we can get started. Thank you.

I would like to also welcome one of our committee members, Dr. David Hager. Glad you could make it.

The rest of the morning session focuses on invited sponsor presentations. The first speaker will be Dr. Andrew Friedman who is director of Women's Health Care Research at Ortho-McNeil. He will present a proposal background and overview

Dr. Friedman.

DR. FRIEDMAN: Thank you, Dr. Guidice, members of the panel. Good morning. On behalf of our organization, we are pleased to have this opportunity to review our proposal for a combined oral contraceptive-folic acid product.

I just wanted to remind the committee members that this is actually not a typical advisory committee meeting where you may be asked to review NDA data to make decisions or recommendations about whether to recommend approval of a drug or whether to remove the drug from the marketplace. Rather, the purpose of this meeting is to review a concept. In this particular situation it's the concept of

combining folic acid with an oral contraceptive product.

Now, at first blush this concept may appear to be counter-intuitive. Why would somebody want to combine something that prevents pregnancies with something that prevents birth defect? Initially it doesn't seem to make sense, but as you'll hear through our series of speakers throughout the remainder of the morning. This concept makes perfect sense.

Folic acid preventable neural tube defects are still occurring in the United States. We've heard that from a variety of speakers this morning. Such a combination product would be able to prevent additional neural tube defects. We are not here to discuss the clinical development plan which will be discussed with the FDA at a later date.

Now, such a combination product would be used primarily by women who elect to use oral contraceptives as their method of contraception and who are currently not taking multivitamins or folic acid containing supplements. This would be the primary target population.

Over the next hour to hour and a half we'll be hearing information and data from a variety of speakers to support the need for such a proposed

product. I will initially address with you our proposal background and overview.

After I speak you will hear from Dr. Godfrey Oakley who is the former Director of the Division of Birth Defects and Developmental Disabilities at the CDC and currently visiting professor in the Department of Epidemiology at the Rollins School of Public Health, part of Emory University.

I should add that Dr. Oakley is a recently elected member of the Institute of Medicine. Dr. Oakley will be talking to you about the efficacy and safety of folic acid for the prevention of neural tube defects.

Following Dr. Oakley's talk you'll hear from Dr. Anna Maria Siega-Riz who is Associate Professor of Maternal and Child Health and Nutrition at the School of Public Health at the University of North Carolina in Chapel Hill. Dr. Siega-Riz will talk to you about the need for increased folic acid intake among reproductive-age women.

Dr. Andrew Kaunitz will then address the group. Dr. Kaunitz is Professor and Assistant Chairman of the Department of Obstetrics and Gynecology at the University of Florida Health Science Center and has worked on some of the ACOG practice

bulletins as they pertain to oral contraceptive use. Dr. Kaunitz will address the group on oral contraceptive use in the United States, pregnancy intendedness and its relationship to folic acid intake.

I will then return to the podium and present a brief summary and some concluding remarks.

We've heard about neural tube defects this morning. In the United States they are the second most common group of serious birth defects, second to cardiovascular birth defects. The neural tube forms in the embryo between days 18 and 28 following fertilization. Failure of the neural tube to close will result in a neural tube defect.

This slide shows two rather disturbing pictures of the more common neural tube defects, spina bifida and anencephaly. Spina bifida occurs when the neural tube fails to close, the lower portion of the neural tube fails to close.

The majority of these infants will survive approximately 80 to 90 percent, but this is a life-altering congenital anomaly often leading to lower body paralysis and sensory loss, loss of bowel and bladder function, hydrocephalus which in turn may lead to multiple operations and multiple hospitalizations.

There is immeasurable personal and family cost caused by children and those around them who are affected by this disorder.

The average total lifetime cost for medical care for this disorder has been estimated to exceed a half a million dollars, and exceeds more than a million dollars in many instances.

In contrast anencephaly results when the upper portion of the neural tube fails to fuse and, in fact, the majority of the brain and brain substance fails to form. In this instance the children -- this is a uniformly fatal disease with fatality occurring either early in pregnancy ending in miscarriage, later in pregnancy ending in stillbirth, and in rare cases where there is a live birth, there will be death shortly thereafter.

We've heard this morning from a number of speakers how folic acid may actually prevent the vast majority of neural tube defects. These are largely preventable by adequate intake of folic acid if folic acid is started prior to pregnancy, and that's a very important point in terms of when folic acid should be started.

We've heard estimates this morning from a number of speakers that the approximate rate of neural

tube defects in the United States is about one in 1,000 or 10 in 10,000. There are estimates that may be higher or lower than this but this is the generally accepted rate.

We've also heard from Dr. Mills and you'll hear later from Dr. Oakley that through intervention trials we know it is possible to decrease the rate of folic acid-preventable neural tube defects down to at least 6 per 10,000 and possibly lower than that. Again, maximum benefit is achieved when folic acid is started prior to pregnancy.

This slide shows a timeline of the events of pregnancy, when it occurs, when it's diagnosed, when the neural tube closes, and when a women is likely to see her health care professional for an initial prenatal visit.

Here you can see that conception occurs around the time of ovulation, about two weeks after a woman's last menstrual period. Two weeks after that a woman would have missed her first menses. This would be the first time that pregnancy could possibly be diagnosed but the neural tube development is already well underway, already starting to close shortly after that. In fact, neural tube closure occurs by about day 28 to 30 after fertilization or

some six to six and a half weeks after a woman's last menstrual period.

Now, those of you in practice or who have gone to obstetrician gynecologists or nurse midwives for care for pregnancy realize that when you call to make an appointment to see your health care professional, the usual time one has to wait until seeing your professional is about four weeks from the time of your phone call.

So even if the diagnosis is made right when the period is missed, the usual time for a first prenatal visit at the very earliest is about eight weeks or after the neural tube has closed. Now this is a problem because folic acid should be started before conception in order to have maximum benefit in reducing neural tube defects.

Once a woman is pregnant she cannot rely on her health care professional for timely counseling about the importance of periconceptual folic acid. This woman would not receive a prescription for prenatal vitamins early enough to minimize her risk of having a neural tube affected child.

Based on an extensive amount of clinical trial data, some of which you've heard through speakers this morning, some of which you will hear

from Dr. Godfrey Oakley, the U.S. Public Health Service developed a recommendation in 1992 that all women of reproductive age consume 400 micrograms of folic acid daily.

The Institute of Medicine reaffirmed this recommendation in 1998 when they suggested that all women of reproductive age consume 400 micrograms of synthetic folic acid in addition to a diet rich in natural folates. A number of medical, nursing, and other professional organizations committed to maternal and child health have embraced this recommendation. Some of these organizations are shown here on this slide.

I would like to give a brief overview of folate and folic acid. I cannot do it to the expertise of Dr. Shane, but I will just give a broad overview to just tell you some of the most pertinent facts and how these terms have been used interchangeably, sometimes incorrectly so.

As you've heard, folic acid, or folate, is a water soluble B vitamin that cannot be synthesized in humans so it requires intake through the diet. It is found in a variety of foods, some of which are shown up here, fruits, green leafy vegetables, etc. Actually, the darker the green color of the

vegetables, the more folate is contained in those vegetables.

As we've heard, folic acid is a synthetic form of folate and is more bioavailable. Almost two-fold more bioavailable than natural folate found in foods. With chronic use or ingestion, folate can be stored in the body primarily in the liver where about half of the stores are kept and also in the red blood cells. The red blood cells then are a good proxy or marker for tissue stores of body folate. As we've heard, folate is required for a variety of chemical reactions as a coenzyme, most notably DNA synthesis.

This is a slide that you will see throughout the series of talks that you hear this morning. What it depicts are the interrelationships between folic acid intake, changes in blood levels of folate, and decreases in neural tube defects.

Serum and red blood cell folate are correlated after equilibrium is reached so after a few months of folate or folic acid regular supplementation or use. Throughout the talks that you hear this morning, references will be made to both serum and red blood cell folate levels where data exist. Both levels are consistent and relevant markers of folate status.

There are a number of ways that an individual can obtain folate or folic acid through diet, supplement, or prescription use, and those are shown on this slide. One can obtain folic acid through a prescription drug. Obstetrician, gynecologist, family practitioners and nurses most commonly would do this with prenatal vitamins which contain up to 1,000 micrograms of folic acid or one milligram.

In addition, probably more in the hematology world, pure folic acid can be prescribed and also in internal medicine treating hyperhomocysteinemia pure folic acid can be prescribed again at a dose of 1,000 micrograms per tablet.

Many of you also are familiar with nonprescription ways to obtain folic acid such as vitamin supplements bought over the counter at the pharmacy or health food store, and many of these preparations have between 400 and 800 micrograms of folic acid in them.

We've heard about fortification of ready-to-eat cereals by Dr. Yetley and also about the grain fortification program which was mandated by the FDA in January of 1998. These are additional ways that one could obtain folic acid through the diet. Finally,

one can obtain folates through natural food sources such as the short list that I showed previously.

So let's look at how successful some of these ways have been to increase folic acid intake among reproductive aged women. Regarding the intake of folic acid through supplement use or prescription products, the March of Dimes has conducted an annual survey since 1995 to determine folic acid awareness and multivitamin use in reproductive aged women. We've seen some of this data earlier this morning.

These educational efforts are tremendously important. It's important to keep reinforcing the message that folic acid is important and how it's important and to do this through public education awareness campaigns should be continued.

Although the data showed this morning was compelling in that awareness has increased, as was stated also earlier this morning, the use of folic acid containing vitamins and supplements has remained relatively flat at about 30 percent of reproductive age women. So despite these aggressive campaigns, it is unlikely that further efforts will dramatically increase the use of folic acid supplements in the general population. The reason for this is really quite clear. It is very hard to change behavior.

Even with education it is very hard to ask someone to do something new, something different, something they are not already doing. Dr. Yetley actually raised this point when she talked about the importance of the grain fortification program, that it's a passive program. It increases folic acid consumption without people having to do anything differently.

Speaking about the grain fortification program, I think we've heard a large amount of data this morning. We'll hear some additional data later this morning that this program has been very successful. We've heard data to suggest that the estimated increase in the daily intake of folic acid has risen by about 200 micrograms per day and that this, in turn, has led to a decrease in neural tube defects on the order of 23 percent. We've heard other estimates of 19 percent, 20 to 30 percent. The bottom line, though, is that this program has claimed some significant successes.

However, as Christine Lewis and others from the FDA have stated in a relatively recent article, the estimate is that the majority of reproductive age women still consume less than the U.S. Public Health Service recommendation of 400 micrograms of folic acid

daily. In fact, their estimate in this paper in 1999 post-fortification was that 68 to 87 percent of women still do not consume this U.S. Public Health Service recommendation.

In fact, the authors go on to conclude that there is a need to explore ways to improve folate intake in targeted subgroups. Specifically reproductive age women while not putting other population groups at risk for excessive intake.

Two years after this article came out, authors from Tufts and the FDA concluded that no level of grain fortification would ensure that all women of reproductive age would consume 400 micrograms of folic acid through diet alone. This conclusion underscores the need for additional vehicles, passive vehicles, to deliver folic acid to reproductive age women who consume less than 400 micrograms daily.

Toward this end, we propose an oral contraceptive folic acid product as one more way, one more vehicle to meet the medical need as stated by Lewis and colleagues and supported by other authors to target women of reproductive age who consume less than the U.S. Public Health Service recommended amount of 400 micrograms of folic acid daily.

There are many of these women out there as

we have discussed. These women can be easily identified through a simple question about whether or not they use supplements or multivitamins. Once they are identified oral contraceptives are a logical vehicle to deliver folic acid.

Oral contraceptives, as you will hear from Dr. Kaunitz, are the most common method of reversible contraception in the United States. Over 16 million women currently use oral contraceptives so with such widespread use oral contraceptives would be an appropriate vehicle to deliver folic acid and reach a large number of women in the target population.

Such a product would be available by prescription only so it would be highly regulated and controlled. Both the quality of the raw materials, the folic acid as well as the sex steroids, as well as who gets the prescriptions. They would be under the care of a health care professional and supervision.

This product would help, in part, to fulfill an unmet medical need in reproductive age women and, as mentioned earlier, would be targeted to those reproductive age women so it would not be given to children or those above the age of 50.

These components, oral contraceptives and folic acid, have been widely studied throughout the

years and have established efficacy and safety. Oral contraceptives have been on the market for 43 years. Oral contraceptives are the most studied medication in U.S. history. Their efficacy is very well established, and they have a good safety profile.

Folic acid, as we've heard from our speakers this morning, reduces the risk of neural tube defects, and there is still the possibility that further neural tube defects could be eliminated or reduced. It also has an excellent safety profile as I will speak briefly to and Dr. Oakley will speak more extensively about.

Folic acid as a prescription product was first approved by the FDA in 1946. It's been approved for 57 years as a drug at the 1 milligram dose. There are more than 1 billion person years of use of doses that are at least 400 micrograms a day. This product has a wide therapeutic index. We've heard about no known toxicity this morning.

In fact, Goodman and Gilman, the textbook used by medical students and physicians throughout the country, states that oral folic acid usually is not toxic. Even with doses as high as 15 milligrams a day there have been no substantiated reports of side effects.

I should mention that in 1986 CFSAN, the group from the FDA that regulates food and supplement use, established a registry for voluntary reporting of adverse events for vitamins and other supplements. To date there is not a single report of folic acid toxicity in this registry.

Now, although underreporting may explain in part some of this finding, underreporting alone cannot explain zero reports. In contrast, look at vitamin A which has numerous reports of toxicity reported in this registry.

I would like to conclude with my last two slides by just summing up why this makes sense. An oral contraceptive folic acid product would ensure that the proposed population would have an intake of 400 micrograms of folic acid daily. This is the amount recommended by the U.S. Public Health Service.

It would not change any pill taking behavior. This is one of the most compelling arguments that I can present to you. It would provide increase in folic acid to targeted women with low intakes through a passive means so it will work.

Compliance is known to be better with one pill rather than two so combining these products into a single tablet would actually improve compliance and

use and would have a further impact on reducing the neural tube defect rate.

This would be a highly controlled and regulated product. It would only be dispensed by prescription only and under health care professional supervision. We're talking about a dose that is already present in supplements that can be bought over the counter without supervision and without regulation.

Each component, as I've mentioned, has good to excellent safety profile. The risks, as we've discussed a little bit this morning and as we'll get into a little bit more with Dr. Oakley's talk, associated with an incremental dose of 400 micrograms of folic acid are negligible, if any, in this proposed population of reproductive age women.

So, in summary, oral contraceptives are widely used by the target population and would be a convenient and effective vehicle to co-administer folic acid. It would provide the recommended 400 micrograms of folic acid on a daily basis and would further complement efforts by the U.S. Public Health Service a variety of professional and medical organizations to further reduce the incidence of neural tube defects in our country.

Thank you for your attention, and at this time I would like to introduce Dr. Godfrey Oakley who will present the efficacy and safety of folic acid for the prevention of neural tube defects. Thank you.

DR. OAKLEY: Thank you. I'm delighted to be here to talk about an opportunity to increase the prevention of birth defects in our country. As a way of a disclaimer, let me indicate that when I was the Director of the Birth Defects Division at CDC, I was trying to figure out how could we get more young women to consume folic acid. The idea of putting folic acid in contraceptive pills came, led to conversations with Dr. Michael Cafferson, and Dr. Cafferson and I are the co-inventors on the patent.

Now, let's get down to business. I would like to discuss and go briefly over my comments today. I'm going to review the efficacy. Folic acid has been shown in randomized control trials to prevent spina bifida and anencephaly.

In contrast to many drug situations, there is enormous effectiveness data already out there. CDC conducted a community intervention trial with 400 micrograms of folic acid that involved over 200,000 women before they were pregnant and there were remarkable reductions in NTDs.

You heard about the grain fortification program today that has exposed more than a billion people to extra folic acid and what we've seen is a decrease in both Canada, the United States and, not shown earlier, but in China and Chile reduction from this. We know effectiveness works.

Finally, I'll talk about safety. As Dr. Friedman said, this is a safe drug the way this product is proposed, which would be to put it in another drug that is used and supervised by a physician as another level of protection for women of reproductive age.

Then for the part of the population that is not women of reproductive age, by targeting sexually active women this will give no more folic acid, not one single microgram of folic acid to anybody 50 or older or anybody that's a child.

I would like to share a data driven dream. That is, we don't have Congenital Rubella Syndrome in this country anymore, and it is a remarkable achievement of American pediatricians, American industry, American health care, parents, everybody. We almost don't have any cases now, and they happen only when they are imported. We've been a remarkable success.

I think we now have the data to allow us to know that if we get enough folic acid into enough women, we can achieve the total prevention of folic acid preventables, spina bifida. I am delighted to be here to try to help move this along.

If I needed any encouragement, and some of you know I don't need much encouragement on this topic, but if I needed any encouragement on this topic, I visited the Spina Bifida Association picnic, the holiday picnic 10 days ago.

I had the opportunity to sit at my table with a young couple who didn't know about folic acid before they got pregnant, and they had a four-month-old daughter with spina bifida. This young child had already had at the age of four months five surgeries to have her shunts revised and had had surgery related to her club feet.

This is just a reminder that this is a birth defect that can't be cured. It must be prevented.

Dr. Friedman has shown you this slide before. I'm going to be talking about the relationship between the intake and the health outcome neural tube defects at first.

Of course, Dr. Mulinare has shown you a slightly updated version of this slide. Since I stole

my version from him about six months ago, it's not quite as slick as his, but you've seen this slide before, and I'm going to mostly talk about these two yellow bars and this yellow bar here.

This is an amazing slide. In my view this is a slide that is worthy of generating the nobel prize for Professor Wald and his colleagues. The MRC just put out a press release after looking at their funded studies for the last 70 years, and they said in the modern medical times this was one of the five most important studies that they actually supported.

To get into this slide you had to be a woman who previously had an affected child with anencephaly or spina bifida, and you had to be agreed to be randomized into a two-by-two design in which half of the women either got 4,000 micrograms of folic acid or they didn't. Among the women who did not get 4,000 micrograms of folic acid, their rate of NTDs were 350 per 10,000 or, if you like percentages better, 3.5 percent.

Among the women who got 4,000 micrograms of folic acid, there was a 75 percent reduction down to 1 percent. It's clear a powerful protective effect demonstrated in a well done large randomized control trial. It makes the point that not all spina bifida

and anencephaly are prevented by folic acid but an awful lot of it is.

That data led the CDC two weeks after the study was published to put out a guideline that was mentioned earlier that all women who previously had an affected child when they were planning to get pregnant should consume 4,000 micrograms of folic acid a day. So, there are women out there who on a regular basis are taking 4,000 micrograms a day. There is some exposure to that dose and it continues to be considered to be a safe dose.

Then the second randomized control trial came. This was roughly 2,500 women who came to their doctor before they got pregnant and agreed to be randomized into a group in which they either got Roche's at that time current prenatal vitamin with 800 micrograms of folic acid or none.

As you can see here, the rates because it's in the general population they are lower, but among the women who did not get the folic acid containing a multivitamin it was about 30 per 10,000. In this study there were no cases in the treated arm. Both the MRC study and this study were called off early by the data mining committee because they were both so powerful protected studies.

Those two studies and some of the case control evidence that Dr. Mills and others talked about led the Public Health Service, the CDC, the NIH, and the Food and Drug Administration to issue on September 11, 1992, the MMWR report that recommended that all women get 400 micrograms of folic acid a day.

You've seen this before so maybe I'll save a little time and move to the third study. This is the effectiveness study. We move from efficacy which has been demonstrated to showing that we have effectiveness. These are data from the large China study where there were over 200,000 women in two parts of the country.

In the northern part of the country the rate of NTDs is very high, one half of 1 percent of all babies have either anencephaly or spina bifida and infant mortality, as it were, of five just from those two birth defects when these babies die. The other part of the study was done in the southern part of China where the rates are about like what they are here, about one per 1,000 or 10 per 10,000.

One motivation for doing this study is that although the Public Health Service made policy that all women should get 400 micrograms of folic acid, there wasn't a single study in which women had

actually gotten only 400 micrograms of folic acid. One randomized control trial had folic acid at 10 times that dose and the other randomized control trial had not only 800 micrograms but it also had multivitamins with it.

Then all the case control studies, the observational studies were mostly of women consuming a multivitamin. Of course, in this country a multivitamin has 400 micrograms of folic acid but it also had extra vitamins.

So this study was done in part to look at would just 400 micrograms of folic acid a day have the protected effect that we sort of deduced that it would, and there is extreme good news here. As you can see from the northern parts where the rates were high the women who were highly compliant, their rates dropped from 50 to 7 per 10,000, more than an 85 percent reduction.

In the south where the rates were lower they dropped from 10 to 6 per thousand among the highly compliant. So here we have efficacy data -- effectiveness data that is highly supportive of the notion that folic acid prevents birth defects.

We've had a lot of discussion on what has happened with fortification this morning. I think I

won't say much other than to note that I don't think it has come through quite as clear in all the presentations this morning but for many years cereal companies have been able to voluntarily add vitamins to their products. Totals had 400 micrograms of folic acid since the middle '70s.

But what is tough to break out from the blood data post-fortification is the changes that other cereal companies have made in their products. To make a long story short, there used to be five products that had 400 micrograms of folic acid per serving, and now there is some place between 50 and 100 so increased consumption occurred passively by people not changing their brands but just by their brands having more folic acid in them.

Having said all of that, there seems to be a pretty good agreement by most people that the current consumption is about 200 micrograms. Think about that as a statistician for just a minute. If the median is getting 200, that means 50 percent are getting less than 200. I mean, there are clearly women -- most of the women still are not getting the 200 micrograms to say nothing of the 400 micrograms that is still the Public Health Service recommendation.

Now, you've seen these data from Dr. Mulinare. This is the prefortification level. This is the transitional time. This is the after fortification among the nine birth defect surveillance programs that try to do a good job of counting the prenatally diagnosed and terminated pregnancies.

These are data from the birth certificate studies so the rates are a bit lower, but I think they respond to one of Dr. Rosenberg's questions in the sense that these are the years when fortification happened, and since fortification it seems to be a plateau. It looks like it actually did happen. We got it over 18 months to 36 months and then we haven't seen further decreases in NTDs.

Now, we had a whole talk by telephone on the Nova Scotia data, and I was glad to hear more details on that. I only have one slide, but I think it's a very important study because it was an island, very intensive look for all cases of NTDs. Of course, before fortification roughly 26 per 10,000 and after fortification roughly 12 per 10,000. I, like the former speaker, think that is too high.

If we've demonstrated in China that we can get down to six, and I agree with Dr. Mills that maybe the number might be five and we really don't know

whether it's five or one or seven or what it is, but I believe we can do better and certainly in Canada this is a nice observation that more folic acid would further reduce the incidence of these birth defects.

These are data from Quebec which also has a very good prenatal diagnosis follow-up system in place so they can add not only the children with NTDs at birth, but those that were prenatally diagnosed and terminated. This study is about 10 times as big as the study from Nova Scotia just because there are more people in Quebec than there are in Nova Scotia.

As you can see, essentially the same data. The rates before around two. The rates after like shortly over one. Of course, it happens and then it kind of plateaus. It looks like we're not going to get anymore benefits from fortification.

Now, let me talk about the other part. I think we've demonstrated that with the health outcome of NTDs, there's no question that folic acid is effective and efficacious. Now, we also propose and others have proposed that by seeing that relationship between plasma folate or serum folate you can predict the reduction in NTDs.

These data were shown to you by Dr. Mills in a slightly different format. They were shown in a

curvolinear because they had linear coordinates. Dr. Wald graphed these same 50,000 -- the data from the 50,000 pregnancies in Dublin, and he used a log-log scale.

The reason for using that log-log scale is that the slope of this line is such that if you double the plasma or red cell levels, you are approximately half the NTD rate. I'll say it again. If you double the blood cell, the plasma or serum folate or double the red cell folate, you are approximately half the NTD rate.

You can see that that occurs all across the rather common levels of plasma or folate in Dublin. This is primarily a nonsupplementing population and a population before -- no fortification and they didn't take supplements.

As Dr. Mills pointed out, we really don't know what the shape of this curve is out past 10 nanograms per mL. Or if you multiplied that by 2.224 in the other units. So we don't know what it is out here. Maybe we'll find out one day, but we can't do a randomized controlled trial to figure out what that is because that would be unethical.

Now, a question that we will be asking the committee is what is the evidence that there would be

residual effect after you stop taking an OC with folic acid in it. Everybody seems to understand if you are taking it and you got pregnant while you were on it, you would be protected. You would be as good as other women taking 400 micrograms.

These are data from some Dutch women of reproductive age, 70 percent of whom were taking OCs. At baseline they have five nanograms per mL folate levels and they took 500 micrograms of folic acid a day. In just four weeks -- just four weeks they had a level that was more than twice what it was at baseline. Even in the first cycle it would be good news and protection.

Eight weeks after stopping they still have a plasma level that is roughly twice what it was at baseline so even eight weeks after these women on the average would have about 50 percent fewer babies with NTDs than they would have had if they had never taken this product.

These data are from studies in men and a few women after having a heart attack. I don't show them to you to be representative of young women, but I do show them to you because these are data that are currently available that show at baseline levels of 6.8, these men and women were fed 400 micrograms for

three months so it's a three-month study. Then they were taken off for three months and measured again.

Even after three months off here the dose was 400 micrograms, there is roughly a 50 percent increase suggesting that these women, if these were women who had been on a contraceptive pill, would have a 25 percent lower risk of having a child with an NTD if, in fact, they had been taking such a product like this before they got pregnant.

Now, I want to talk about the safety for a bit. Folic acid has an excellent safety profile. Hard to dream of a drug with a more safe profile. It's been available by prescription in the 1 milligram levels for 57 years. It is currently recommended to women who previously had an affected child to take 4,000 micrograms a day when planning a pregnancy.

I agree with Dr. Shane there is no data to suggest that this drug is toxic in any way. A study that I almost mentioned in answer to someone's question is that there is a study in Boston at the time of birth in which women -- it was a nutritional study, a history study, in which they looked at blood folates on the fetal side and blood folates on the mother's side, and they looked at it across large differences in intake from no extra folic acid to

6,000 micrograms a day.

There was a three-fold concentration on the fetus' side for serum across that whole level. This is set up for babies to get enough folate. Babies need folate because they need to make cells, and you can't make cells without DNA, and you can't make DNA without folic acid, so this is set up that way.

With red cells it did just as Dr. Shane suggested. It plateaued, and I forgot exactly where it plateaued, but at some level above a milligram a day it began to plateau in this group of women.

So, we have all that data, but we also have the data from the randomized control trials which is the usual data committees look at. And we have the randomized control trial in England, the MRC study and the Hungarian study and, again, no suggestion of adverse effects from the consumption of 4,000 micrograms or 800 micrograms.

Of course, the large Chinese study, 200,000 women who took 400 micrograms for around a year there were no indication of any adverse effects. Of course, these children are being followed up by the CDC in order to make sure and to be able to tell if there might be some unexpected effect, but so far nothing has been reported.

Now, let's talk about this tolerable upper limit a bit. It is true that the Food and Nutrition Board, while making policy for something that would be to the whole population, not a health care provider, set a tolerable upper intake level. They set it as 1,000 micrograms of synthetic folic acid for people who would not be under a physician's supervision.

I think it's important, as Dr. Rosenberg talked about, the data that were used. The data essentially for this, as they said, limited evidence that excessive folate may precipitate or exacerbate neuropathy in vitamin B-12 deficient individuals.

Most of the data came from studies, three cohorts in the late 40s and early 50s in which people were diagnosed with pernicious anemia who were being adequately treated with liver extract, and they were deliberately taken off of an effective therapy and given large doses of folic acid because they thought at that time maybe folic acid would prevent this. The doses ranged from 5,000 micrograms a day to 50,000 micrograms a day.

Never any discussion about toxicity from that level of exposure. Of course, if you take someone off an effective therapy, and you treat them with a drug that is not the effective therapy, and

it's a serious disease like pernicious anemia, they are going to get sick again.

It turns out 25 percent of these people didn't get sick again. Probably had folate deficiency or something. A third of them got sick again with their neuropathy but no anemia. A fourth got both and another fourth got the other. These are the data that lead to the hypothesis that there might be a masking issue.

The point of this is that this is a very cautious level. No one should have the idea that consuming 1,010 micrograms of folic acid is going to make anybody sick. That is not the point of this recommendation. I have been in circles where I thought that was misunderstood so I just wanted to make sure that people understood what the quality of the data was.

Then there was the -- and the lowest dose that this was observed was at 5,000 micrograms that took a five-fold protective effect so that is where this upper intake level comes from of 1,000 micrograms of folic acid.

And the office report from the IOM put this statement in their document. "In general, the prevalence of vitamin B-12 deficiency in females in

the childbearing age is very low, and the consumption of supplemental folate at or above the upper limit in this group is unlikely to produce adverse effects."

This is said for women who are not seeing a doctor to get more folic acid. These are women who get folic acid from just having fortified products.

So let me summarize. The efficacy of folic acid in lowering the risk and preventing neural tube defects has been adequately demonstrated in well done randomized controlled trials. We know it is highly effective from studies done in communities and the evaluation of fortification programs in the United States, Canada, and in Chile.

One point that I didn't make in my talk and in the summary I just would like to respond to, and that is when we try to figure out what is the least effective dose. For me the question is what is the lease effective dose that will prevent almost all of the birth defects.

It is not the least effective dose at which you might get five percent or 20 percent or 40 percent. It is the least effective dose. What is the lowest dose that we could get all. I agree with Jim we don't know exactly what that is, but the default position for the IOM and for CDC and the FDA still is

400 micrograms.

On the safety issue, it is a safe drug made even safer in this situation because women are going to get this extra folic acid under a health care provider's supervision. It's made safer for older people and children because no older person or no child will get any folic acid from this product.

Vitamin B-12 deficiency in reproductive age women is unusual, and, as I said just in the previous slide, even the Institute of Medicine thought that it was very unlikely that women would have any adverse effects from going over a thousand micrograms of folic acid a day.

Then the final bullet is wouldn't it just be wonderful to prevent more kids from having folic acid preventable birth defects, and that's what we can do by having this product available to health care providers and their patients. Thank you.

I got wound up just a little bit and I forgot to introduce the next speaker. The next speaker is Dr. Anna Maria Siega-Riz who is a Professor of Nutrition at the University of North Carolina, Chapel Hill.

DR. SIEGA-RIZ: It's a pleasure to be here today. It's actually just a pleasure to be able to

stand up. For some reason this doesn't seem to be going as we would like. Can we get my next slide, please? Well, good, maybe this will be a stretch break, and people can move around a little bit. That might get you awake. Here we go. This is my slide. There we go. Perfect.

So I'm going to be talking to you today about folate status among women of reproductive age. I'm a nutritional epidemiologist by training, and I actually focus on the perinatal period.

There's three points to be made with my talk today. Basically ones that you have heard in slightly different versions from our previous speaker, but basically that we can obtain folic acid through diet or multivitamins. Second, that the fortification program has really not benefitted everyone equally.

There are still many individuals that do not consume the Public Health Service recommendation of 400 micrograms on a daily basis. And the fact that we can actually identify women with low folic acid intake by using some simple questions.

I believe it's important to keep in mind these relationships shown in this slide and that the previous two speakers have also alluded to. I'll be talking about each one separately.

So when we are looking at the relationship between the dose of folic acid and red blood cell or serum folate levels, we have this nice study done by Wald and colleagues that actually provided individuals with varying levels of folic acid for three months and then measured serum folate levels.

As you can see from this slide, there is actually a very nice incremental increase in median serum folate levels with increasing dose of folic acid. And as has previously been shown, with 500 micrograms of folic acid given imperfectly every other day -- I think Dr. Oakley just presented the results given on a daily basis -- but even having people who are not very compliant take it every other day, you still see after four weeks of treatment a doubling in the serum folate levels. And after discontinuation for eight weeks, the levels are still elevated almost double above what the baseline levels were.

Now focusing on the relationship between folic acid intake and NTDs directly without having to go through increases in red blood cell or serum folate. There was a nice study done by Moore and colleagues that was just published in the epidemiology journal that actually showed the relationship between total folate, folate intake from both diet and

supplements and actually adjusted for bioavailability and the risk of NTDs. As you can see in this slide, it actually depicts a very nice decreased relationship with increasing dietary folate intakes.

In fact, for those women who took greater than 1,200 dietary folate equivalents compared to the women in the lowest group, this was associated with a 77 percent reduction in the risk of NTDs.

I know you guys have seen this slide, but you are going to see it a couple more times during my talk. I just think it's phenomenal that we can actually show this very nice relationship between red cell folate and the prevalence of NTDs. It has been pointed out several times that we really don't know how much further this decreased risk can go if we move red blood cell folate out further.

Well, how do we know where we are as far as in the United States? In order to monitor both dietary intakes and folate status in the U.S., we need to accomplish that with data from nationally represented surveys. We are lucky enough to actually have two such data sets, the NHANES data set and the continuing survey food intake for individuals.

The NHANES is very strong in the fact that it collects not only dietary intake information, but

also upon medical examination they collect blood so that we can actually look at both red blood cell and serum folate levels. The continuing survey of food intake for individuals which was last done prior to fortification in '94 and '96 collected very good dietary data and social demographic information.

I bring this up because these data sets have actually been used to model the effect of what fortification would have done to dietary intakes among women of reproductive age.

This was a nice study done by Christine Lewis published in the American Journal of Clinical Nutrition that actually used data from prior to fortification, the NHANES 1988 to '94 data sets, and the CSFI '94 to '96. They used the food consumption patterns in those two surveys and then took the food composition tables that were associated with those surveys and estimated the amount of folic acid that would have been contributed to the diet due to fortification. They didn't reanalyze foods. They just estimated the effect.

Then they looked at based on those food consumption patterns what would the percentage of individuals who actually would meet the Public Health Service recommendation just based on dietary intakes

alone. What you can see is that for 11 to 19-year-olds, only 13 to 21 percent of women would be meeting the Public Health Service recommendation through fortified foods. In fact, 27 to 32 percent of 20 to 49-year-old women would actually be meeting the recommendation.

This correctly led the authors to conclude, as you heard before by Dr. Friedman, that post-fortification, 68 to 87 percent of reproductive age women would not be consuming the Public Health Service recommendation of 400 micrograms per day.

Therefore, they concluded that we needed to explore other ways to provide folate intake to a targeted subgroup of women such that it would also not affect younger individuals and older individuals. This kind of a conclusion is really the impetus for this kind of product that is being proposed today.

Well, where are we in terms -- I think you saw this slide. Dr. Yetley actually provided the results, and then either Dr. Mills or Mulinare, I can't remember right now, actually had the graph. This actually shows it a little bit more in depth. Where we have the levels of red blood cell folate, because that's really what we're interested in, prior to fortification in green and then orange after

fortification.

Here is the mean. You can actually see that, in fact, we have increased it substantially. At the 10th percentile, the 50th percentile, and the 90th percentile you can see, in fact, that the whole distribution has shifted to the right so we have increased blood levels.

But the other thing I want to point out is that the median 50 percent of women are at 264. The 10th percentile is at 166. I want you to keep that in mind as I show you this next slide which I know you are nauseated over, but I think it's important to realize that the median where 50 percent of women are at, it's still associated with the risk of about 25 NTDs per 10,000 live births. Then, in fact, if you go to where the 10th percentile is, that's going to be associated with about 40 NTDs per 10,000 live births.

If you remember, the 90th percentile was at 423. It has been alluded that if you are at that level of about 400 nanograms per milliliter, we don't want to call it the optimal range, but it is a good range because, in fact, at that range, NTDs are only at about .8 per 10,000 live births. In fact, our goal is actually to move women down this line to actually prevent more NTDs.

So how can we actually identify low consumers? Well, based on previous research there have been several methodologies that have been used to identify who are low consumers. These have been questions related to supplement use, and they can be questions related to use in the last two days, the last week, or the last 30 days. It has been used both by CDC and NHANES. Or even consumption of cereal in the past 24 hours, that has been used by NHANES and CSFI.

Whether you ask these questions in any one of these formats, you can actually identify women with lower levels of serum and red blood cell folate if, in fact, they are a nonconsumer, a nonconsumer supplement, or a nonconsumer cereal. Let me show you some of that data.

This is a very nice study done, the Georgia Family Planning Study that was funded by CDC at Emory. In fact, in a group of women attending these family planning clinics, they actually looked at those women who took supplements right here versus those women who did not take supplements and measured their serum. And you can see the fact that there is a statistically significant difference. There is a four nanogram milliliter difference between the two and this was

regardless of cereal intake.

We can actually duplicate this study using the NHANES data which is what I've done here. In fact, using the NHANES question of, "Did you take a supplement in the last 30 days," we can distinguish women so that, in fact, women who actually reported taking a supplement in the last 30 days had a red blood cell folate of 325 versus those who didn't at 251. You can even see the difference in the median.

Now, this 75 nanograms per milliliter difference if you go back to the wall of data is actually you can estimate that there would be a 27 percent reduction in the risk of NTDs if you could get the women who were unsupplemented to the supplemented level.

So I think it's interesting to note that based on the scientific evidence to date that despite numerous educational efforts in this country both by physicians and the March of Dimes, there is still only 30 percent of women who are taking a supplement or who are reporting taking a supplement on a regular basis because, in fact, we know that that's probably even less so if we really measured compliance.

Even after fortification and the studies that have come out estimating the number of women who

would meet recommendations, just this past year the ACOG, the American College of Obstetrics and Gynecology, has actually concluded that folic acid intake from dietary sources alone are insufficient to meet the recommendation.

And I think it's interesting to note that in that Georgia Family Planning study that I just reported to you that there were 17 percent of women who reported using the supplement. There were 42 percent of women who were using oral contraceptives so, in fact, if you could supplement or fortify oral contraceptives with folic acid, you actually would be moving this 17 percent to 42 percent of the population who would be meeting the Public Health Service recommendation.

So, in summary, I think we can say that not all women of reproductive age have benefitted equally from fortification because their maternal red blood cell folate values aren't all up to where we want them to be.

With the simple question about the use of multivitamins with folic acid, subpopulations with lower folate values can be identified, and an oral contraceptive folic acid product would actually help many reproductive age women to meet the Public Health

Service recommendation.

I think it's important to understand that this is a very targeted product. This product is being targeted to sexually active women so, therefore, we can make a difference.

Now I would like to actually introduce to you our next speaker, Dr. Andrew Kaunitz, who will be talking about oral contraceptive use and pregnancy intendedness and folic acid intake. Thank you.

DR. KAUNITZ: Thanks for giving me the opportunity to speak this morning. My name is Andrew Kaunitz. After completing an OB/GYN residency in Chicago years back, I spent two years in Atlanta as an EIS officer in the Division of Reproductive Health at CDC. Since then I've been with the University of Florida where my responsibilities include patient care, teaching, and research. This morning I'll be discussing oral contraceptive use, pregnancy intendedness, and folic acid intake.

I would like to start with an overview of my brief presentation. I'll be pointing out that oral contraceptives represent the most common choice of reversible birth control used by U.S. women. Because oral contraceptives are rapidly reversible, many women conceive soon after stopping oral contraceptives.

We recognize that in consistent, highly motivated users the pill, oral contraceptives, represent a very effective form of birth control. In typical use, however, the overall annual failure rate appears to be in the ballpark of eight per 100 OC users annually. We also recognize that some groups of oral contraceptive users experience substantially higher failure rates.

I'll present data from Oregon that indicate that pregnancy intendedness strongly predicts folic acid intake at the time of conception, and I'll go on to conclude that an oral contraceptive combined with folic acid would represent a sensible approach to reducing the risk of neural tube defects in offspring of some of our reproductive age patients.

Looking at national survey data which examines contraceptive use by U.S. women, we recognize that, overall, somewhat over 16 million women are currently using oral contraceptives in this country making the pill far and away the most prevalent reversible method of birth control used by U.S. women. We are talking about large numbers here.

We also recognize that ovulation returns rapidly after women stop the pill. The survey data tells us that about 11 percent of OC users will

discontinue the pill in any given year which would represent about 1.8 million women stopping the pill annually.

About a third of these, or about 600,000, stop birth control pills specifically to conceive and because, again, fertility does return rapidly after women stop the pill, we can anticipate that the conception rate within three months of stopping the pill would approximate 50 percent.

The majority of women who stopped the pill or, for that matter, stopped any method of birth control for the purpose of conceiving, failed to notify their clinicians promptly. What that represents is a lost opportunity in terms of preconception counseling.

We recognize that when used consistently in highly motivated consistent daily tablet takers, oral contraceptives represent a very effective method of birth control indeed. Package labeling currently for oral contraceptives suggest a 0.1 percent annual failure rate.

This means that among 100 women taking the pill for a year, we can anticipate fewer than one pregnancies or contraceptive failures in that group of 100 women taking OCs for a year. The high efficacy,

however, of birth control pills is limited to those patients who are consistent daily pill takers day in and day out.

In contrast, we see a very different picture with typical use of the pill. In a perfect world all oral contraceptive users would be perfect users of the pill and would never miss a pill and would take every pill properly. However, oral contraceptive users, as with all patients, are human, and, as with any chronic medication, imperfect use is common.

National Survey of Family Growth data, which forms the basis for class labeling for oral contraceptives, suggest that overall typical users experience about a five percent failure rate. More recent analysis of National Survey of Family Growth Data, in fact, would suggest about an 8 percent overall failure rate.

When subgroups of women are analyzed in the National Survey of Family Growth, for instance, teenagers of low-income background failure rates as high as 30 percent or more are observed.

We recognize, of course, that the discrepancies between the very low failure rates with perfect use, on the one hand, and much higher failure rates with typical use, on the other hand, relate to

consistent versus inconsistent or incorrect use of oral contraceptives. Such incorrect or inconsistent use of the pill has been estimated to account for as many as one million pregnancies in U.S. women annually.

I would like to now focus on the concept of pregnancy intendedness. Overall, we recognize that about half of the pregnancies we take care of in U.S. women represent unintended pregnancies, but for purposes of this presentation, the concept of intendedness is important when we look at pregnancies because of the strong association between pregnancy intendedness and periconceptual intake of folic acid supplementation.

The study I've located in the literature that has best identified this association comes to us from Oregon. In the next three bar graphs, I will be presenting data from this Oregon data base.

Overall, these investigators who surveyed post-partum women, women who had recently delivered in the state of Oregon, noted that based on the reports of these recently delivered women, among women with intended pregnancies about 50 percent -- almost 50 percent reported taking folic acid supplements at the time of conception. In contrast, about 15 percent,

far fewer women who had unintended pregnancies, reported taking folic acid at the time of conception.

Looking at subgroup analysis, when the Oregon investigators divided their analysis by age, notice that the same association held whether older women or teenage women were analyzed. But when the focus was on teenage women with unintended pregnancy, note that only 6 percent -- that's correct, only 6 percent of teenage women in Oregon with unintended pregnancies reported taking folic acid supplementation at the time of conception, the time when it's needed.

We can do better. The other subgroup analysis I'll present relates to income. Once again, this predictive association between pregnancy intendedness and folic acid supplementation at the time of conception held whether higher or lower income women were examined. The Oregon investigators noted that in low-income women with unintended pregnancies only 11 percent reported taking folic acid supplements at the time of conception. Again, we can do better.

To summarize, a large number of U.S. pregnancies, as well as deliveries, are associated with recent or current use of the pill. Many reproductive age women including those using oral contraceptives under consume folic acid

supplementation. Those least likely to consume adequate folic acid at the time of conception include those not intending pregnancy. This group obviously includes, as I pointed out, a large number of oral contraceptive users.

For these reasons, adding 400 micrograms of folic acid to an OC formulation would provide the recommended amount of folic acid to at-risk, as Dr. Siega-Riz pointed out, sexually active women, the group of women we want to target, for more folic acid intake at the time of conception. This would reduce neural tube defects in women currently or recently using oral contraceptives.

Thanks very much, and at this time I would like to ask Dr. Friedman back to the podium for a summary and conclusion of our presentation.

DR. FRIEDMAN: Thank you, Dr. Kaunitz.

In closing, I have two slides which will summarize a lot of what you've heard today from our speakers and also includes points made by previous speakers this morning.

You've heard from a number of speakers this morning that neural tube defects are common, serious congenital anomalies that are largely preventable with adequate folic acid intake. You've also heard,

especially from Dr. Siega-Riz, that a large number of reproductive age women do not consume the amount of folic acid recommended by the U.S. Public Health Service.

You've heard from Dr. Oakley, Dr. Shane, and others that folic acid is highly safe. It has a wide therapeutic index. Dr. Siega-Riz has underscored that although grain fortification has resulted in higher median folate intake, higher blood levels, and a reduction in neural tube defects, that many women, especially those at the lower end of the folic acid consumption curve, still do not consume the recommended amount of folic acid daily.

Dr. Kaunitz has discussed oral contraceptives, that they are the most commonly used form of reversible contraception and are a highly effective form of contraception. They are rapidly reversible. So using oral contraceptives as a potential vehicle to deliver more folic acid to more reproductive age women would potentially reach a large number of these women.

Oral contraceptives has a good safety profile. However, many women will conceive while taking OCs largely due to incorrect and inconsistent use, and many will conceive shortly after

discontinuing oral contraceptives as fecundity is normal at that time.

Women who do not intend to conceive are less likely to use folic acid supplements, and Dr. Kaunitz has discussed this in the Oregon PRAMS study. This makes unintenders and, as we said before, all women taking oral contraceptives do not intend to conceive, so these women are particularly vulnerable to not having adequate intake of folic acid on a daily basis. The proposed population for such a product can be easily identified. It is those women who do not take supplements or multivitamins.

To summarize, combining oral contraceptives with folic acid would provide the U.S. Public Health Service recommended amount of folic acid to many reproductive age women, would reduce the number of neural tube defects in this country with negligible, if any, incremental safety concerns.

On behalf of the sponsor and our consultants, I would like to thank you for your attention and I would turn this over to the Chair, Dr. Guidice.

DR. GUIDICE: Thank you, Dr. Friedman. I would now like to open this next session to questions from the committee starting with Dr. Darney and then

Dr. Rosenberg.

DR. DARNEY: Thank you. Phillip Darney, University of California, San Francisco. Any member of the -- any of the presenters could answer this question. It seems to me that what we need is a calculated risk benefit ratio, and we're not quite clear about the risk but we are clear about the benefits.

We could begin that with an estimate of the number of women needed to treat to prevent a case of NTD. I wonder if that's been done. I think it is possible to estimate that number needed to treat. If there are 16 million users of birth control pills in the United States, how many do you estimate would use this particular pill? Do I understand correctly that there would just be one kind of pill that contained folic acid? If the number needed to treat is very large, then having only -- you might not reach very many people.

DR. FRIEDMAN: We've presented in a briefing packet a model that shows assumptions based on the Wald data and some of the serum data from the Georgia Family Planning Clinic study to give some broad sense of potentially how many people this could reach. The FDA, in fact, did a calculation when they were

considering grain fortification and estimated that they may protect against 116 neural -- prevent 116 neural tube defects on an annual basis, and its assumptions can be challenged, but the point being that a large number of women use oral contraceptives.

It's impossible to predict the penetration of such a product in the marketplace, but we do know that there are a large number of women who do not consume the U.S. Public Health Service recommendation. Although no specific number can be predicted with absolute certainty that such a product would have an impact in reducing some neural tube defects with negligible incremental risk.

Dr. Cafferson, would you like to respond as well?

DR. CAFFERSON: Phil, if I understand part of your question related to the notion that the options would be so narrowed by this proposal that the numbers of women who could advantage themselves from this would be severely limited.

I think it's safe to say -- well, No. 1, the purpose of our getting together today is to consider the concept alone but I think it is entirely safe to say that if the concept seemed to be a reasonable and acceptable one, we would want to make this as widely

available as possible.

Our products, for example, cover about, between our estrogens, progestins, the dosages would cover about 80 percent thereabouts -- I would have to get you the exact numbers -- of the type of oral contraceptives used in the U.S. right now. The intent would not be to funnel into one particular option but, again, this portion of the discussion is premature.

However, I'm optimistic so we'll see. Did that get at your question? By the way, on the numbers needed to treat, we have not done those calculations because we have been basing this on the general concept of OC users.

DR. DARNEY: My point -- question was directed at the fact that you could do such a calculation, but there are so many birth control pills available, 20 or 25, that this particular group of pills might not reach many of the 16 million pill users. It might not reach enough of them to make much impact on the condition.

DR. FRIEDMAN: I mean, there's no way one can predict with certainty. Historically, the products from our company have had a fairly broad penetration. A lot of people would have the potential option of using this product. It could prevent some

neural tube defects. That, I think, is unquestionable. How many is open to debate, but wouldn't just preventing some be enough with no incremental risk without having a precise number?

DR. DARNEY: Are you asking me the question? Yes, it would be, but I am saying you could prevent more if it were more universally available.

DR. FRIEDMAN: Well, we would hope that would be the case.

DR. GUIDICE: I think the goal of our committee is the concept, and I'm not aware that this would necessarily preclude or be limited only to this particular birth control pill. Perhaps other companies that serve the 16 million users may also then opt to add this unless there is something in the whole process that I'm not understanding through the FDA. Would this not be an option for other companies as well?

DR. GRIEBEL: We've been sidebarring on that, and we're not sure of the implications of the patent that was mentioned earlier we have on this so, from a regulatory standpoint, we don't know the answer to that.

DR. GUIDICE: Thank you. Dr. Rosenberg and then Dr. Stanford.

DR. ROSENBERG: In exploring with you the concept, I would appreciate some clarification on the issue of whether the concept here is that the target group for this proposed prescribed drug that has a combination of oral contraceptives and folate would be those people that were identified as having low -- likely to have low folate intakes, or is the concept that all people that would be getting oral contraceptives would be prescribed the combination? That's one question.

And the other question is, and perhaps Dr. Kaunitz or somebody can help me with this. The concept of putting together folic acid with oral contraceptive would also imply that that combination would be sensible at a metabolic level. I've heard very little here about a lot of the older work that indicated that there was an interaction between estrogens and folic acid metabolism.

I know that there's been much less of that since the dose of oral contraceptives have decreased over the past few decades, but what is the current understanding of the nature of the interaction between estrogen and folic acid with respect to the metabolism of one or the bioavailability of one in relation to the other?

DR. FRIEDMAN: Okay. I'd like to answer those questions. In answer to the first question, the proposed population would be those women who elect to use oral contraceptives as their method of contraception and who do not take vitamins or supplements containing 400 micrograms of folic acid. It would be up to the individual prescriber to decide if additional women could benefit and those decisions would be made on a case-by-case basis.

In response to your second question, I would like to give a brief response and then ask Dr. Lynn Bailey from the University of Florida to add any comments that she may have. Early studies looking at the potential interaction of oral contraceptives and folate suggested that oral contraceptives, and these were the old formulations as you mentioned with extremely high doses, may lead to lower serum folate levels. I can think of two papers by Shojania in 1969 and 1972 that made this suggestion.

However, more recent case controlled studies containing 70 women and 48 adolescents that were published in the last three to four years suggest no such interaction with current low-dose formulations. I would like Dr. Lynn Bailey to add any other comments she may have.

DR. BAILEY: I think the best data to address is Dr. Rosenberg's data from the HANES survey in which the folate status of oral contraceptive users versus nonusers was compared, and there was no difference. This was in women in terms of their calorically adjusted intakes. There was no difference in folate status in oral contraceptive users and nonusers.

DR. GUIDICE: Are there any other comments on the metabolism or excretion or the interactions?

Dr. Crockett has a comment specifically to that.

DR. CROCKETT: I guess in follow-up to your question, I would like to know specifically about if you have tested the pharmacoavailability of combining the oral contraceptive with the folate in a combined pill taken at the same time?

The secondary question to that, why are you considering putting them in a single pill instead of putting it in the placebo pills like we do with the iron? Would that maybe be a different concept to explore where you would put higher doses in for just that week and not have to worry about bioavailability problems?

DR. FRIEDMAN: The question about doing

pharmacokenetic or pharmacobioavailability studies was raised. The point really of today's meeting was to discuss the concept, not the clinical development plan, but clearly such a bioavailability study would be a very reasonable thing to consider. Following today's meeting and pending the outcome of today's meeting we would meet with the FDA at a later date to discuss the appropriate clinical plan.

Your question about whether it would make sense to consider putting folic acid in the last seven days of a 28-day pill pack, the so-called inactive pills or non-steroid containing pills was also raised. We feel it would be more advantageous to women to have 28 out of 28 days of folic acid exposure to maximize their benefit and to make sure that they receive 400 micrograms of folic acid on a daily basis.

DR. GUIDICE: Dr. Stanford and then Dr. Tobert and then Dr. Emerson.

DR. STANFORD: I'd just like to point out a couple of implications from the FDA's model on page 39, the briefing book, as I understood it at least. They did a model based, assuming that the 400 micrograms of folate would be added to the oral contraceptives of all 16 million users in the United States. They are modeling about 107 NTDs prevented,

of which 24 would be prevented among women who were also taking a multivitamin.

That seems to me just to be a little bit -- I want to be clear about that. We are talking about is it being targeted at those who are already taking a multivitamin or not, and this model includes apparently 24 being prevented among those already taking a multivitamin.

The other implication of the model of the 107 prevented, you can just do a quick back-of-the-envelope calculation. If there are 16 million -- a little over 16 million users, that's about 160,000 number needed to treat per case prevented.

But that would be presumably identical for women taking folic acid supplements, or at least additional folic acid supplements in the case of the 24 prevented that were already taking supplements. In other words, the number needed to treat would presumably be the same for just taking an additional folic acid or combining it into the pill.

DR. GUIDICE: Thank you. That's actually in the sponsor's book on page 39.

Dr. Tobert.

DR. TOBERT: Yes. This question is for Dr. Friedman or Dr. Oakley. It concerns the choice of the

dose of 400 micrograms per day. My question is really is that enough to optimize the reduction in NTDs? In the first place, if a woman gets pregnant while she's taking the oral contraceptive, then she was missing a good number of tablets usually, so she wouldn't be getting 400 micrograms a day.

In the second place, I understand that body pools of folate are large but not every woman is going to conceive within three months after stopping the oral contraceptive.

If she conceives six months later, would there be any advantage to a higher dose of folic acid? In other words, I think this is an imaginative idea, creative idea, but I'm wondering if it's optimized and perhaps the dose of folic acid should be higher.

DR. FRIEDMAN: I'm going to ask Dr. Oakley to respond to that question.

DR. OAKLEY: As Dr. Yetley said in her slide, there is always uncertainties in making policy decisions, and so here is another place where there clearly is some uncertainty. Most of the data that is available is at least 400 micrograms of folic acid and that was what the Public Health Service did in '92. Of course, the Institute of Medicine group in '98 reaffirmed that number. The China study shows us it

makes a lot of difference in NTD rates.

I have a bias, maybe like yours, that maybe even more than that might be good, but I think we don't have the evidence for that other than the fact that we don't know where that curve from Dublin actually plateaued because there are no data to tell us where it plateaus. One day, hopefully, we'll know that, but we don't know that yet.

I do think that you raise another issue, and we didn't show slides on this, but if you look at people who take 400 micrograms, 600 micrograms, 800 micrograms, or a milligram for three months and then stop, at three months after being off the residual level is higher for those -- these were men, mostly, who were post-heart attack. Theirs were high if they took a milligram so you certainly raise an important issue.

Oh, there it is. This is just the slide. Fantastic. So you can see what I just said is true. It's on this slide. Basically, if you have a higher dose your residual levels are going to be higher. Thank you very much.

I read another paper that I think is very interesting, it's someone trying to guess at what is the optimal dose for homocysteine. I think a group of

people from Holland. Or, at least, I just read. I think it's just been published. I think there was some discussion on that end point as to whether it should be 400 or 800, and it's some place still in that range.

I think they suggested that maybe 400 might be enough on the homocysteine side. But, of course, the fetus, which has much more rapidly dividing cells than an adult does, is likely to need even more folic acid than an adult.

DR. TOBERT: Actually, to that last point, if I may, I mentioned the SEARCH trial earlier. The investigators of that trial decided they required 2 milligrams of folic acid as well as 1 milligram of B-12 which also reduces homocysteine a bit to get the maximum effect on homocysteine.

DR. OAKLEY Just a comment on that. I think that people doing studies want to make certain that if it's a negative study, it isn't negative because the dose wasn't big enough. I don't think that I'd ever heard that out of Nick Wald's mouth, but, in fact, you've heard it out of Nick Wald's mouth that there was a very small study from Wales that used 4,000 micrograms which was before Nick designed the study. When Nick knew that and then just wanted to make sure

that there was enough.

Clearly 4,000 is probably enough, and I would agree with you that some place in the 400 to 800 range. Jim probably thinks it's a bit less and the bottom line is if we had all the data we needed, we could make the decision and know exactly what we don't know and we may never know.

DR. GUIDICE: Thank you.

Dr. Emerson.

DR. EMERSON: I just wanted to clarify on your slide 14 you showed a diagram of the causal pathways that seem to imply that you thought there was maybe a pathway that led from intake to decreased NTDs that wasn't reflected in the serum levels. Is that divined?

DR. FRIEDMAN: If we could have slide 14 up. You might consider this a design flaw. We debated this extensively, and you happened to pick it up. Basically, no, we are not suggesting an alternate pathway. Rather, what this was meant to show is that there are data to suggest that this relationship holds.

And there are data that basically bypass measuring biomarkers for folate and show that increased intake leads to decreased NTDs. It is not

suggesting an alternative mechanism. Rather, the path of the data. Thank you for bringing that up.

DR. GUIDICE: Dr. Montgomery Rice and then Dr. Green.

DR. RICE: This is to Dr. Kaunitz. In the Rosenberg study what percentage of those patients were taking OCPs as a method of their contraception within three months of conceiving? Oral contraceptive pills within three months.

DR. KAUNITZ: The question from Dr. Rice is in the Oregon data of the recent moms surveyed what was their contraceptive use pattern at the time they conceived. To my knowledge, Dr. Rice, the investigators did not report that in their article.

DR. RICE: So they reported unintended pregnancy but didn't ask the people if they were using anything?

DR. KAUNITZ: It was in a pediatrics journal.

DR. RICE: So they assumed that they weren't?

DR. KAUNITZ: They may have the data but to my recollection -- we can look here. We have the article here, and I'll take a look and make sure I'm not wrong because I may be. In reading the article I

don't recall any presentation about contraceptive use at the time of conception. I'll look right now.

DR. RICE: So all of them were unintended then probably if they weren't using anything.

DR. KAUNITZ: What they did focus on was intendedness of the pregnancy at the time of conception.

DR. RICE: Okay.

DR. OAKLEY: So then they asked questions about the intendedness rather than asking about methods of contraception?

DR. KAUNITZ: I don't believe they reported contraceptive use by this cohort of women, but I need to look again to make sure I'm not missing that.

DR. GUIDICE: Thank you. We have time for two quick questions before we break for lunch. Dr. Green and Dr. Stanford.

DR. STANFORD: My comment is just to her question. There are different ways of measuring intendedness. The PRAMS way of measuring intendedness is to say, "Did you have your pregnancy sooner than you wanted, about the right time, or later?" It doesn't say anything about, "Were you using birth control?" It just asks about timing and that's how they measure intendedness in PRAMS and that's what

those data are based on is PRAMS.

DR. RICE: What is PRAMS?

DR. STANFORD: Pregnancy Risk Assessment and Monitoring System. It's a CDC based system for monitoring pregnancies in a number of states.

DR. GUIDICE: Thank you.

Dr. Green.

DR. GREEN: Dr. Guidice, thank you. This may not be short, I have to say, but I'll try to be as brief as I can. It does somewhat address an issue that we haven't yet addressed. It returns to the question of safety.

First, let me reiterate, I think, what Dr. Mills said which I think summarizes very nicely the reason why I raise this point, and I believe, to perhaps paraphrase him, he said that lack of evidence of toxicity does not equate with evidence of a lack of toxicity.

The reason for my comments specifically are that much of what we have seen and, indeed, I do agree with that, address the issue of toxicity with respect to large doses. That's very apparent from some of the data that Dr. Oakley showed.

And also just for purposes of clarification, and I think that Dr. Rosenberg will bear me out, in

relation to the Institute of Medicine's study in which the question of upper limits and safety issues were addressed, the important consideration and the reason for the caution that was expressed in that report stem not so much from the studies that Dr. Oakley referred to in that high dose range of 5,000 micrograms and up, and there were several of those, but rather -- and it was an arduous search through the literature -- rather single case reports that appeared in the literature with respect to dosages of folate below 1,000 micrograms and, in fact, in some cases even below. If my memory serves me correctly, we were able to identify six such individuals.

Now, that in and of itself doesn't really prove anything one way or another. We've heard, I think, compelling evidence to say that in the target group this imaginative approach, and I agree that it is as somebody said previously, to increase folate intake in women of reproductive age represents a relatively small risk in terms of the masking of the untoward effects with respect to pernicious anemia.

But there is another issue that is gaining a lot of attention, and what I refer to here is the whole field of epigenetics, and the fact that largely based on some animal work but also now being

supplemented from some human work.

There is evidence that comes forward, and I'll address briefly the animal work, fully acknowledging that mice are not humans, but, nonetheless, the observations that have been carried out on a particular strain of mouse, the agouti mouse, which has transposable elements in the upstream region of this particular agouti gene very nicely and excitingly show the effect of epigenetics specifically from the point of view that supplementation with methyl groups, and it's known that methyl groups play a key role in the control of certain genes in the upstream promoter region.

There are islands that are rich in what are called CpG islands, lots of cytosines that control the regulation of those genes. The administration of large doses of a combination of folic acid as well as, I believe, choline and methionine, altered not in the maternal dams themselves but in their offspring the expression of this gene to the extent that there were changes which some, I think, might conclude were beneficial. Specifically, that those offspring instead of being light colored yellow mice were dark colored mice.

Also, that the obesity that occurs in the

light colored variety was counteracted so that the offspring were less obese so there would apparently be if you take that into the human context a beneficial effect. Indeed, some of the effects have increased. Methyl groups might be beneficial, but equally so there may be some that we don't know about at this stage that could be deleterious. This has been raised and largely is a theoretical question in the literature.

I'll read just one line, if I may, from the conclusion or summary of a paper that appeared in Molecular and Cell Biology by an author by the name of Waterland who says, and based on the experiments that I described, and that supplement I see that was given to the agouti animals was folic acid B-12, choline, and betaine.

The conclusion is "These findings suggest that dietary supplementation long presumed to be purely beneficial may have unintended deleterious influences on the establishment of epigenetic gene regulation in humans." This is purely theoretical and purely speculative.

I raise it only because I think that in essence there are a lot of unknowns in this field and there is no literature to cite other than the

literature that I have mentioned that comes from animals. There are suggestions that there may be epigenetic factors at work in other diseases.

I'm not talking here about folates and methylation but epigenetics in general. The best example of which would be disorders where there are differences in parental imprinting in, for example, the Prader-Willi Syndrome and related disorders. I'm sure many of the group here are aware of those.

With those remarks I'm not in any way wishing to suggest that we have concrete evidence, it is merely to emphasize that the evidence that we have is based on large doses and toxicity questions. We do not have any evidence at this stage in terms of long-term for the obvious reason that changes -- global changes in folate nutrition in this country have been of relatively recent duration. Thank you.

DR. GUIDICE: Thank you.

DR. FRIEDMAN: If I may, I would like to ask Dr. Steven Zeisel, Professor and Chair of the Department of Nutrition at the University of North Carolina, to just respond to some of the comments made.

DR. ZEISEL: Dr. Green's point is that there may be unanticipated effects of folic acid

administration. It is true that methylation of promoter sites in genes can regulate that gene expression. It's a very important part of developmental biology.

The agouti study is in an animal model, mice. I look at another methyl donor, choline, and it's very clear that pregnant mice, if given a choice, choose a higher methyl diet than they are offered by normal animal lab chow, and so it may very well be that the agouti study is describing the effects of restricting mice artificially to a diet that they wouldn't have selected as a pregnant animal that is low in methyl groups, and that optimal may be the higher amount.

I think, though, to put everything in perspective, you have to think about that we are asking the woman to take 400 micrograms of folic acid as a public health recommendation. Whether she takes the folic acid from a vitamin pill or from cereal or from a birth control pill that contains it doesn't change her relative risk. By making this option available to women, we are only trying to help a public health recommendation be met and not introducing a really new risk to the woman.

DR. GUIDICE: Thank you. I have a question

along those lines. Is there any evidence of any increased imprinting disorders over the period of time in which folic acid has been supplemented such as -- I mean, Prader-Willi is very rare. Beckwith-Wiedemann is extremely rare. I'm wondering if there are any data on that.

DR. GREEN: To the best of my knowledge there are no data that are available. I raise this, as I say, only as a theoretical consideration and that increased levels of folate as, I think, Professor Zeisel has indicated, could have beneficial as well as potentially deleterious effects. I certainly agree with his statement that this does no more than to recommend or to create an option whereby the recommended level would be attained by a fraction of the population.

DR. GUIDICE: Dr. Mills and then Dr. Wenstrom.

DR. MILLS: There is a potential confounding issue here, and that is that there is a distinct possibility that some assisted reproductive technologies are increasing the rates of Beckwith-Wiedemann and Prader-Willi and Angelman Syndrome.

I mention that in part to underscore the problem that we have that if there is any complication

of a high exposure to folic acid, it's unlikely we are going to be able to detect it because everybody is exposed. It's difficult to do the usual strategy of investigation which is to compare and expose to an unexposed group.

DR. GUIDICE: Thank you. Dr. Wenstrom for the final comment.

DR. WENSTROM: I was just going to mention that there is a group in Baltimore that has been keeping track of the number of Beckwith-Wiedemann Syndrome children born as a result of assisted reproductive technologies, and in that small series -- well, I mean, it's a large series when you consider how rare that is -- they found no difference in reported folic acid use between mothers who did or did not give birth to the baby with Beckwith-Wiedemann which suggests it's something relative to ART itself and not necessarily diet.

DR. GUIDICE: Yes, and also the procedure that's been implicated as more ICSI as opposed to just general in vitro fertilization. Almost across the board all women who go to ART programs get folic acid supplementation as part of their regimen.

Thank you. So we will now reconvene at 1:15 for the open public hearing. The committee has a

reserved section of the restaurant here in the hotel called the Tarragon Room for lunch. Thank you.

(Whereupon, at 12:31 p.m. off the record for lunch to reconvene at 1:15 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:21 p.m.

DR. GUIDICE: Please take your seats, everyone. Before we begin the afternoon session, I am told I need to read a particular statement for general meeting matter, and that is that both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning

of your statement, however, it will not preclude you from speaking.

So I would like to call the first speaker, Eileen Carlson and then followed by Douglas Sorocco from the Spina Bifida Association of America, Spina Bifida Foundation.

MS. CARLSON: Good afternoon, everyone. My name is Eileen Carlson. I'm from Washington, D.C., and my brother and my son both have spina bifida, the nation's most common permanently disabling birth defect which affects approximately 70,000 Americans.

As you all know, recent studies have shown that if all women of childbearing age were to consume 400 micrograms of folic acid daily prior to becoming pregnant and throughout the first trimester of pregnancy, the incidence of spina bifida could be reduced by up to 75 percent.

Former CDC and Prevention Director Jeff Koplan has stated that the agency's folic acid prevention campaign has reduced neural tube defect births by 20 percent. While progress has been made in convincing women of the importance of consuming folic acid supplements and maintaining diets rich in folic acid, each year approximately 4,000 pregnancies still are affected by spina bifida.

Clearly gains must be made in educating health professionals and women of childbearing age of the importance of consuming folic acid prior to becoming pregnant. Our nation must consider and implement new and creative ways to facilitate women's consumption of adequate amounts of folic acid to reduce the risk for spina bifida pregnancies.

So as you consider the public health benefits of allowing oral contraceptives with folic acid augmentation to be sold, I would like you to consider the challenges of life for individuals and families affected by spina bifida. This is my story.

In 1967, my brother Danny was born with spina bifida, myelomeningocele, and hydrocephalus. Although Houston, Texas, had major medical facilities, our obstetrician had my father transport his newborn son to the children's hospital in our family station wagon. But we were lucky; if Danny had been born a hundred miles away, he most likely would not have survived.

Today he lives by himself in an apartment and is reasonably healthy. He has endured scores of surgeries throughout his life -- he claims the number is 36 -- and has never been able to walk. Like many adults with a severe disability, particularly those

who must rely on a wheelchair, Danny has encountered many serious obstacles -- sometimes insurmountable -- in his efforts to find meaningful employment, make friends, develop romantic relationships, and become an active participant in his community.

When my husband and I began to think about starting a family, I spoke with my OB/GYN who said that I was not at an increased risk of having a child with spina bifida. Well, he was wrong. Just for your information, he is now a professor at a very prominent medical school.

I, however, had read the recent research showing that folic acid can prevent many occurrences of neural tube defects. When I learned that I was pregnant, I began taking prenatal vitamins which included folic acid. But three months into my pregnancy we learned that our baby had spina bifida because during a high level sonogram his head showed the typical "lemon sign" and his lesion was visible through his sonogram.

Had I been taking birth control pills with folic acid prior to my pregnancy, the level of folic acid in my system could very well have made a difference in my son developing spina bifida. Naturally, when we learned about his spina bifida we

were devastated.

We made plans to deliver Sean by C-section to avoid any further damage to his lesion at a medical center with a NICU. I began eating like crazy to fatten our baby up in case he was premature. When I began having premature contractions, I went on bed rest. However, our son, Sean, was born full term at 37 weeks weighing 7 pounds, 9 1/2 ounces, and very healthy in spite of his disabilities.

He spent ten days in the NICU and a special care nursery, and his healthy cries even sparked the comment, "Who's the kid with the lungs?" He had two surgeries before he came home to close the lesion on his back and to place a V-P shunt in his brain for hydrocephalus. His hospital bill came to more than $100,000.

The first few years of Sean's life were a constant parade of doctor visits, diagnostic exams, physical therapy, and four more surgeries. These years were naturally a real challenge to our emotions, our family stability, as well as our finances. In spite of Sean's physical problems, we made special efforts to expose him to the world around him and provide opportunities for social interaction and play.

We were aware of the risk of learning

disabilities in children with spina bifida, which my brother suffers from, and some of which were recently shown to be due to a lack of experience and social interaction in the early formative years. We also decided not to try to have any more children on our own because of the risk that they, too, might have spina bifida.

Today I'm happy to say that Sean is doing very well. He's 6 1/2, has leg braces and walks with a walker. He has even walked a half a mile and up three flights of steps but he still needs a wheelchair for long distances. He is bright, happy, very social and at this point he's mainstream in a regular first grade classroom in a D.C. public school. So far he is on target academically. He has many friends.

One of the biggest challenges in his life is incontinence which most people with spina bifida must struggle with in varying degrees all their lives. He wears diapers and has to be changed a couple of times a day at school. Our public school does not have -- most D.C. public schools do not have elevators so we are going to have to be looking for a different school for him sometime soon.

We know that Sean is likely to need more surgeries in the future to repair a clogged or broken

shunt or tethered spinal cord, straighten out twisted bones or a twisted spine, enlarge his bladder, or to relive pressure from the abnormal amount of fluid in his spinal cord also known as syringomyelia.

However, we consider ourselves truly fortunate. We have good health insurance that pays for most of our medical bills including a $5,000 wheelchair, $7,000 leg braces. We are blessed with very abundant medical facilities in this area including three excellent spina bifida clinics.

In the realm of experience with spina bifida, Sean is truly one of the lucky ones. I am actively involved with the local chapter of the Spina Bifida Association, and I've seen firsthand the challenges and burdens that many other families must face.

Twelve-year-old Mark has never walked, is developmentally delayed, gets his nourishment from a feeding tube, and has been hospitalized repeatedly for life-threatening bowel obstructions.

Fifteen-year-old Holly, who walks with only a small leg brace, was doing great, but she was recently hospitalized for tethered cord surgery, faces bladder enlargement surgery as well, and possible liposuction for her lipomyelomeningocele.

Cameron was born doing great but suffered from tethered cord and his physical abilities have been severely impaired. He had to go through, I think, four surgeries by the time he was six months old.

Some of our kids and adults must breathe with a respirator and some suffer from severe scoliosis that twists their bodies like pretzels. As one mom has said, having a child or suffering from spina bifida is like going through a minefield. You never know when something is going to come up and, boom, there's another major medical problem or another surgery.

These medical and physical challenges can damage families, break up marriages, and cause serious financial burdens. Some estimates suggest that the lifetime cost of a person with spina bifida is $1 million.

I hope that my experience has given you a snapshot of what it is like to face the challenges of spina bifida. We love our son just as he is, and he is truly perfect in our eyes. But at the same time, we would do just about anything to take away his spina bifida.

One of our greatest frustrations is the lack

of public knowledge about spina bifida and about how to reduce the risk of a spina bifida pregnancy, even among health care professionals which is truly shocking, especially in this country. But the greater tragedy is that some babies are being born with spina bifida because their mothers were not aware that simply taking folic prior to pregnancy could have prevented this birth defect.

I believe that including folic acid in oral contraceptives is an important step both for preventing the occurrence of spina bifida and for helping inform the public at large, OB/GYNs, women of childbearing age, and others in the public health community. How many seriously crippling birth defects are 75 percent preventable with the simple step of taking a vitamin?

I am very grateful for this opportunity to testify for this effort and I wholeheartedly urge your support and thank you for your consideration of my views.

DR. GUIDICE: Thank you.

Douglas Sorocco. Please limit your comments to no more than five minutes. That's for all speakers. Thank you.

MR. SOROCCO: Good afternoon and thank you

for allowing me to share my story with you today. My name is Doug Sorocco and my wife Kristen and I live in Oklahoma City. I am also an individual living with spina bifida. I'm a former board member of the Spina Bifida Association of America and founder of the Youth and Adult Alliance.

The Youth and Adult Alliance is the subcommittee of the SBAA Board that reaches out to young adults and adults with spina bifida. I appreciate this opportunity to speak with you today as you consider the public health benefits of allowing oral contraceptives with folic acid augmentation to be sold. To that end, I would appreciate your consideration of the challenges of life for individuals such as myself who live with spina bifida.

From a very early age my parents stressed upon me the fact that because of the spina bifida I would need to be able to earn my living using my mind. Professionally, I'm a partner in the intellectual property law firm of Dunlap, Codding & Rogers, and I specialize in biotechnology and life sciences. Notwithstanding this fact, however, neither myself nor my firm have any financial impact by these proceedings.

I was born in between two generations:

people born with spina bifida prior to the widespread use of shunts and those born thereafter. Those of the prior generation and I only survived because we did not need shunts. After the introduction of the shunt, however, a huge "bubble generation" has come about. This bubble generation has survived even in face of the fact that they are more medically involved than most of us who didn't survive prior to this period.

This bubble generation is decreasing in number, however, as the knowledge and importance of folic acid consumption is having a significant impact on decreasing the number of pregnancies affected by spina bifida.

My entrance into the world was also very abrupt. I am my parents' first child, and they had no prior knowledge of my having spina bifida prior to my being born. The lesion into which my spinal cord had grown wasn't even diagnosed or fixed until I was almost two years old. Today this lesion would be repaired within hours of birth.

As far as my parents were concerned, however, I was fixed after my back surgery (a notion that was not dispelled by my neural surgeon) and, therefore, did not have to be treated any differently or have any special accommodations made.

My parents had the same expectations and hopes for me that they would have for any child. Unfortunately, the terribly complex medical issues encountered by my so-called "bubble generation" required that my parents' attitudes and the ways that they treated me and their attitude or philosophy must be changed or modified somewhat in application to this new generation.

The success I achieved should not have really happened. Although my parents' ignorance or lack of knowledge was not significantly detrimental and may, in fact, been helpful is not a model that should be advocated or adopted. Everything I have accomplished and will accomplish is because of my parents and the way they raised me to be self-sufficient, independent, and fearless, traits that most parents of children with spina bifida try to instill in their children.

With respect to this more medically involved generation, however, these traits must be supplemented with proper, aggressive, and proactive medical intervention. In this manner, both independence and the health of the individual can be maintained. I must admit, however, that the fearlessness or willfulness, as my mother would call it, is not a

trait she would necessarily call a success.

Although I'm not perfect and I have a lot of things that I want and hope to accomplish in my life, all the success that I have had, once again, is due to my parents and the unconditional support and love of my wife.

There is a third factor that cannot be dismissed -- I'm lucky. I'm extremely lucky. I am lucky that my lesion was not complete. Some nerves did remain intact and I can walk. I am lucky that I did not have hydrocephalus or require a shunt. Finally, I'm lucky that the misleading and inaccurate medical advice my parents received concerning my spina bifida was not fundamentally detrimental to my health and development.

Unfortunately, in many areas of the U.S. misleading, inaccurate, and inadequate advice that does negatively impact individuals with spina bifida is currently being given. False or inaccurate information, as Eileen mentioned, is leading to the decline in the health of individuals with spina bifida and in many cases premature and certainly preventable death. Many women do not know of the fact that consumption of a simple B vitamin is capable of decreasing the incidence of spina bifida up to 75

percent.

Notwithstanding the "parade of horribles" that I and Eileen and other individuals with spina bifida can list, I am extremely fortunate in comparison to others with spina bifida. When I first became involved with the Spina Bifida Association of America, however, I was overly eager and naive. I published my work phone number in the national newsletter and invited individuals with spina bifida to contact me.

The number of calls completely overwhelmed by office staff. I received call after call from adults who had nowhere to turn. These adults could not obtain appropriate medical care. They could not participate or be fully involved in social activities.

Finally, these individuals with spina bifida were being foreclosed completely from being able to fully participate in their communities. While each one of us acknowledges that spina bifida has in many ways shaped our character and made us stronger individuals, we would gladly forfeit these "benefits" in lieu of a life without limitations.

Although I have, once again, been extremely fortunate in my life, ignorance can no longer be the accepted standard of care. While I certainly believe

that parents, family, loved ones, and medical providers are the primary determinants in an individual with spina bifida's life and success, the government does have a role to play.

The complexities of this birth defect necessitate coordinated, robust, and fully integrated and funded programs to promote the lives and health of all those affected with spina bifida and, most importantly, the preventive measures such as ensuring that all women of childbearing age know that they should consume adequate levels of folic acid prior to becoming pregnant.

Spina bifida is a complex, infuriating, and to our families and friends, an oftentimes frustrating problem. Folic acid, while not a cure-all, is the best hope for preventing the further occurrence of spina bifida and decreasing the emotional, physical, and certainly the financial impact that spina bifida has on our families and ourselves.

While the Centers for Disease Control and Prevention has reported progress in convincing women of the importance of consuming folic acid supplements and maintaining diets rich in folate, each year approximately 4,000 pregnancies still are affected by spina bifida. Clearly our nation must do more to

educate health professionals and women of childbearing age of the importance of consuming folic acid prior to becoming pregnant.

As part of such an effort, I believe that we must now undertake new and creative initiatives to facilitate women's consumption of adequate amounts of folic acid to reduce their risk for spina bifida pregnancies. The fortification of breads and grains is one step in the right direction and another would be including folic acid in oral contraceptives.

I am very grateful for this opportunity to testify on this behalf. Thank you.

DR. GUIDICE: Thank you very much.

The next speaker comes from the Reproductive Health Technology Project (RHTP) and is Ms. Kirsten Moore.

MS. MOORE: Good afternoon. Thank you for this opportunity. I am the President of the Reproductive Health Technologies Project, a nonprofit advocacy organization based here in Washington, D.C. Our organization does not receive any funding from any pharmaceutical company.

Our mission is to advance the ability of every woman to achieve full reproductive freedom with access to the safest, most effective, appropriate,

affordable, and accessible technologies for ensuring her health and controlling her fertility.

For over a decade we have worked to expand women's access to safe and effective contraceptive technologies, and we strongly support the development of this particular product, a combined oral contraceptive/folic acid product.

In the interest of time, our statement is available and will be included in the docket. I'll skip through the many reasons why. You've heard them from the presentations this morning. I would just like to put before you some of the specific considerations we would like to raise with this committee.

Although the number of birth defects prevented by a combined folic acid oral contraceptive product may be relatively small, the public health benefits of this product outweigh the risks. Extensive clinical data supports the safety and efficacy of both folic acid as a means to reduce neural tube defects among newborns and oral contraceptives to prevent pregnancy. Therefore, any clinical research programs should focus on questions relevant to a combination product.

A combined product provides an important

bridge between contraception and pregnancy, a transition that is fluid for many women. For example, more than 16 million women in the U.S. currently use some form of oral contraception. Of those, approximately 6 percent stop OC use within 12 months to become pregnant.

Furthermore, although the majority of women taking oral contraception do not currently intend to conceive, neither human nature nor technology is perfect, and there are more than 1 million unintended pregnancies each year among contraceptive users, more than half of which are carried to term.

No. 4, a combined product has the potential to increase adherence for oral contraceptives and intake rates for folic acid. For example, the currently "inactive" pills in the monthly oral contraceptive cycle will contain folic acid in the new product, thereby giving women a reason to continue taking oral contraceptive pills throughout their entire cycle. Similarly, because so many women use daily oral contraceptive pills, their intake of folic acid will increase overall.

Fifth. Finally, a combined oral contraceptive/folic acid product holds significant potential for women in low resource settings where

serum folate levels are often low and resources and access is limited.

Although this is not a part of the FDA's mandate, when we asked the company about the availability of this product for such populations, they advised us of their intent to pursue such options and have had preliminary discussions with the U.S. Agency for International Development. We certainly hope similar efforts would be made here in the U.S.

Assuming that an oral contraceptive/folic acid product continues to maintain the functions of each original compound, we believe a combined product has the potential to improve the overall health of women and their newborns and support its development.

Thank you for your consideration of these views.

DR. GUIDICE: Thank you.

The next speaker is Dr. John Grossman.

MR. GROSSMAN: Good afternoon. I want to thank the FDA, Dr. Guidice, and her panel for allowing me to participate in this important process that will serve the interest of women and their families.

My name is John Grossman. I am Professor of Obstetrics and Gynecology, Microbiology and Tropical Medicine, Prevention and Community Health, and Health

Services Management and Leadership at the George Washington University. I'm also Executive Vice President of the Society for Gynecologic Investigation.

For the record, my comments do not reflect the positions of either of these organizations. I am here today to speak to the panel sharing my own perspectives. These are based on nearly three decades of clinical practice, most of which has been in the service of women with significantly complicated pregnancies and my professional service as an educator and policy maker in prevention of community health.

I'm addressing the panel today because I believe that this proposal has great potential to benefit many women. I have no financial relationship with the sponsor, nor with their competitors, and I have no financial interest in this product whatsoever.

The association between folic acid deficiency and neural tube defects is well-established. Policy statements and campaigns to increase the percentage of women of childbearing age who consume the recommended daily allowance of folic acid by credible and prestigious entities such as the March of Dimes, CDC, Institute of Medicine, NIH, American Academy of Pediatrics, ACOG, as well as many

other agencies speak to the importance of this public health measure.

In 1992 the USPHS recommended fortification of the U.S. food supply with folic acid. The FDA's subsequent action in 1996 to initially permit and subsequently require the addition of folic acid to specific flour, breads, and other grains was an important first step in reducing the incidence of neural tube defects in the United States. Several sources of epidemiologic evidence suggest that this action has reduced the incidence by 20 to 30 percent.

Unfortunately, this approach falls short of reducing the burden of disease by an additional 30 to 50 percent that might be achieved through optimal folic acid supplementation overall. More importantly, the North Carolina Birth Defects Monitoring Program and other agencies have clearly identified a subpopulation of minority and undereducated women of childbearing age who are at high risk for folic acid deficiency and subsequent pregnancies complicated by neural tube defects.

For a variety of reasons, many of these women are unlikely to benefit from any of our current approaches including nutritional fortification, use of vitamin supplementation, or early diagnosis of

pregnancy and initiation of care.

Although no child should develop a preventable malformation, this vulnerable population of women are economically least well-prepared to deal with such misfortune. I believe that the sponsors have demonstrated that folic acid supplementation of birth control pills is safe and effective for its intended use and that it has potential to benefit not only this group of women and their families but many others as well.

The families of the 2,500 babies born in the United States each year with neural closure defects each incur additional lifetime costs that are at least $500,000. Reducing the burden of disease by the full 50 percent estimated to be achievable by full folic acid supplementation should reduce by more than $600 million the additional new health costs per year, to say nothing of the pain and suffering that could be avoided.

I urge the panel to recommend approval of this concept because it would be an important next step in that direction. Folic acid supplementation of birth control pills represents a safe and effective approach to reducing the prevalence of folic acid deficiency in women of childbearing age by utilizing

the established scientific advances of both medicine and public health for the benefit of all women and their families. Thank you for your attention.

DR. GUIDICE: Thank you.

The next is a representative from the National Association of Nurse Practitioners in Women's Health. The speaker is Susan Wysocki.

MS. WYSOCKI: Hello and good afternoon. My name is Susan Wysocki and I'm a women's health nurse practitioner as well as the President and CEO of the Nurse Practitioners in Women's Health which is located in Washington, D.C. Neither myself nor my organization have any financial incentive for speaking at this hearing.

What our incentive is is the fact that NPWH was founded in 1980 to assure the provision of quality health care to women of all ages by nurse practitioners. As nurse practitioners, we place a very strong emphasis on health promotion and disease prevention. This emphasis on prevention includes preventing problems during pregnancy and problems to the developing fetus.

You've already heard about neural tube defects and the role of folic acid, but I would like you to focus on one very important aspect of this.

That is that folic acid and its ability to prevent these defects has a very small window, seven weeks of pregnancy. That is often the challenge to us as nurse practitioners.

We emphasize planned pregnancy including the intake of folic acid prior to conception and throughout those first weeks of pregnancy. However, our abilities to reach every woman and to impact her decision really are very imperfect. We appreciate the fact that efforts have been made to get folic acid in other passive ways to women to decrease the rate of neural tube defects, but we haven't achieved everything that is possible.

Oral contraceptives, as you know, are the most popular reversible method of contraception in the United States. Highly effective in preventing pregnancy but you just heard not perfect. In fact, approximately 1 million unplanned pregnancies occur in OC users and in the United States.

In particular, because these women are using oral contraceptives and not planning to become pregnant, then they aren't and may not be using folic acid. They are not motivated to do so. In addition, many of these women have a delay in pregnancy and they miss that seven-week window to seek the advice of a

health care professional early on in that pregnancy.

Providing the public health service recommended 400 microgram daily use of folic acid via passive method as in oral contraceptives would be guaranteed to provide 400 micrograms daily to women without changing prescription-writing or pill- taking behaviors.

Chronic use of combination OC folic acid product would increase body folate stores and could prevent these defects in unplanned pregnancies and even pregnancies that are planned shortly after discontinuing oral contraceptives.

In summary, we strongly support this concept. This product would increase folic acid consumption in low-intake women and would make another major step in the health of women and the health of pregnant women in the United States. Thank you very much.

DR. GUIDICE: Thank you.

The next speaker is Felicia Stewart who represents the Association of Reproductive Health Professionals.

DR. STEWART: Members of the committee, we appreciate very much the opportunity to appear before you today. My name is Felicia Stewart, and I'm the

Chair of the Board of Directors of the Association of Reproductive Health Professionals which is an international organization of 12,000 health professionals who are researchers, clinicians, and educators in the field of reproductive health and family planning.

I also serve as an Adjunct Professor of Obstetrics, Gynecology and Reproductive Sciences at the University of California-San Francisco and am the Co-Director of the Center for Reproductive Health Research and Policy there.

On behalf of the ARHP I am very happy to provide these comments, and they do represent the opinion of the organization with regard to combining folic acid supplements with oral contraceptives.

Like many of the speakers before, I have included in our testimony, and it is available to you in written form, many points that have been made several times but our overview points, and I would just like to comment on the points that we haven't already heard about.

ARHP supports the expansion of contraceptive options to meet the diverse needs of U.S. women. We feel that a product that contains folic acid has the potential to help prevent serious birth defects among

children born to women whose intake is lacking in this vitamin.

Certainly it is hard to overstate the importance of this kind of prevention effort in view of both the financial and, most importantly, the personal and human costs involved in this particular condition.

Because neural tube defects develop early in pregnancy, it is very common, as Ms. Wysocki just pointed out, for women not to be aware of the pregnancy at all during the time interval in which supplementation would be essential.

Although many women do begin taking supplements in advance, many women do not, and the most recent data this year from the CDC PRAMS Review indicating that only about 30 percent of women are taking an appropriate level of folic acid supplementation and that less than half of all women take any kind of a multivitamin during the months before pregnancy is of concern to us.

Certainly fertility rapidly returns when women who have been using oral contraceptives stop. Often their pregnancy can be initiated before they would have any idea that this had occurred.

Despite the fact that oral contraceptives

are effective, we do have a very significant number of women who discontinue them for various reasons and become pregnant, have an unintended pregnancy, or become pregnant while they are taking the method but not able to use it correctly and consistently in a way that provides the effectiveness that we would otherwise hope oral contraceptives would provide.

So an oral contraceptive supplemented with folic acid is a convenient and effective possibility that may well prove to be of significant benefit to women in reducing this risk.

There is another very important potential benefit that none of the speakers have mentioned that I think deserves to be underscored and that is that the fact that a provider is explaining to the woman what this pill is and what the folic acid is for and what the whole concept is about means that providers will be reminded and prompted to address the issue of planning for pregnancy and making sure that women have a chance to understand the precautions that are important in ensuring optimal pregnancy outcomes.

I would be hopeful, frankly, that this may, in fact, turn out to be a very important benefit in terms of reducing the number of women who begin pregnancy smoking or begin pregnancy not realizing the

importance of alcohol consumption or use of medications or drugs that may be toxic or illegal drugs.

By addressing this issue of dealing with pregnancy as something that you plan for and really try to make sure you're in your healthiest best shape is something that we'll be reminded to do just by the fact that we're giving women a new product that contains a concrete example of a good first step in accomplishing that task.

For these reasons, ARHP respectfully recommends that the FDA allow further progress in the development of this oral contraceptive containing folic acid because we believe that such a product could be an important benefit for women in the United States and internationally. We thank you very much for the opportunity to make these comments.

DR. GUIDICE: Thank you.

The next speaker is Melinda Ray from the Association of Women's Health, Obstetric and Neonatal Nurses.

MS. REID RAVIN: I'm not Melinda Ray. I'm Claudia Reid Ravin, and I am speaking in her stead today. I am a certified nurse-midwife currently working for the Association of Women's Health,

Obstetric, and Neonatal Nurses, or AWHONN. Thanks for the opportunity to be here.

I am speaking as a representative of AWHONN's 22,000 health care professionals. AWHONN members are registered nurses, nurse practitioners, certified nurse midwives, and clinical nurse specialists who work in hospitals, physicians' offices, universities, and community clinics across North America as well as in the armed forces around the world.

AWHONN receives financial support for educational programming from Johnson & Johnson. However, neither the association nor myself have a financial incentive for support of this proposed product.

You've heard the benefits, and I won't repeat them here. AWHONN supports policies that encourage women of childbearing age to consume 400 micrograms of synthetic folic acid every day. We also maintain that nurses have the responsibility to inform their patients of the benefits of folic acid consumption during routine visits.

As primary care providers, nurses play a significant role in promoting primary prevention health behaviors. Nurses, therefore, have a

responsibility to provide counseling on a host of health issues including contraceptive choices as well as prevention of birth defects.

Women generally are low consumers of folic acid with only 30 percent of all women consuming a vitamin supplement with folic acid. Women who are not considering pregnancy are believed to be even less likely to consume folic acid on a regular basis because their focus is on preventing pregnancy rather than birth defects.

Each year over 70 million American women use oral contraceptives in an effort to prevent pregnancy. However, roughly 1 million women a year become pregnant while taking birth control pills and half of these unintended pregnancies go to term. As a result, it is vitally important that the folic acid message be conveyed to women not thinking about getting pregnant.

While women may recognize the need to take folic acid, actually changing behavior by purchasing foods rich in folic acid and/or adding it to one's daily pill taking routine is another issue. A 2002 March of Dimes survey indicated that while contemplators of pregnancy are more likely to take multivitamins with folic acid, 25 percent who take a multivitamin forget to take it every day. This

behavior is not unusual. Research into medication taking habits indicates that as many as 20 percent of patients have difficulty using their medications consistently.

It is our opinion that the inclusion of an oral contraceptive that includes folic acid would help health care providers communicate a strong public health message that preconceptual folic acid is important.

In addition, providers can be assured that women of childbearing age taking this product are receiving the recommended daily allowances of folic acid. The addition of 400 micrograms of folic acid supplement to an oral contraceptive provides the health care provider with a unique counseling opportunity.

We know that health care providers should screen women of childbearing age for folic acid consumption in an effort to promote taking a daily multivitamin and to prevent neural tube defects. We also know that 53 percent of women not taking a daily multi-vitamin indicated that they would likely do so if their health provider simply encouraged them.

The potential availability of a combined oral contraceptive gives providers an additional

option and prescriptive choice that can be a flag to have a discussion with a patient who may be either unaware of the benefits of folic acid or not see themselves as needing folic acid because they are not yet contemplating pregnancy.

Since the science indicates that preconception consumption of folic acid is critical for the prevention of birth defects, and statistically 50 percent of pregnancies in the United States are unplanned, we assert that the woman who does not wish to become pregnant may be at the greatest risk of being a low consumer of folic acid.

The desire of the woman to prevent pregnancy through the use of oral contraceptives should be seen as an ideal opportunity for counseling on the benefits of folic acid consumption. Thank you.

DR. GUIDICE: Thank you.

The next is a representative for Healthy Mothers, Healthy Babies National Council on Folic Acid. The contact person is Donna Gentry.

MS. BOLES: Good afternoon. My name is Anita Boles, and I'm the Executive Director of the National Healthy Mothers, Healthy Babies Coalition. In my role as the current chair of the National Council on Folic Acid, I am pleased to give brief

comments before this committee on the concept of an oral contraceptive that includes a folic acid supplement.

The National Council on Folic Acid would like to thank the Committee for the opportunity to discuss this important issue. The council is a partnership of over 80 organizations whose mission is to improve the health by promoting the benefits and consumption of folic acid. Let me also say here that the council has no financial incentive for speaking at this hearing.

As we are all aware here, folic acid, a widely available vitamin B, is critical for proper cell division and growth. It is especially important during the early weeks of pregnancy and when the embryonic neural tube, which later becomes the brain and central nervous system, is forming and closing.

We know that defects in the closure of the neural tube result in the development of a group of birth defects commonly referred to as neural tube defects. We also know that the consumption of 400 micrograms of folic acid taken prior to conception and early in gestation can prevent as many as 70 percent of neural tube defects.

In the late 1990s the National Council on

Folic Acid began an educational campaign targeting two separate audiences, the pregnancy contemplator and the non-contemplator. The contemplator, of course, are women who are thinking about or planning a pregnancy; while non-contemplators are women who are not currently thinking about having a baby.

In spite of our diligent educational efforts, and the efforts of many, many groups across the country, as you just heard through the AWHONN testimony, a 2002 March of Dimes survey indicated that only 30 percent of women of childbearing age, that's ages 18 to 45, take a vitamin supplement with folic acid every day and 25 percent of those who take the multivitamin forget to take it every day.

This data suggest that women generally remain low consumers of folic acid even while contemplating pregnancy. Following that logic, the National Council on Folic Acid members assert that the non-contemplators of pregnancy are at an increased risk of low folic acid consumption. We assert that the addition of a folic acid supplement to an oral contraceptive routine for the non-contemplator makes sense for two reasons.

First, by putting folic acid in oral contraceptives, we can ensure that women who are

actively trying to prevent pregnancy can radically reduce the risk of an neural tube defect affected pregnancy should a contraceptive failure occur.

Each year, as we are all aware, over 70 million American women utilize oral contraceptives in an effort to prevent pregnancy. And despite the pill's high rate of efficacy, roughly 1 million women a year become pregnant while taking birth control pills. Half of these unintended pregnancies go to term. Supplementation of a birth control pill with folic acid will provide these non-contemplators with the recommended protection level of 400 micrograms of folic acid a day and provide some piece of mind to women and their families in the event of an unplanned pregnancy.

Second, the supplementation of folic acid in an oral contraceptive makes sense because folic acid is one of the few water soluble vitamins that is retained in the liver and red blood cells for a period of up to three months. While more research is needed, early studies suggest that the folic acid that remains in the system may afford some level of protection in the prevention of an NTD-affected pregnancy. Many women choose to take oral contraceptives because of the ease in converting back to a fertile state.

When a woman decides to stop taking oral contraceptives, health care providers, of course, have the responsibility to counsel women about folic acid supplementation. However, women who may have not seen a health care provider or who have become pregnant within the first month of ceasing the pill consumption, maybe even before they begin taking their folic acid regularly.

The potential for an added three months protection for the new contemplator of pregnancy may have a tremendous impact on the prevention of neural tube defects. This is why the National Council on Folic Acid respectfully recommends to this Committee to allow the development of an oral contraceptive that includes 400 micrograms of folic acid. We believe that such a product can help in the fight to reduce the incidence of birth defects in this country.

Again, on behalf of the National Council on Folic Acid, thank you for the opportunity to provide these comments in support of the concept of an oral contraceptive that includes a folic acid supplement. Thank you.

DR. GUIDICE: Thank you.

Our next speaker is Ms. Sonya Oppenheimer.

DR. OPPENHEIMER: My name is -- excuse me.

I don't have much of a voice but I came anyway. My name is Sonya Oppenheimer. I'm a developmental pediatrician, Professor of Pediatrics, and Director of the Division of Developmental Disabilities of Cincinnati Children's Medical Center in Cincinnati, Ohio.

Most important, I've been the Director of the Spina Bifida program at the hospital since 1970, a long time. This program serves all children and adults with spina bifida that are born in our tri-state region. In addition, more recently, we've been providing prenatal counseling.

I'm appearing at this hearing because I have a strong personal commitment to continue to support all efforts to prevent this significant birth defect. I have no financial relationship with any company or group that might be impacted by this meeting.

In the early '70s, and it's interesting listening to everybody because I've been around for a while, the young president of the Spina Bifida Association, which was newly formed at that time, and a man who was also the father of a young child with spina bifida, and I attended a CDC-sponsored conference at the urging of Dr. Oakley to discuss the possibility of adding folic acid to bread in an effort

to decrease the incidence of the birth defect.

At that time the conversation was much different than what I'm hearing today. It was, "This is nonsense. What are you doing? There's no proof." On and on and on. We enthusiastically supported an aggressive research program to prove the effect of folic acid. There, however, at that time were obviously still questions if folic acid was the only answer so supplementation of food was abruptly dropped.

During the past 20 years, as you've been hearing, research appears to have confirmed the effectiveness of folic acid in decreasing the incidence of spina bifida. This currently brings us to the recommendation to supplement folate in birth control pills.

Ohio's Bureau for Children with Medical Handicaps has a state committee which is rather unique. In this committee, which is rather unique, in this committee there are representatives from the six clinics in Ohio that serve children and adults who have spina bifida. this allows us to track the number of infants born in Ohio.

All the clinics over the past few years have seen a drop in the number of children born with spina

bifida. But, unfortunately, we do not have the numbers of pregnancies that have been terminated and that is a number we should not forget because it's a lost number and those people who elect to terminate the pregnancies suffer a great deal when they have made such a decision.

Prior to 1999 in our clinic we average about 20 to 25 newborns a year. In 2003 we've had 11 new babies born and I have direct knowledge of at least two pregnancy terminations. Of interest, three of these new babies that were born do come from -- the parents come from a lower socioeconomic status and are having tremendous troubles in trying to help their child keep the appointments understand what's happening. And a couple of them, indeed, are considering abandoning those children.

We've routinely asked about folic acid use and the usage, as we've heard, is very variable. I'm not going to repeat numbers that we've been talking about but when folic acid supplementation was first entertained in the '90s everybody said, "Hey, Sonny, great. You won't have a job anymore. You are going to be out of business because there won't be any other babies born."

Unfortunately, that's not what's happening

and we keep seeing all of the problems that are occurring including not even mentioning the problems that the adults who we also serve are having as they have gone into adulthood. I hope you strongly consider the proposal to add folic acid to oral contraceptives. Thank you.

DR. GUIDICE: Thank you.

The next is a representative from Planned Parenthood Federation of America. The contact person is Vanessa Cullins.

DR. CULLINS: Good afternoon to all and thank you so much for giving me the opportunity to speak today.

My name is Vanessa Cullins. I'm Vice President for Medical Affairs for Planned Parenthood Federation of America. I have no personal financial relationship with the sponsor. Planned Parenthood affiliates do, indeed, purchase oral contraceptive products from the sponsor.

We have 124 affiliates across this nation that operate over 850 health care clinic sites. Planned Parenthood Federation of America enthusiastically supports folic acid supplementation of oral contraceptives.

The addition of folic acid to oral

contraceptives is an important public health measure that allows women to postpone pregnancy while simultaneously preparing for future healthy pregnancies. Such supplementation is the true embodiment of the meaning of family planning; that is, deciding whether and when to have children and ensuring an environment in which every child is wanted, loved, planned for, nurtured, and provided for.

As you've heard, the incidence of neural tube defects could be reduced by 50 to 70 percent if folic acid supplementation precedes pregnancy and is continued at least seven weeks through gestation. Dietary folic acid fortification has resulted in approximately 20 to 30 percent decline in neural tube defects which means an additional 20 to 50 percent decline is possible.

The public health impact of adding folic acid to oral contraceptives goes way beyond reductions in neural tube defects. The very act of adding folic acid to oral contraceptive pills enables an important dialogue opportunity between the clinician and the woman, as alluded to by Felicia Stewart earlier.

Both the clinician and the woman have the opportunity to move beyond the issue of the moment --

that is, pregnancy prevention -- and begin a dialogue about preventive measures that should be employed in the present to prepare for the healthiest possible future pregnancy.

It allows for a teaching moment when a clinician can give anticipatory guidance about the importance of vitamin intake during the time period when pregnancy is contemplated, suspected, or diagnosed with the first prenatal visit has not yet occurred. For neural tube defects preventable through folic acid intake, this information is critical.

Adding folic acid to oral contraceptives is personal, societal, and the medical recognition that most women using reversible contraception plan to become pregnant in the future. Adding folic acid to oral contraceptives also acknowledges that when unintended pregnancy does occur, whether from method or use failure, the best possible situation for the woman and for the ongoing pregnancy is a situation where she is at least physically prepared to nurture an ongoing pregnancy.

These concepts are important to all women intending future childbearing and are especially important to the woman who has delayed childbearing in order to more fully participate in civil and

professional endeavors in addition to fulfilling her role as a mother.

In this increasingly technological society, many women find it necessary to delay childbearing in order to complete educational and skill attainment required to reach their professional aspirations. Fecundity drops with age. For this reason, when the women who has delayed pregnancy decides to conceive, it is imperative that she attempt and achieve conception in the best possible physical condition.

Folic acid supplementation will assist in achievement of this goal. Adding folic acid to oral contraceptives is a public health measure similar to adding fluoride to the drinking water. The difference is that adding folic acid to oral contraceptives can be successfully targeted only to the intended beneficiaries; that is, women of childbearing age.

This measure will positively benefit millions of women and millions of pregnancies over the course of time. It is estimated that eight out of 10 women take oral contraceptives at some point in time in their reproductive lives. Many of these women have been on more than one oral contraceptive formulation. Many of these women will benefit from the addition of folic acid to an oral contraceptive formulation

because there is pretty high probability that that woman may be exposed to that formulation at some point in time in her life.

In any given year 60 million of 70.1 million women of reproductive age are taking oral contraceptives. We do not know precisely how many of these women have low folic acid intake. We do know low folic acid intake tends to occur more frequently among women of low socioeconomic status, the very women who in general is at risk for environmentally induced poor pregnancy outcomes.

While folic acid supplementation will only have an effect on the incidence of neural tube defects, the potential for dialogue because of the addition of folic acid to oral contraceptives opens the door to discuss other measures that will likely improve pregnancy outcomes. As mentioned before, the issues around early prenatal care, preconception weight loss, smoking cessation, nutrition, etc.

While a product containing folic acid will be most beneficial to those women with low folic acid intake, the beauty of this concept is that women with adequate folic acid intake will not be harmed. The primary concern of excess folic acid intake is that of masking vitamin B-12 anemia. This is an issue for the

elderly and is not an issue for healthy reproductive-age women taking oral contraceptives.

Four hundred micrograms is the proposed daily dose for oral contraceptives. Four hundred micrograms a day is the recommended amount of folic acid by the Institute of Medicine and the United States Public Health Service.

This dose is less than 10 percent of the 5,000 microgram dose a day that may temporarily correct anemia due to vitamin B-12 deficiency. The bottom line is that there is very, very little downside to the addition of 400 micrograms of folic acid to oral contraceptives and the potential benefit of supplementation of oral contraceptives with folic acid is substantial for women, their pregnancies, their families, and society. Thank you.

DR. GUIDICE: Thank you.

I'd now like to call, please, Mr. Douglas Rose.

MR. ROSE: Thank you. It's a pleasure to be here. My name is Douglas Rose. I'm president of Irwin R. Rose and Company in Indianapolis, Indiana. We are a commercial real estate firm specializing in apartments and multifamily housing across five states. I'm here on behalf of my wife and family. I'm here as

a parent of a child who was born with birth defects. Our youngest, Emily, age 4, was born with achondroplasia which has nothing to do with the subject matter you are contemplating here.

While medical science knows a great deal now about achondroplasia -- for example, the gene has been identified where a genetic insult occurs. The location on the gene, etc., has been identified -- the prevention science is a long way from reality. Fortunately, that's not the case with folic acid preventable birth defects.

By the way, let me state, if it wasn't implied, I have no financial interest in anything being discussed here and I'm here at my own expense on my own time.

I'm here to urge the FDA to approve the marketing of this drug-drug combination as quickly as possible for, at a minimum, the benefit of the hundreds of thousands of women -- I've heard the figure here this afternoon a million women each year -- who become pregnant while taking oral contraceptives or those women who become pregnant having stopped taking oral contraceptives.

Approval of this drug-drug combination, these two drugs which are already approved drugs,

will, I believe, have a dramatic impact on women's public health in the United States. Some of the facts are not in dispute. Not nearly enough of the eligible population of women of reproductive age are receiving the recommended daily dose of B vitamin folic acid.

That's a shame. It's tragic. It's tragic that today in Indiana and across America babies continue to be born with this most devastating birth defect. When we learn about these issues and begin reading about these issues, it's difficult to describe to you how shocked and angry we were when we discovered that many of these cases could have been prevented by simply introducing B vitamin folic acid. It's shocking. What you have before you today is a wonderful opportunity to advance women's public health, advance the health of babies. Every baby deserves to be born free of birth defects with an opportunity to live a full life.

Every family with a child without birth defects is a child helped. I know a little bit about the challenges the families face. I liken birth defects to acts of terrorism. I know that may sound odd, but terrorism is indiscriminate. It's devastating. It crosses socioeconomic lines. It has lifelong impacts.

It impacts not only the baby who is born with the birth defect but the child's siblings, parents, extended family. There are no words sufficient that I know of that can adequately describe what a family deals with when they bring home a child born with birth defects.

I really appreciate this opportunity. If I appear to be nervous, that's because I am. Standing in front of all of you leading experts is quite overwhelming to me. I felt this was important enough to come here and speak my mind for just a few minutes.

When our daughter was born, we were determined, while she will have many opportunities and a full and complete life. yes, with difficulties that will lie ahead, we were determined to make a difference.

Each of you now have an opportunity to make a difference for hundreds, perhaps thousands, of women and their families and their healthy babies. You each should be very proud of this opportunity that you have. So many families will be grateful. I'm grateful to you for this opportunity and wish you all happy holidays. Thank you.

DR. GUIDICE: Thank you.

The next is an organization, American

College of Nurse-Midwives, and the speaker is Deanne Williams.

MS. WILLIAMS: Good afternoon. I am Deanne Williams. I'm a nurse mid-wife and I'm Executive Director for the American College of Nurse-Midwives. Even though I've spent quite a bit of time preparing for and getting here and waiting for my opportunity to speak, you'll be glad to know that I don't have anything to say that you haven't already heard and I'm not going to take your time because if I were sitting there, I would be getting a little cranky right now.

I will summarize one summary statement: That you've heard from the nurse-midwives, you've heard from the nurse practitioners, you've heard from the obstetrician/gynecologists, you've heard from the clinics that are providing these services that this is an important decision that will have a significant impact, and I urge you to move speedily to approving this request. Thank you.

DR. GUIDICE: Thank you.

And our last speaker is Dr. Richard Falk who represents the American Society for Reproductive Medicine.

DR. FALK: I think I should represent the Washington Redskins, being last. I should say I have

no financial incumberances which will affect my testimony.

My name is Richard Falk. I'm a gynecologist and reproductive endrocrinologist. As Linda said, I represent the American Society for Reproductive Medicine. The Society is a multi-disciplinary organization of approximately 9,000 members representing every state, the District of Columbia, and more than 100 foreign countries.

The mission of the Society is the advancement of art, science, and practice of reproductive medicine central to which is the health of women and their children. It's difficult to be entertaining and informative at this juncture after following so many erudite speakers but, as we all know, hearing the lyrics again and again tend to make us remember the song so I'll read our brief statement. The full statement is outside.

It is well accepted that consumption of folic acid supplements during early pregnancy reduces the incidence of neural tube defects by 50 to 70 percent. The U.S. Public Health Service now recommends that all women capable of becoming pregnant supplement their diet rich in natural folates with 400 micrograms of synthetic folate acid.

The oral contraceptive pills are a widely utilized method of contraception. In the year 2000 12.9 million married and sexually active unmarried North American women used this medication. Despite its proven efficacy there are approximately 1 million unplanned pregnancies in OCP usage annually.

Approximately half of these pregnancies result in a live birth. Because these are unanticipated pregnancies, it is likely that most of the women have not supplemented their diets with folic acid. In addition, oral contraceptive usage is associated with decreased intentional absorption of folates and some studies have shown diminished plasma folate levels as well.

Combining the recommended 400 micrograms supplementation of folic acid with an oral contraceptive would increase the body stores of folate and would be expected to result in a decrease in neural tube defects in children born of unplanned pregnancies.

The ASRM, therefore, enthusiastically supports the development and distribution of a combined OCP folate preparation. Thank you.

DR. GUIDICE: Thank you. I would like to thank all of the individuals for sharing their

experiences and their comments and also the organizations for their comments.

There were several other individuals and organizations who may be sitting in the audience and have expressed a desire to speak additionally and their filing of this information actually occurred after the deadline so we will be unable to accommodate them at this time but we would like to thank you for being here.

In addition, we had some letters, one of which came from the March of Dimes and the other from Dr. Vladimir Vartileky from the University of Alabama in support of this concept.

As charged to the Committee, one of our charges in addition to the discussion is to provide advice to the FDA with regard to particular issues for the issue at hand. There is a list of five questions, and I would like to now open the floor for the Committee to discuss these five questions.

The first question is -- and I would like to reassure the Committee also that there will be time for discussion about these questions as we go forward and perhaps other issues that may come up as well.

The first question is: "Are further increases in folic acid intake, beyond what is

available from fortified cereals, likely to result in public health advances in preventing further neural tube defects?"

Is there any discussion on this by any of the Committee members drawing from what you have read in your packets and also from the presentations today?

Dr. Darney and then Dr. Montgomery Rice.

DR. DARNEY: Phillip Darney. I assume this increase means if more women were taking folic acid, rather than a change in the mean serum concentration of the population; that is, an increase in prevalence rate, rather than an increase in dose.

DR. GUIDICE: I think that is an excellent question to ask our representatives from the FDA for clarification, please.

DR. GRIEBEL: I think what we're asking is does it -- that first part of the phrase is in addition to the food fortification, would additional supplementation which would be further increases in folic acid intake -- so basically we're referring to the concept that we are discussing today.

DR. GUIDICE: Is that clear? Dr. Rice.

DR. RICE: I assume that you also mean what will be able to be required in the diet, plus if a person was taking supplement. So are you saying

beyond that, if they were taking the supplement as prescribed, oral contraceptive plus folic acid, they wouldn't be taking anything else additionally other than what's in the diet.

My question was to Dr. Yetley, I believe, the people who spoke earlier. When you look at the 25 foods that you say people commonly take in their diet that have supplement, if you look at an average diet, what is the maximum amount in general a reproductive age woman actually gets in that consumption, if you look at the variety of foods that a person typically gets in a day? Is that that 200 number that we're talking about that people are getting? What is that amount? You know what I'm saying? If I eat some cereal and drink some milk and then I have a salad and some chicken for lunch, if I eat those type of things, what am I typically going to get in a day?

DR. YETLEY: Well, obviously there's a wide range of intakes. I think the other point is that we don't have a good accurate estimator. I mean, we can make estimates but they are probably significantly underreported.

I clearly is feasible for a woman and not without a lot of stretching to achieve a good diet plus additional fortification folate from the diet,

particularly if she eats breakfast cereals or other foods that are highly fortified. It is certainly feasible and not a huge stretch of the imagination to get there.

I think what you have is probably a lot of women who may or may not have good diets but are not in addition taking either a supplement or a breakfast cereal, which I think, is where at least at the current time, the recommendation is. I don't know whether that answers your question or not, but if you make an estimate of could they get a good diet eating fruits and vegetables, dairy, whatever, following dietary guidelines of the U.S. Government, yes.

DR. RICE: So they can get that 400, but we know that they don't based on when you look at the NHANES data, etc. When you look at the typical -- when you do those surveys, you know that they are not actually getting it.

DR. YETLEY: Let me just make a comment. There was a lot of emphasis this morning on the Lewis, et al., paper and I am a co-author of that paper so I wanted to put some cautions in interpreting that paper. That paper was done before fortification had been implemented. We didn't know at that time what the marketplace would do and the marketplace responded

much more significantly and to a much larger degree than we estimated in that paper.

We also did not have good analytical data on the folate content of foods. Now that we have better data we know that we underestimated on that. For a number of reasons, that's a very significant underestimation of actual intake, and, therefore, overestimation of how many women don't meet the dietary pattern.

My guess is I would rely more on the serum data because I think that tells you how many women aren't, from whatever sources, actually getting sufficient folate. I would recommend you look at the serum and red cell data rather than the dietary data which is very fraught with error and probably underestimations.

DR. RICE: Okay. Thank you.

DR. GUIDICE: Is there any further discussion with regard to this particular question?

Dr. Lipshultz, Dr. Dickey, and Dr. Rosenberg.

DR. LIPSHULTZ: This is just kind of a point of information. That is, we're being asked to comment on "likely to result in advances," and I'm just trying in my own mind to quantitate these advances in terms

of the 16 million women.

I did not understand the response from the representative from Johnson & Johnson as to whether or not this combination will be available for all companies or is this specifically for a Johnson & Johnson product and, if so, how many of the 16 million women will be able to profit from this combination?

DR. GUIDICE: Would someone from the sponsor like to respond? Dr. Friedman.

DR. FRIEDMAN: The question was about how many of the 16 million women who currently use oral contraceptives could potentially benefit and about potential availability of such a product to other makers of oral contraceptive products?

DR. LIPSHULTZ: The question is is this restrictive in the ability to combine these two, or is this going to be just globally available to all manufacturers?

DR. FRIEDMAN: Well, currently we are here today really to discuss the concept to see if the concept itself makes sense to this committee. We feel it does and have presented arguments to that effect.

With regard to issues of other companies, it's a little premature now to speculate on their interest in such a product. Johnson & Johnson has

always been open to discussion of co-licensing or co-marketing products with other companies and would remain so. But at this point in time, it is, I think, very premature to speculate on how that could play out over time.

DR. LIPSHULTZ: I mean, I think you could give me just idea as to the marketplace in terms of oral contraceptives and Johnson & Johnson. Are we talking about 50 of women use Johnson & Johnson oral contraceptives? 80 percent, 40 percent? I mean, if you could just generally give me an idea. I mean, I'm sure you have these numbers available.

DR. FRIEDMAN: Dr. Cafferson will address your question.

DR. CAFFERSON: The answer is no, I don't have numbers available for a prospective product but when we're talking about -- you'll tell me if I'm addressing your question appropriately. Given the current usage patterns for estrogens and progestins, the type estrogens, the type progestins, the type regimens for those products that would be available to any company, in this case ours, for development with folic acid, it would exceed, I believe, probably 85 percent of current usage of pills.

So I think that may get at what you are

after. If we look at norethindrone products, if we look at levanorgestrel products, if we look at ethinyl estradiol, etc., if we take it in the broadest sense of what this could mean, it could be very, very broad coverage. However, as Dr. Friedman mentioned, we are really here focusing on the concept itself. I understand, Dr. Lipshultz, you are after the broader -- what might the public health consequences be.

DR. LIPSHULTZ: The reason I'm doing that is because the numbers that we hear today are based on 16 million women taking pills. Now, is that a realistic number based on the combination? Will 16 million women be able to get this combination?

DR. CAFFERSON: As far as being able to get this combination, certainly they would be able to get any combination and would be prescribed appropriate combinations, but I think part of that question -- another response to that question is to remember that we are currently, and have been for years, the dominant suppliers of oral contraceptives in the public sector as well. The availability of these pills, we believe, would be broad.

DR. GUIDICE: I think one of the issues -- I'll get to you in just one second -- I think what Dr. Lipshultz is getting at, and may be in the minds of

others around the table as well, is whether the 85 percent of 16 million, and clearly there would be -- well, there would likely be other individuals who would benefit from this besides the 16 million women who are currently taking OCPs, but does Johnson & Johnson make 85 percent of those pills? I think that's the question that is being asked.

DR. CAFFERSON: The answer is --

DR. GUIDICE: Or components of them.

DR. CAFFERSON: Yeah. The answer is no. We have about 40 percent of the market that now I'm referring to. However, zero of that 40 percent contains folic acid. The question, as I understood it, was what could the availability be versus what restrictions on that availability might be. So there are two different questions but you have both answers.

DR. GUIDICE: Thank you.

Dr. Emerson.

DR. EMERSON: Just to follow up on that, I think what we are really being asked to talk about here is the public health impact of making this decision. There is no product at hand; there is no issue.

But even if there were a product at hand, if the person walked in here talking about doing this who

currently had a .01 percent of the market share, there's this issue of is this is a good product, a good idea of putting it in there, they are looking at the possibility of marketing such a product and hopefully capturing more of it.

I think that's what we have to address more than truly the Johnson & Johnson question specifically is the idea of whether there would be a public health benefit. The question at hand here, just starting out, is there room for improvement in folate intake or is everybody already taking everything they are going to take.

DR. GUIDICE: Dr. Rosenberg, did you have a comment you wanted to make?

Yes, Dr. Mills and then Dr. Hager.

DR. MILLS: I'd like to address that question in terms of particularly what Dr. Rice was asking earlier, following Dr. Yetley's comments. I think there are two ways to attack this. One is to look at the reduction in neural tube defects that we have currently experienced. A number of the speakers this afternoon talked about a 20- to 30-percent reduction. I think it's very important to note that is based on incomplete data and that is probably not an accurate reflection of the current achievements.

The better the data, the greater the reduction. If you look at the Canadian studies, they are in the range of 50 percent. I think the real question is: Can we do better than 50 percent? That is, is there another 20 percent of neural defects that are fully preventable? And there may be, but I don't know for sure that there are.

The second way to address that question is to look, as Dr. Yetley suggested, at the blood levels. If you look at a red cell folate level, saying that 400 is target, and I admit this is just based on reasonable evidence, not great evidence, then there's still a number of people who are not meeting that goal. So that using the red cell folate as your standard, there are a number of people who could benefit from additional folic acid. I would just suggest those as ways of approaching the question.

DR. GUIDICE: Thank you.

Dr. Hager.

DR. HAGER: I would just indicate that I do think that this is a broader topic than just the concept. Not a single one of the public speakers said "an oral contraceptive" with folic acid supplementation. They all said "oral contraceptives" with folic acid supplementation. Although we are

discussing a concept, I believe it is important to the function of the committee that we indicate that, in my opinion, that we see this as a concept that needs to be applied like we would herd immunity. This is for the best public health impact.

We're talking about if folic acid is beneficial, and certainly there is some evidence that indicates that folic acid can decrease the risk of neural tube defects, then we need to be sure that concept is conveyed to benefit all women who would be exposed to the use of oral contraceptives, rather than just limiting it to one product.

Regarding the public health effects, we don't truly know the number needed to reduce further that risk of neural tube defects. We need information on that. We don't know the effectiveness after 90 days or so as far as binding and the amount that is still left in plasma levels. We don't know about women who discontinue so we need some further follow-up.

I would say that I think the public health implications based on what we have heard are that folic acid certainly can benefit. I would hate to see us limited to a single product.

DR. GUIDICE: Thank you.

Dr. Dickey, you had a comment?

DR. DICKEY: Well, again, I think if we answer the question that has been posed to us, it really doesn't have anything to do with what our sponsors talked about. The question is simply: Are further increases in folic acid intake likely to result in an improved public health outcome?

It's not that it's not available technically. You could get it through diet, you could get it through multi-vitamins, but it's clear to me as you read through the material that we have a substantive portion of the population at risk that is not taking advantage of diet, vitamin supplements, or other mechanisms, and that the answer to this question -- quite aside from this specific concept -- the answer to the question about folic acid intake is yes, our society could benefit from further mechanisms to make folic acid available.

DR. GUIDICE: Thank you.

Dr. Tamura.

DR. TAMURA: Let's assume that we are going to say yes to this first question. Then I would like to know, considering that the national decline in the rate of NTDs already happened before we knew that folic acid was indeed effective to prevent NTD, and

also ever since this mandate by FDA that so-called enriched cereal and grain products should be fortified with folic acid started in 1998, then we saw further decline in NTD prevalence.

Now my question is: If we answer yes today, how we are going to monitor that our answer would be correct or not? That's what I would like to know.

DR. GUIDICE: And I'm wondering who might provide us some insight into that, either on the committee or from the FDA.

DR. RICE: Again, we are not -- we're talking about a concept today. I am assuming that, regardless of what our vote is for this, that there are going to be lots of additional or some additional studies that are going to answer a lot of the questions related to safety, toxicity, dosage, etc. So I think those questions will then be part of what the FDA will do when they assist with the development of studies that will hopefully begin to develop this product.

So I am assuming that we are only here to talk about the concept and address those issues and then that nothing is going to come to market for a while because there's got to be some phase -- maybe some Phase 1 but definitely some Phase 2 trials, some

other trials that look at what the appropriate dose is and what are the safety issues associated with it, what are the pharmacokinetics that are associated with combining them. I think those issues will be answered with the properly designed studies. I definitely would like to know if I'm wrong in making that assumption.

DR. SHAMES: No, you are correct. There are -- we need to address the concepts here. There are lots of details that we are not talking about that really we can't talk about here. There are regulatory issues and legal issues that we haven't even totally addressed ourselves.

We have constructed these questions in such a way that at least we can know if we should even move forward on this concept, so that's really what we're talking about.

DR. GRIEBEL: But I would like to add that if there are important issues that you think that we need to know more about such as specific safety information that you would need to know before you felt comfortable with this, we would like to hear what those are and people's ideas on how to get those answered.

DR. GUIDICE: Dr. Tolbert.

DR. TOBERT: I would like to comment on an issue which surfaced a few minutes ago. There seemed to be an implication that Johnson & Johnson, who I presume have intellectual property in this area, should put it into the public domain because this is an important public health advance. It is an important public health advance, and I hope it's very widely available. But lots of other products of pharmaceutical companies are, as well. I mean, there would be no pharmaceutical industry if the pharmaceutical industry did that. I presume what will happen is Johnson & Johnson will market oral contraceptives containing folic acid. That may give them an advantage over their competitors. Doctors may write prescriptions preferentially for those products, but that's how the system works. These products will be available to anybody who cares to take them and any doctor who cares to write the prescription for them.

DR. GUIDICE: Thank you.

Dr. Rosenberg.

DR. ROSENBERG: In exploring the concept, I think it's already been mentioned that we really should be talking about folic acid intake beyond what is currently contributing to folic acid nutrition in the diet, not just fortified cereals. That point has

already been made. It's important to reflect on whether we are trying to increase folic acid nutrition or trying to increase simply the intake of crystalline folic acid. They are not exactly the same, and I think that that does deserve a little further clarification.

To add to that, I would say does the concept include the idea that for public health reasons we really want the woman who conceives to be in the best possible health, the best possible nutritional status for her own health and for the health of the fetus and, therefore, is it unreasonable to think that this concept should allow consideration of more than folic acid being added to a drug which is used preconceptionally.

It's true that there's this powerful relationship in the research between folic acid intake periconceptionally and prevention of neural tube defects. But is part of the concept here is an opportunity to deliver improved nutrition to women in a way that would have an impact on their periconceptional or preconceptional nutrition status. This is a leading edge example. Is that part of the concept in the view of the FDA?

DR. SHAMES: I just think that we first have

to get past this one supplement that has a clear benefit and if we haven't solved that here at the Committee on a scientific level, then we have to go and try to see if we can address it on a regulatory level. If that all works out, then we can talk about other things. I think we need to get over this first.

DR. ROSENBERG: But it is a concept that we're talking about here.

DR. SHAMES: Well, I would like to hear what you have to say about this particular concept first, I think.

DR. GUIDICE: I hope these are comments that are relevant to the concept at hand.

DR. CROCKETT: I would like to make a motion that we end discussion on Question No. 1 and move to a vote, please.

DR. GUIDICE: Okay. A motion has been put forward that we end discussion on Question No. 1 and put it to a vote. It's been seconded and this committee doesn't usually have motions and approvals, etc. However, I think we have heard the entire range of issues. I think we are probably in a very good position right now to take a vote unless there is someone who has a burning issue.

Is this a burning issue, Dr. Green?

DR. GREEN: I'll let you judge that. It's an issue that concerns a point that was brought up, and a very relevant one, by Dr. Mills in this discussion that speaks to, I think, Question No. 1, and I don't think we'll be able to come back to it, which is "Are further increases in folic acid likely to result in public health advances?"

Certainly I would agree with the overall notion that 400 micrograms figure on red cell folate would be a good yardstick to do that. What I have not heard -- and please forgive me if there is information that was presented that addresses this issue -- is whether the value, 400 or any other level, when you look at the distribution curve for red cell folate in the population at large and the effects of increased folate intake, the effect that would have on the shift of that distribution curve, would affect the fraction of the population that might be at greatest risk, specifically, from what we've heard, those where we are addressing an issue of gene-nutrient interaction, particularly the TT homozygotes.

Is there any information? I mean, one would predict, given that this is a common polymorphism, that the distribution of red cell folate is going to be trimodal within that population. This may not be

apparent from looking at a distribution curve but my question is if you look at the left-hand side of that curve buried within that group surely must be the TT group. And the question is: Does 400 micrograms of red cell folate -- is that attainable for that group?

DR. GUIDICE: Dr. Mills, since you were commented upon --

DR. MILLS: Since I got tagged.

DR. GUIDICE: Right.

DR. MILLS: There are some data. Unfortunately, I can't give you chapter and verse but there's a paper by Ann Malloy looking at the Irish cohort that showed how the TT allele relates to folate levels and whether that can essentially explain the folic acid effect, or, actually to be more specific, what proportion it can explain. And there's a great deal that is independent of the TT, if that helps to answer the question.

DR. GUIDICE: Thank you. Many of the comments that had been made around the table including this one and also the issue of potentially other supplements or, at least, conceptually added to oral contraceptives can certainly be, I hope, included in our recommendations to you beyond these six questions for subsequent evaluation and consideration by the

Agency.

I would like to move forward and restate Question No. 1 and then I will go around the room and pick on people; that is, to ask directly of the voting members for their yes or no answers. The question is: "Are further increases in folic acid intake, beyond what's available from fortified cereals, likely to result in public health advances in preventing further neural tube defects."

For each question we'll start on different sides of the room, so people don't feel particularly picked upon, but at this time I would like to begin with Dr. Hager, please.

DR. HAGER: Yes.

DR. GUIDICE: Dr. Patten.

DR. PATTEN: Yes.

DR. GUIDICE: Dr. Darney.

DR. DARNEY: Yes.

DR. GUIDICE: Dr. Green.

DR. GREEN: Yes.

DR. GUIDICE: Dr. Crockett.

DR. CROCKETT: Yes.

DR. GUIDICE: Dr. Rice.

DR. RICE: Yes.

DR. GUIDICE: Dr. Wenstrom.

DR. WENSTROM: Yes.

DR. GUIDICE: Dr. Emerson.

DR. EMERSON: Yes.

DR. GUIDICE: Dr. Shane.

DR. SHANE: Yes.

DR. GUIDICE: Myself, yes. Dr. Greene.

DR. GREENE: Yes.

DR. GUIDICE: Dr. Tamura.

DR. TAMURA: Yes.

DR. GUIDICE: Dr. Rosenberg.

DR. ROSENBERG: Yes.

DR. GUIDICE: Dr. Dickey.

DR. DICKEY: Yes.

DR. GUIDICE: Dr. Lewis.

DR. LEWIS: Yes.

DR. GUIDICE: Dr. Lipshultz.

DR. LIPSHULTZ: Yes.

DR. GUIDICE: Dr. Macones.

DR. MACONES: Yes.

DR. GUIDICE: Dr. Stanford.

DR. STANFORD: Yes.

DR. GUIDICE: For the record, that was a unanimous round of yeses. Thank you all.

The second question is: "Can we define a subpopulation among women of reproductive age that

needs additional folic acid?" We have heard through several different talks today about some subpopulations, including women of lower income. I'm just wondering if there is any discussion about this. Also including, I guess, for genetic polymorphisms.

Dr. Rice.

DR. RICE: Linda, we haven't spoken about diabetics or epileptics. I know they have more neural tube defects. For people taking antiepileptic medications, has folate supplementation been shown to reduce neural tube defects in that population of patients? I know there's some work by Abereese in some models that shows that it did and I'm just wondering. Dr. Greene is shaking his head no, so he's going to share it with us.

DR. GREENE: To the best of my knowledge, there is not yet any data suggesting that folic acid supplementation is efficacious in reducing the incidence of neural tube defects amongst women with diabetes mellitis. I don't know that that's been studied in women with epilepsy.

DR. WENSTROM: It has been studied, and it works if you're taking one of the drugs that acts as a folic acid antagonist like carpomesopine. Valporate has a very high risk of neural tube defects but it

works by a different mechanism. I believe it affects the homeobox gene. But the folic acid antagonist would respond to folic acid supplementation.

DR. GUIDICE: Yes, Dr. Crockett.

DR. CROCKETT: I think our speakers this morning did a really nice job of presenting several different options about identifying subpopulations that need additional folic acid supplementation. I think some of those suggestions that they had or that they used in the studies were either testing directly the serum or RBC levels of the folic acid or identifying by questionnaire those patients at higher risk for neural tube defects or those not adequately taking dietary supplements or adequate dietary intake to achieve the recommendations. So I would say that the answer to No. 2 is yes and suggest that we use those markers to explore how we would further define that subset.

DR. GUIDICE: Dr. Wenstrom and then Dr. Hager.

DR. WENSTROM: I would like to ask why we would need to do that. Thinking back to, for example, giving pregnant women multivitamins. If you are eating a balanced diet, you really don't need them, although there is a small proportion of pregnant women

that would benefit.

Instead of trying to figure out who those women are, we just suggest that they all take multivitamins. Since folic acid has such low risk and is so inexpensive, do we need to identify a subpopulation? I mean, wouldn't that make it more expensive and to what end?

DR. GUIDICE: Dr. Greene.

DR. GREENE: In studies done of women who were counseled about the importance of folic acid and about which foods were rich in folic acid -- this was in the days prior to supplementation of flour -- it was demonstrated that there was not a significant improvement or, at least, not to the levels recommended for folic acid intake merely by dietary counseling, that women didn't really achieve adequate levels of folate intake until they took a dietary supplement.

Now, I don't know -- I haven't seen data about that done since fortification of the food supply, but clearly before the food supply was fortified, just merely counseling women didn't get the job done.

DR. WENSTROM: Can I clarify what I meant? That's not what I meant. I meant if we're talking

about putting folic acid into birth control pills, I would say is there any down side to just offering that to all women? Why do we have to pick out women that would particularly benefit since it's low risk and inexpensive?

DR. GUIDICE: Dr. Mills, Dr. Dickey, and then Dr. Lewis.

DR. MILLS: I think the concern is that people, at least the people in the Institute of Medicine report thought that 1,000 micrograms was the upper limit that we wanted people to be getting per day. Just doing a little fast math, if someone is already taking a vitamin tablet, that's 400. If they are eating Total for breakfast, apparently the average serving that a woman actually takes is about 600 micrograms per day. Then you've got the fortified foods

So I don't think I would want that woman being told to take an oral contraceptive that contains folic acid. That would be my rationale for trying to separate out the women who are having a low intake of folic acid as compared to those who may be having a high intake.

DR. GUIDICE: I skipped over Dr. Hager so before Dr. Dickey --

DR. HAGER: Well, I would agree with that. I think we do want to include as many people as possible, as we have all said, but we do need to be careful about those who are already supplementing or you have adequate dietary supplementation as well as exogenous supplementation as you were saying. I think what this question points out to me, and we have heard today, the need for improved educational methods.

Apparently the methods that we have used and we have failed as physicians, for which I apologize, to adequately emphasize this to our patients in obstetrics but we need to come up with some new ways to not only enhance supplementation but to educate women about their need to take supplements and to improve their diet.

DR. GUIDICE: Dr. Dickey.

DR. DICKEY: Unless I don't recall accurately, the 1,000 is a somewhat arbitrary number. The IOM has said it. They have attempted to say that to avoid things like masking pernicious anemia but, in fact, again from a safety perspective, particularly in the reproductive-age group for women, there is little data I recall seeing suggesting that you would be harming somebody if you got them above 1,000.

I think in terms of Question 2, yes, there

are some subpopulations we've heard today. They tend to be young women. They tend to be people with unintended pregnancies; therefore, perhaps, not motivated to supplement. Certainly low income. Some data we might have to extrapolate, but if you look at both Canada and the China study, maybe those people who live in the north where there is less easy access to some of the high folic acid foods.

But I think it comes back down to what Dr. Wenstrom has said. It's cheap, it's very safe, and so even though you can identify populations, I'm not sure what you gain by identifying populations within the subgroup of women of reproductive age.

DR. GUIDICE: Dr. Lewis and then Dr. Emerson.

DR. LEWIS: I would almost turn the question around. It's not that it's a subpopulation that needs additional folate, but a subpopulation that might be harmed by additional folate. The questions that -- not the questions but the criteria that were posed this morning, as you said, Dr. Crockett, they are adequate, you know, dietary supplementation and so on.

I mean, that identifies the people who probably already have adequate folic acid and offering them a birth control pill that contains folate

probably is not so beneficial. But also from the study this morning, women who conceived some 50 percent of intended pregnancies were not taking folic acid supplementation. There is a huge area of the population that needs education about the importance of folate supplementation.

DR. GUIDICE: Dr. Emerson.

DR. EMERSON: Well, I guess my question was do we have to define needs or can we go on the definition based on the recommendation that women of childbearing age should be taking 400 micrograms supplementation in which case identifying the subpopulation is easy. It's the women who aren't.

DR. GUIDICE: Yes, you have a comment?

DR. SHANE: It's not quite true because the women who are not taking the pill are supposed to be getting half of that from fortified food. Food is fortified specifically for this problem, the NTD problem, although it's had other advantages, possibly, in reducing homocysteine.

The idea of food fortification was to reduce the instance of NTDs. Taking the pill on top of the fortification is actually giving more than the recommendation, although it probably would not be a problem to do that.

DR. GUIDICE: Dr. Wenstrom.

DR. WENSTROM: But I still believe Nick Wald's paper. In his analysis he predicted that, at this level of fortification, the incidence of neural tube defects would drop by 20 percent. And that's what we've seen, which, to me, suggests that the fortification isn't optimal. Adding extra folic acid on top of that would be expected to decrease the incidence further.

DR. GUIDICE: Dr. Darney.

DR. DARNEY: I agree with Dr. Wenstrom. It seems to me that all the data we've seen identifies the group needing the supplementation as those who would be more likely to take birth control pills. I think a bigger problem is that the very ones who are likely to need it most are the ones who are least likely to take birth control pills, but it could only help.

DR. GUIDICE: Yes, Dr. Patten.

DR. PATTEN: Yes. I'm not a clinician and I need some information from a clinician. Is serum folate a routinely conducted part of blood work and, if not, is it prohibitively expensive to conduct?

DR. ROSENBERG: The answer is no and no.

DR. GUIDICE: Dr. Hager.

DR. HAGER: Just one other things about identifying a subpopulation. If we identify and label a subpopulation, it may have the adverse effect of saying to those individuals not in that population, "You don't need as much folic acid."

My concern is and I think I'm hearing that we want all women to understand they need folic acid. Now, is there a maximum dose above 1,000, above 2,000? I don't think that's real clear. But we don't want to convey to a population or subpopulation of women that you don't need supplementation in my opinion.

DR. GUIDICE: So the issue, I guess, before the Committee is how we advise the FDA, whether we answer the question or whether we change the question and reflect what I think I'm hearing around the table, although I'm not sure there's a completely unanimous agreement on this.

The issue is that there is variable usage, both usage of cereals and other foods, and it appears that the supplementation efforts have not gotten women of reproductive age up to the amount of folic acid to maximize reducing neural tube defects down to whatever that unknown percentage is or unknown incidence is.

What I'm hearing is that it's better to supplement everyone with the additional benefits. As

we heard from several of the individuals during the open public hearing, there will be discussion about health and taking care of one's self in either planning a pregnancy or during the first trimester and during the whole pregnancy. So there are added benefits to this entire approach which really go beyond the whole issue of just adding folic acid to birth control pills.

So it seems that there is an opportunity to supplement via a mechanism of supplementing folic acid to birth control pills that will target a certain population, i.e., women who are taking birth control pills, some of whom are not taking enough folic acid and some of whom are probably maybe even more than they need, but that the safety margin is quite significant and so why does it matter? Why do we need to identify anyone? As you mentioned, part of routine prenatal care and the routine blood draw is not to draw a serum folate level.

So I will ask the Committee whether they would like to actually answer two questions. One is: Is there a need to identify subpopulations, and then, secondly, can we identify subpopulations?

Dr. Mills and then Dr. Macones.

DR. MILLS: I actually see this as a very

simple clinical management issue. I think that when the woman walks into the clinician's office. The question is, "Are you taking a supplement containing 400 micrograms of folic acid?" If the answer is yes, you say, "Good," and you do not give them the oral contraceptive with folic acid.

If the answer is no, you say, "You should take an oral contraceptive with folic acid." I think that is going to avoid the potential problem of overexposure to folic acid because, as Dr. Shane pointed out, the average women is getting 200 micrograms of folic acid right now through food fortification. If she's taking a supplement, she's getting 600 micrograms of folic acid.

There's nobody that I know of who thinks that taking more than 600 micrograms of folic acid is going to substantially increase a protective effect. We're talking more about whether 400 micrograms is sufficient. So I don't see any benefit to giving someone who is already taking a 400-microgram supplement additional folic acid.

I do think there could be a risk. I also don't see it as a difficult problem to determine who should get it and who shouldn't because the woman who isn't taking a supplement is a likely candidate in

terms of needing it. The woman who is already taking a supplement doesn't need it.

DR. GUIDICE: Thank you.

Mr. Macones.

DR. MACONES: Yes. Related to that, I guess why we're having this debate about whether or not we should be giving this folic acid supplement and birth control pills to all patients is because we don't know, at least I didn't see data about, how sensitive and specific asking that exact question is.

If you ask a woman if she's taking a folic acid supplement, how often will she not have an appropriate red cell folate level? To me without knowing the sensitivity and specificity of asking questions like that or asking about someone's diet, I don't think we could really adequately answer that first question.

That, to me, would seem to be a very important study to do, to actually assess whether or not asking simple questions like that accurately predicts what someone's red cell folate level is. If they do, then we can end this debate. If we detect 100 percent of the patients, we can ask simple questions and just, again, give this supplemented birth control pill to those people.

On the other hand, if it's not very sensitive, if we only detect 80 percent, given the very low risk, we might just consider giving it to everyone as Dr. Wenstrom pointed out.

DR. GUIDICE: Dr. Greene and then Dr. Montgomery Rice.

DR. GREENE: In part the answer to this question is getting into the next question which is the issue of potential toxicity. I would like to just make two points. One is, with respect to what you were saying, Jim, what are you worried about if the woman is eating her Total and taking her multivitamin and also, by the way, taking a birth control pill that has 400 micrograms? Obviously that gets to the next question.

The other thing I think that we need to consider as a practical matter is that the more complicated you make medicine, the less likely it is to get done right. I think that we have to anticipate the probability that if oral contraception -- if supplementation with oral contraceptive pills with folic acid catches fire, as it were, and seems like a good idea, it's unlikely that pharmacists all over the country are now going to start stocking the 20 or 25 different brands of birth control pills with and

without folic acid in them.

So I think we have to anticipate the possibility or probability that, if this seems like a good idea, it's probably going to happen with most of, if not all, oral contraceptives and pharmacists are not going to double their shelf space to carry those with and without a folic acid with all of the other combinations of steroids that are available and dosage regimens that are available, sequential, etc. I think we have to anticipate that, looking a little bit down the road.

DR. GUIDICE: Dr. Rice.

DR. RICE: Dr. Mills said something that was sort of, in my opinion, contradictory to all these other presentations that showed that one slide over and over again, which is that the plasma folate level and NTD risk, that as that concentration went up, we did see a decrease in neural tube defects. So there may be some potential in taking more than 600 micrograms.

If I remember, the Wald paper talked about if you took 1 milligram versus 5 milligrams, the incidence of neural tube defect did continue to decrease. This concern that 400 is enough, I mean, that's somewhere else down in our questions. But I

don't understand what you were saying about the 600 micrograms, that nobody would agree that at 600 micrograms there is any more protective effect because that's not what the literature is saying, unless I'm interpreting it incorrectly.

DR. GUIDICE: Dr. Mills.

DR. MILLS: There are a number of case control studies that showed a major reduction in neural tube defects in women who were taking 400 micrograms of folic acid a day, so that's the first point.

The second point is that we don't know exactly how many micrograms of folic acid it takes to raise your red cell folate to 400. I would suggest that if you take it religiously, in other words, if you don't skip three or four times a week, that you probably will raise your red cell folate to over 400 with 400 micrograms per day.

And the Wald study, which actually is the Leslie Daly study, doesn't go all the way out. In other words, there's a point where there weren't enough exposures to know what the effect is so it's not clear, as we were discussing this morning, whether increasing the amount of folic acid that you take in is actually going to continue to decrease the rate of

neural tube defects.

I want to state again that there are two kinds of studies. It's a shame we didn't actually have someone who talked about all of the studies reducing neural tube defects with food fortification because there are U.S. studies which show a drop from around 19 to say 30 percent and those studies were incomplete.

They didn't have available to them data on all the pregnancies. They didn't have data on all the terminations. There are Canadian studies which show a drop to 50 percent with almost the identical fortification level. Those studies did have all the prenatal terminations, the still births, and all the other outcomes.

So the point that I want to make is that, with an exposure of approximately 200 micrograms per day in fortified food, the good studies show a 50 percent reduction so I don't think that the data suggest that you need 600 micrograms per day, particularly since we are already getting that 200 in food, whether women are taking supplements or not.

DR. GUIDICE: Dr. Wenstrom and then Dr. Dickey.

DR. WENSTROM: Some people would say a

reduction -- you said you could get a 50 percent reduction. I guess that is in reference to the Nova Scotia trial. But there are other studies that suggest we could reduce it even further but we're talking about two different things. I think we started off talking about safety and then started talking about efficacy.

The MRC trial used 4 milligrams a day and none of those women had problems as a result. So if someone is taking 200 in their diet and then takes a 400 milligram supplement and then also gets it in birth control, that is still less than the 4 milligrams those women took without any adverse effects. I think the upper limits beyond which you would see some toxicity are probably very high.

In terms of efficacy, that 4 milligram trial reduced the recurrence risk by more than a 50 percent reduction. It was a 78 percent reduction. You could argue that an increased dose could have further benefits without increased risk.

DR. GUIDICE: Dr. Dickey, you had a question?

DR. DICKEY: A question for Dr. Mills, I think, because I think I'm saying the same thing Dr. Wenstrom is saying. It's not an issue of whether the

current data mostly points at 400 micrograms. The question is: Is there data that suggests that there is a substantial safety issue if patients -- if people taking folic acid find themselves at a 1,000, 1,200, or up to 4 milligrams.

DR. GUIDICE: Just a quick reply and then Dr. Emerson because we are sort of blending questions here.

DR. MILLS: The Institute of Medicine recommended a thousand micrograms of folic acid as the upper limit so that their data suggested that there was a problem. Ten percent of pernicious anemia occurs in this age group so there is definitely a vulnerable population for that. That's basically as much as can be said about that.

There are also questions now about whether you start to block the effects of methotrexate when people get high folate levels. That is the very early stage of investigation so that we don't know that.

We could ask the FDA experts over here what people would be getting if they started taking an oral contraceptive with folic acid on top of a multivitamin and fortified cereal. I think you're going well over 1,000 micrograms a day, and I just don't think it would be safe given that I don't see any additional

benefit in that population.

DR. GUIDICE: Dr. Emerson.

DR. EMERSON: My comment is just one about being careful with the percent reductions. It's not absolutely clear to me that our target should be a certain percent reduction. It's not absolutely clear to me that our target shouldn't be reducing the level to 6 per 10,000, which some slide or another was putting forward this idea.

Canada had a higher rate of neural tube defects. It's easier to have a big percentage decrease when you have a bigger rate to start out with, particularly if what you are attacking is perhaps an environmental cause rather than some genetic cause.

So, you know, going to Canada versus the United States and we have the one study in China that showed big differences between the northern part and the southern part. This is what makes it difficult. We don't have the data to say whether we really can reduce it that much more, but there is certainly some suggestion that it can be reduced more.

And then the safety question that comes up is going with that 1,000 milligram dose and saying how hard and fast that is. We do have roughly 900

subjects that got the 4 milligrams per day. We've got roughly 3,700 in Hungary that got 800 micrograms per day which is a fairly sizable safety population.

DR. GUIDICE: So we have Question No. 2, or Question 2(a), I guess, and that is -- I would like to impose on Dr. Wenstrom to pose a question to the Committee about whether or not there needs to be a subpopulation defined.

DR. WENSTROM: You'd like me to reword Question 2?

DR. GUIDICE: No. Actually, I would like for you to reword your comment about the lack of necessity for Question No. 2.

DR. WENSTROM: Considering the large safety margin of supplemental folic acid, is it necessary to identify a subpopulation who would be the only people to get additional folic acid.

DR. GUIDICE: Okay. For this I would like to call again upon members. Since you have answered one question so you know where you are now, just going around the table starting on this side with Dr. Stanford.

DR. STANFORD: I would say that -- I mean, we don't absolutely know for sure, but if we're talking about women of reproductive age, we're talking

about 400 micrograms and not higher levels. I would say the reasonable answer is we probably don't need to subidentify.

DR. MACONES: No.

DR. GUIDICE: To identify a subpopulation.

DR. LIPSHULTZ: No.

DR. LEWIS: No.

DR. DICKEY: No.

DR. ROSENBERG: I think we do need to identify subpopulations. I think the rationale for this is that there are populations whose protective effects are not being achieved.

I think that we, therefore -- and I think unless you totally reject the safety issue and accept the idea that there are no safety issues and that there's a very wide safety margin and, in a sense, therefore, reject the position of the Institute of Medicine, I think there is a need for defining subpopulations and I think they can be defined.

DR. TAMURA: No.

DR. GREENE: I would answer the question that, yes, we can identify a subpopulation that needs additional folic acid. I would also argue that they are the ones who are least likely to be aided by this proposal.

DR. GUIDICE: The question at hand is, "Is it necessary..." It's not the question written down. This is 2(a). "Is it necessary to identify a subpopulation in reproductive-aged women?"

DR. GREENE: No.

DR. GUIDICE: I vote no.

DR. SHANE: I think we should, and I think the exclusion should be people who are taking vitamin pills really. It's a very simple population to identify.

DR. EMERSON: I'll go with that same variance, that there is not a need to identify a population that can take the supplementation; but once they have already taken the supplementation, they don't need to do it twice.

DR. WENSTROM: But we're talking about the same thing, right? Whether they get the supplement in the form of a pill or whether they get the supplement in --

DR. EMERSON: That's what I mean.

DR. WENSTROM: So you're not defining a subpopulation that should only be taking a supplement, right? You're just saying if they are already taking a supplement they shouldn't take another one.

DR. EMERSON: That's correct.

DR. WENSTROM: So really you're voting no then if they are not identifying the subpopulation.

DR. EMERSON: I'm not identifying the subpopulation to get supplementation except if you were to say we've already got some people out there who are getting it.

DR. WENSTROM: Okay. I say no also.

DR. RICE: No.

DR. CROCKETT: No.

DR. GREEN: I say yes for the reasons that were given by Dr. Shane. I would also point out that there's no -- we have no indication as to the duration for which anyone taking an oral contraceptive with folate in it would be taking such a supplement.

DR. GUIDICE: Dr. Darney.

DR. DARNEY: Yes, we can identify a subpopulation.

DR. GUIDICE: We're asking is it necessary to identify a subpopulation. I guess it has been --

DR. DARNEY: No.

DR. GUIDICE: Okay.

DR. PATTEN: Yes, I think you do need to define a subpopulation. It would be those women who are not taking multivitamins with the 400 milligrams. I think it will not be so easy to identify those

women, however.

I think the simple question is, "Are you taking a multivitamin?" I think a more difficult question, unless all multivits have 400 micrograms of folic acid, is to ask a woman, "Are you taking a multivitamin with 400 micrograms of folic acid?" I think many women could not answer that. Tell them to bring their bottle of vitamins along to the clinic visit.

DR. GUIDICE: Just to clarify, the supplementation includes women who are on the multivitamins or women who would need oral contraceptives with folic acid. I don't want to change your vote, but just to inform you that for that interpretation the answer would be no.

DR. PATTEN: Wait a minute. I'm saying you do need to identify women who are not taking multivitamins with 400 micrograms of folic acid. That's what my yes means.

DR. GUIDICE: Okay. Thank you.

Next, Dr. Hager.

DR. HAGER: No.

DR. GUIDICE: Okay. Thank you.

Yes, Dr. Stanford.

DR. STANFORD: I'd just like to second Dr.

Macones' suggestion that there really need to be some studies about what is the sensitivity and specificity of the question, "Are you taking multivitamins" for a gold standard of red cell folate levels. I think that would be a very valuable background piece. That's just something for the FDA.

DR. GUIDICE: Thank you. Now to answer Question 2(b). The result of that was 14 no and 4 yes. And Question 2(b) then is directly written here: "Can we define a subpopulation among women of reproductive age that needs additional folic acid." This is women beyond those who are --

DR. LIPSHULTZ: I'm sorry. Didn't you negate this second part by changing the first part?

DR. GUIDICE: I think that we have. I just want to be sure that the FDA has enough information from us. You don't need us to do the second part? Okay. Then Question 2 has been answered.

We could have a break at this point and come back in 10 minutes or complete No. 3 but I think this may spur quite a bit of discussion, so let's take a ten-minute break.

(Whereupon, at 3:36 p.m. off the record until 3:47 p.m.)

DR. GUIDICE: Would everyone take their

seats, please, so we can continue. The third question is: "Are there any safety issues associated with folic acid supplementation targeted at reproductive-aged women? If so, what are they and would these safety issues not be a concern below a certain level of supplementation and, if so, what is that level." I don't see a question about above a certain level but perhaps we can entertain that as well.

Dr. Crockett.

DR. CROCKETT: I'll start this one. I have a couple questions about this. It struck me as we were going through this discussion about safety and toxicity, which I realize are not the same thing. Folic acid is already approved with a category A labeling which means that there have been studies showing its safety in the first trimester of pregnancy.

As we discussed the safety issues concerned with folic acid supplementation in this target population, I think it's important for us to keep in mind that we do have the second patient to keep in mind, the fetus. And as we were going through our talks this morning I kept hearing there's not enough data on the higher end of the safety spectrum. There's not enough data. We don't have studies. We

don't have this.

I'm wondering -- and I'm going to pose this to the FDA or whoever can answer it -- where did the studies come from that gave it a Category A pregnancy rating and where were they this morning because I think that would be helpful.

DR. GUIDICE: That's a very good point. Could someone from the FDA enlighten us in that regard?

DR. GRIEBEL: We don't know the answer to that. We don't know the exact studies that were done.

DR. GUIDICE: Okay. Does anyone around the table know?

Yes, Dr. Rosenberg.

DR. ROSENBERG: No, I don't have the answer to that but I would just elaborate further on the question. We have from the Institute of Medicine, I think, a number that has to do with safety or upper level with respect to pregnancy. I don't remember what that number was, nor do I remember how that was derived. Was that derived on the basis of specific data or was that -- my guess is it was just an extrapolation from the adult data.

But it does raise the question of whether there is information that indicates the safety range

for the fetus with various doses of folate. We obviously have the experiment of the 4,000 micrograms, which were an effort to prevent recurrent neural tube defects, but I'm not aware of how much work we have about the range of folate doses and the effects on early fetal development.

DR. GUIDICE: Dr. Wenstrom and then Dr. Darney.

DR. WENSTROM: Even if our FDA representatives can't tell us the data, if folic acid has already been approved, unless we have reason to suspect that it behaves differently when it's combined with an oral contraceptive, why do we need to answer this question again? By its very approval, hasn't that question already been answered?

DR. MONROE: Well, our questions are all sort of interrelated and related to if you felt that adding additional folic acid would be meritorious. We wanted to know if you have some concerns about at what level would you then be concerned about toxicity. You've had some general discussions about that and that was the purpose of that question.

So what you're sort of implying is there's no upper bound. Well, we don't have any such data that would say that. So we wanted to know from the

Committee up to what level would you not have any concerns, were you to feel that additional supplementation would be of benefit.

DR. GUIDICE: Dr. Rice.

DR. RICE: I guess we would side with you all. You all have already approved 1 milligram dosages, correct? I mean, if I get 200 from the diet and then let's say I take another 400 with the supplement and then, oops, I end up taking a birth control pill with another 400, I'm just at my 1 milligram.

I mean, if you already have it approved for safety at 1 milligram, what's the question? I mean, are you asking would we be concerned if we wanted to have 4 milligrams? Maybe we would, but we would expect that before that what would happen, there would be some safety studies done before that level would be approved.

DR. GUIDICE: Yes.

DR. ZEISEL: It might help if you consider that every obstetrician in this room is prescribing vitamins for pregnant women that contain folic acid and contain 800 of folic acid, or a milligram depending on the preparation. If you're worried about fetal health, think about that you all for years have

been prescribing 800 or a milligram of folic acid to every woman who has a baby -- is going to have a baby with you.

DR. MONROE: I would just like to say that is not exactly analogous because there you are talking about just for the duration of a pregnancy, If you are going to add this to a supplement that a woman might be taking for four or five years, the level which might not be a problem for eight months might not be equally safe over a course of four or five years. I'm not sure if they are identical questions.

DR. GUIDICE: Dr. Rader and then Dr. Shane.

DR. RADER: I think there's a little confusion, and it's probably because our drug regulation for folic acid goes back to the '70s. It's not approved for pregnancy. I think that's a misnomer. It's approved to treat the megaloblastic anemia that may come up; it's a megaloblastic anemia treatment.

On the labeling, according to our old regulation of a product of 1 milligram that would be given in that dose, it has to bear the label that doses above about .1 to .25 milligrams of folate may mask the anemia vitamin B-12 deficiency. There's a labeling stipulation on that old drug regulation.

Now I know it's old and hasn't been updated but it's not, quote, approved for pregnancy. It's approved to treat megaloblastic anemia so this is a whole different matter, just so you're not taking up something that is a blanket assumption. It isn't approved for pregnancy. It's approved to treat a disease.

DR. CROCKETT: I understand that. I guess I didn't phrase that correctly. You're absolutely right. It's indicated for the megaloblastic anemia, but it's got a pregnancy category safety rating of A and almost nothing we use has an A.

DR. RADER: Well, we know that the regulation goes back at least to '75 and before so whether there were a lot of good studies done or whether those studies would pass muster now is an open question. It's a very, very old regulation that wasn't updated at a time when -- it was just like left there like a grandfathered-in thing. The nature of the studies done, I'm not certain we could even find that now from that many years ago.

DR. CROCKETT: In that case, I would like to make a suggestion to the FDA that in the process of following this up that those studies get pulled up and looked at.

DR. RADER: That's if we can find them.

DR. GUIDICE: Dr. Shane.

DR. SHANE: I was going to mention -- probably most people are aware -- that before folic acid was isolated it was described as the Wills Factor which was factors that were missing in megaloblastic anemia pregnancy. So where we often think about megaloblastic anemia with B-12 deficiency and worry about the aged getting too much folic acid, in pregnancy if someone is megaloblastic they think folate deficiency, not B-12 deficiency.

Having said that, when we discuss folic acid it's not always clear to me that people understand that we're talking about very large doses of folate being supplied to people compared to what they used to get in the diet. it's not a trivial small extra amount of folate.

As I mentioned, the 200 micrograms of folic acid that is really supplied with fortification, although it doesn't meet the 400 micrograms suggested by IOM and others is equivalent to an RDA, essentially, of food folate. And most people before were not receiving the RDA of food folate. RDA is enough for 97.5 percent, so it's pretty much a doubling of the folate intake of the population just

for the 200.

The concern about folate toxicity -- it's really not toxic. It's not a traditional safety issue. It's a masking issue. The folate itself isn't toxic. Having the targeted population in this case reduces some of the concerns about that kind of safety, but it's not eliminated entirely because ten percent of the people who develop megaloblastic anemia are in this age group. So there's less of a concern than if the whole population was getting this amount of folate but there is still a concern that remains which should be thought about.

DR. GUIDICE: Yes, Dr. Wenstrom.

DR. WENSTROM: Can you give that a number for me? I mean, if ten percent of megaloblastic anemia patients are reproductive-age, how many pregnancies per year -- there are 4 million pregnancies a year. How many would include a mother with pernicious anemia?

DR. SHANE: Ralph would probably know that better than me.

DR. GREEN: Actually, I had this question earlier over lunch from someone. I have to say as a disclaimer that it's only an estimate. My estimate came from data on the overall prevalence of pernicious

anemia in the population which conservatively ranges around one to three percent so let's take a figure of two percent.

If you take that, generally speaking, if you apply that figure to the elderly population who are, as we've heard, considered to be at greatest risk, in the U.S. population, currently we're talking about 35 million people in that age category, and two percent of that population is around 600,000, so getting on at maximum to about a million. Now, that's the elderly population.

If we extrapolate from that and say that ten percent overall of pernicious anemia might occur in the age group of women who are of childbearing age, then it would be ten percent of that figure at maximum. So ten percent of 600,000 would be 60,000 potentially but, again, there are a lot of assumptions there. There are a lot of estimates there, and I'm sure there are people here who could find fault with that reasoning.

DR. GUIDICE: Dr. Wenstrom.

DR. WENSTROM: It's just hard to believe because I've never seen a case in a pregnant woman. Has anybody?

DR. HAGER: I've never.

DR. ROSENBERG: B-12 anemia?

DR. WENSTROM: Pernicious anemia.

DR. GREEN: Can I just --

DR. WENSTROM: My concern is masking pernicious anemia.

DR. GREEN: I'm sorry. Can I just clarify that I'm not talking about during pregnancy. Again, I think the important point that was made on the other side of the table from the FDA is that we're talking about a possibly five- to ten-year duration of taking this amount of folic acid. I agree it's excessively rare. I have seen cases. It's excessively rare during pregnancy, but we're dealing here with increased folate intake over a period that could extend over several years.

DR. GUIDICE: Dr. Montgomery Rice.

DR. RICE: I need some of the nutritionists to help me with this. Tell me if I took a milligram a day tablet, if you can, what level am I going to have in my serum and when are you going to become concerned about it for a safety reason? Then explain to me this cumulative effect, this theoretical cumulative effect that we are kind of alluding to because this is a water- soluble vitamin. So help me with this from a pathophysiological point of view.

DR. SHANE: Well, I don't subscribe to the cumulative effect. I think what happens is you build your stores up at a certain level of intake. It's not really stores. It's just that it happens to be in tissue. There's no sort of store waiting to be used for anything. It's being used. Above a certain level, you get rid of it essentially.

DR. RICE: Right. So you max out in your tissue. You have a saturation level.

DR. SHANE: You max out so it's not going to be -- there are really probably no harmful effect per se for having the maximum level, you probably don't need the maximum level but there will probably be no harmful effects per se.

But pernicious anemia is a condition that develops over many years and you're talking about a large population, a small percentage of which may be developing pernicious anemia. They are losing their ability to absorb B-12 and you reach a point where your stores disappear, and you don't display the anemia. That's really the safety concern.

DR. RICE: But they are developing the pernicious anemia, but they are not developing it because of a cumulative effect. They are developing it because they are taking a dose that got them to

that point --

DR. SHANE: No, no. There's some discussion about whether high folate will exacerbate the symptoms of B-12 deficiency but I don't think there is any real evidence that's the case. The concern is the masking. If you have very high folate stores, it can prevent the symptoms of your B-12 deficiency because the anemia is due to an induced folate deficiency. Do you understand? So if you don't get the anemia, then you may develop a neuropathy which is much more difficult to treat.

DR. RICE: Okay. And then the 1 milligram. If I'm taking that 1 milligram dose, what is my serum level going to be?

DR. SHANE: The serum level is going to be probably twice as high as if you were taking the 400 micrograms.

DR. RICE: Okay.

DR. GUIDICE: Dr. Wenstrom.

DR. WENSTROM: It isn't in this book, but I read an editorial by Dr. Wald saying that if you don't identify pernicious anemia until you've had neurologic symptoms, that doesn't mean that they are permanent and they are usually entirely reversed with therapy. His argument was that even if folate masks the

symptoms of pernicious anemia, once you recognize it, it's entirely treatable. Do you think that's true?

DR. GREEN: I think our knowledge on that is if there has been B-12 deficiency resulting in neurologic damage of greater than six months duration, then there is pretty good evidence that a considerable proportion of the neurologic damage is irreversible, so it's really a question of how severe and for how long. Any unrecognized B-12 deficient myeloneuropathy that goes six months or longer is at risk of being irreversible.

DR. GUIDICE: So it sounds like we have identified a population where there are not so much safety issues but masking issues and, therefore, safety issues. Is this correct? Does the group agree upon this?

DR. RICE: But we're already doing that in practice. A large percent of our patients takes a supplement of multivitamins which may have 400 micrograms every day and they eat their fortified cereal, etc., etc. So they are already getting some dose that may be getting up to some upper limits.

Since we fortified foods and since we now have the dosages in multivitamins, etc., are we seeing an increase in the incidence of pernicious anemia

being masked by excessive amounts of folate?

DR. GUIDICE: Anyone? Yes. You have a comment?

DR. OAKLEY: Godfrey Oakley again. I just wanted to make clear -- I heard some confusion -- and that is it should be clear that folic acid doesn't cause pernicious anemia. I mean, you lose intrinsic factor. That's how you get pernicious anemia.

If you lose intrinsic factor and you've got anemia or you get neuropathy, then you can go see a doctor. You can have a B-12 level and so on. The concern here would be would someone not showing up because they had been on enough folic acid to keep the anemia from coming up.

What is toxic about that is not getting B-12. It's not because you are getting folic acid. Of course, if a clinician has a suspicion, then he or she could order a B-12.

And I think Dr. Mills' paper sort of speaks to this a little bit. I think it's the only data out there post-fortification. As I understand it, they essentially didn't find any evidence in the elderly who were at risk for having a problem from the current fortification that has gone on. Now, you could do a different study and so on, but the current evidence

doesn't suggest that there's a problem.

DR. GUIDICE: Dr. Crockett, Dr. Shane, and then Dr. Darney.

DR. CROCKETT: I have a real problem trying to answer No. 3, and I think we have identified one very important factor. But the most disturbing thing to me is that we are being asked to have a discussion about safety issues when there is no good study for us to refer to.

It kind of makes our discussion a moot point. What I would like to suggest is that the FDA as they develop a clinical trial plan with the company, that they recommend that there be toxicity testing and safety testing. This is a question that is going to come back to the FDA or a similar committee at a future time once it's tested and done.

I think there is a tendency, because folic acid is a nutrient or a nutrition supplement, to not look at it as a bioactive drug, and I think that is a mistake. I think that it should be looked at as any other drug with appropriate Phase 1, 2, 3 trial testing and develop it.

DR. GUIDICE: Thank you. I lost my roster of people. I think Dr. Darney was in the queue and Dr. Mills next.

DR. DARNEY: I wanted to pursue Dr. Montgomery Rice's issue and ask whether or not a relatively high dose or overdose beyond the minimum daily requirement of folate is more effective in masking. Or does it not matter how much you take; it's masked even at a low dose of supplementation.

DR. SHANE: You need large doses to mask effectively. As I mentioned this morning, before people realized there was such a thing as B-12 and they thought folate was the factor missing in pernicious anemia patients, large doses of folate were given and did treat the hematological symptoms.

I think it was five or 10 milligrams, wasn't it, Ralph? Five to 50 milligrams, so that's why you don't get five to 50 milligram folate pills now at your local drug store.

DR. DARNEY: So wouldn't that 400 we're talking about be trivial in relation to 50?

DR. SHANE: No. I thought the question here would be -- there is a 1 milligram limit out there from the IOM report. Is there a reason why that should be changed for this particular population? Of course, when one sets these upper limits, they are supposed to be set for safety considerations. Not that 1.1 is bad for you and one is okay but one should

be fine and maybe five would be fine, but you don't know so you set it at one to be on the safe side.

People may think, for this particular group where pernicious anemia is less likely to be a problem than in the overall population that includes the elderly, then maybe a high level might be okay. But without going into all the details about why a particular upper limit is set, it's difficult to just give a number.

DR. GUIDICE: Dr. Mills and then Dr. Rosenberg and then Dr. Lipshultz.

DR. MILLS: As Barry has suggested, all of the data we have on masking was due to therapeutic errors, so it's never been studied systematically. The lowest dose of folic acid that has been associated with masking is 400 micrograms.

The IOM and other groups have picked 1,000 micrograms as the safe upper limit, in part because they thought that was the dose where it looked from very incomplete data as if masking became a real serious problem. That is a guess based on limited data, but there was a reason for saying 1,000 micrograms was the limit.

The other point I want to bring up is that this isn't the only issue. If you gave people larger

and larger doses of folic acid, eventually you would reach a point where drugs that work by antagonizing folate would be compromised and methotrexate is a good example of that. It essentially just works by blocking the folate enzyme.

That's why the abstract I mentioned this morning suggesting that women who have the highest blood folate levels were the least likely to respond to a therapeutic dose of methotrexate for ectopic pregnancy because that may be the first sign I know of in the literature that people are starting to reach the levels of folate where you are blocking those effects.

There are a number of reasons why that would be a very serious problem. As you all know, methotrexate has a great number of clinical applications including as a chemotherapeutic agent, and it could be very tricky to identify that kind of a complication in the sense that you would simply see more people dying of cancer who were getting a recurrence of cancer, but it would be awfully hard to pin down that it was because methotrexate was being compromised by a very high folate level.

DR. GUIDICE: Thank you.

Dr. Rosenberg.

DR. ROSENBERG: With respect to masking, meaning that vitamin B-12 deficiency anemia, megaloblastic anemia, responds to folate and, therefore, its diagnosis is delayed or masked, there is data, as Jim Mills indicated, that indicated that one can see that kind of hematologic response in doses as low as 400 micrograms, even though a lot of the earlier work was done with larger doses when it was thought that these large doses of folic acid might be the appropriate treatment for pernicious anemia even before B-12 was discovered as the actual cause.

I remind you that there is also this literature which shows that not only do some of these doses of folic acid -- which may in the early days have been ranging from two up to five or six milligrams -- not only were they able to change the hematologic picture, but while these people were being erroneously treated with folic acid, many underwent significant worsening of their neurologic problem, leaving open the question of whether that was simply a delay in the treatment with B-12 or a result of the interaction of folate and B-12 which we know occurs in certain metabolic cycles.

So I think to use the word masking as the description of the toxicity risk here is okay as long

as we understand the complexity of what we're talking about. I do agree with the challenge to the FDA or whomever, that this is an area that is still not well defined and we are dealing with safety concerns without much data upon which to base our judgment.

DR. GUIDICE: Dr. Lipshultz, Dr. Friedman, Dr. Darney.

DR. LIPSHULTZ: I think this discussion is going on long, perhaps longer than necessary because we are trying to make a round peg fit into a square hole. I mean, it's called a supplement but clearly this has gone beyond a supplement and we are now back to trying to discuss safety on a drug that has never been studied rigorously the way a pharmaceutical needs to be studied.

I think if this is going to be packaged with a pharmaceutical, it needs to be studied like a pharmaceutical and has to be moved out of the realm of an additive or a supplement. I think really to answer this question is very premature because it's never been studied the way it should have been studied, had it come to market as a pharmaceutical drug.

DR. GUIDICE: Thank you. Dr. Friedman.

DR. FRIEDMAN: There are just a few points I would like to make. One is just to remind everyone

on the committee that the Institute of Medicine recommendation of an upper limit of 1,000 is for people who are not under the care or the supervision of a physician. This would be a prescription product. That's No. 1.

No. 2, if you think of how people could get to 1,000, we've talked about examples of people taking their multivitamins, eating their Total. Those things have B-12 in them so many of these people will be getting B-12 as well. I think that's important to realize.

The third thing is we're not talking about giving a whopping dose. We are talking about an incremental dose for a woman, every day, of 400 micrograms so I would ask the question what is the likelihood that an incremental dose of 400 micrograms could cause safety concerns?

If we remember the figure that 30 percent of reproductive-age women are currently taking a multivitamin every day and 16 million women are taking birth control pills every day and they've done so chronically, there is a lot of clinical data out there, basically in-field data that attest to the safety of this combination.

DR. GUIDICE: Dr. Darney and then Dr. Green.

DR. DARNEY: I wanted to disagree with two of my colleagues. We're talking, as Dr. Friedman said, about supplemental dose, not a therapeutic dose. So I don't see that -- I don't understand why it would require a complete re-review and classification as a medicine.

In regard to the methotrexate issue, all patients who receive methotrexate are under a physician's care and we always ask them before we treat GTD or ectopic pregnancy, "Are you taking vitamins and don't eat your spinach?" so that we don't have that effect occur.

DR. GUIDICE: Dr. Green.

DR. GREEN: Just a very brief comment about one thing that I think is very important to point out to the entire panel here with respect to the comments made by Dr. Friedman. That was the comment about the protective effect of vitamin B-12 in any of the multivitamin supplements or the breakfast cereals which contain vitamin B-12.

That is to point out that the disease that we're concerned about here, malabsorption of vitamin B-12 caused by pernicious anemia, will not respond, will not respond, to the amount of vitamin B-12 present in these multivitamin preparations or

breakfast cereals, generally 5 micrograms, nowhere near enough because they are malabsorbing so they would absorb at best a fraction of a microgram.

DR. GUIDICE: Thank you. Dr. Lewis.

DR. LEWIS: I would sort of propose that we reword this question: Are there any safety issues within the realm of the limits set by the Institute of Medicine -- because we are wandering all over the map here from talking about 5 milligrams down to 400 micrograms -- associated with folic acid supplementation and, if so, what are they?

Then we've heard allusions to cases of vitamin B-12 deficiency being masked by as little as 400 micrograms of folic acid which is clearly an important observation. If these are in the realm of case reports, I think we have to think of that differently than if it's a specific incidence among people who are receiving that much medication.

I assume the Institute of Medicine researched this fairly intensively before coming up with that limit, and I think we are well within that limit with what we're talking about.

DR. GUIDICE: Well, it seems that we're at a point where we perhaps can look at question No. 3, perhaps with the modification of the IOM. I think the

major point of this question is to identify women who would be at risk in terms of folate supplementation.

One of the issues -- one of the groups that we seemed to have identified, since we've spent a lot of time discussing, is women with pernicious anemia or who will develop pernicious anemia. There was also a mention of women yet to undergo methotrexate therapy. We haven't really discussed some other groups, women who are on antiepileptic drugs. So there are several groups that are in a special category with regard to folate supplementation.

One would expect that if physicians are prescribing oral contraceptives with this supplement, that this would be part of the counseling and interaction with a health care provider. And I would assume that something would be done, certainly, in the labeling of the combined product.

So I would like to ask the Committee -- I think we've had enough discussion. We have two other questions after this, and we haven't really touched upon one of them. But if we could go around the room now and take a vote on "Are there any safety issues associated with folic acid supplementation targeted at reproductive-age women?".

And if someone wants to add the 1,000

milligram maximum -- I don't know if there is a consensus on this -- I'm sorry, microgram maximum on this. Is there a consensus in the Committee about adding that, the IOM recommendation of 1,000 micrograms?

Dr. Hager.

DR. HAGER: Would it not be possible to pose the question as you are regarding safety issues, that the safety issue that we're all talking about is basically dosage. And the answer is that we don't have enough information. I don't think gestational trophoblastic disease is an issue.

PA may be in a very small group of patients, but it seems to me that the safety issue that we're all hinting about is dosage and we don't have enough information. It certainly seems as though there's not a major problem with current doses of the supplement of 400 micrograms.

DR. GUIDICE: Dr. Wenstrom.

DR. WENSTROM: I think the major safety issue is taking it without being prescribed by a doctor. In fact, it sounds like taking it as part of a birth control method would be safer because you would be under a doctor's care and you would be evaluated for all these possible risks.

I think the safety issues are for those women that goes to Sam's Club, buy a quart of folic acid and take it unsupervised. So, really, I think the safety issue is taking it without being supervised by a physician. You don't even have to mention the dose. I guess what I'm saying is if you're being seen by a clinician at regular intervals, most of the concerns we have would be identified by that physician, right?

DR. ROSENBERG: I don't know how serious we want to be about the specificity of the question. Is this question now about are there safety issues about folic acid supplementation in reproductive-age women? It doesn't say "if delivered with a oral contraceptive." I'm not sure what the intention of the question is.

DR. RICE: Maybe the FDA can help us with what they really want us to answer. I thought they wanted us to answer that if there was a product that was available or contraceptive pills and it had 400 micrograms of folic acid in there, would that be a safety concern based on the amount that women are getting in their fortified and maybe the amount they would get in a multivitamin. Would that be a safety issue? Is that what the question is?

DR. GRIEBEL: Yes.

DR. RICE: Okay. Can we answer that question since they said yes?

DR. GUIDICE: Now we can have a simple yes or no vote. Let's start then with Dr. Hager.

DR. HAGER: No.

DR. GUIDICE: Dr. Patten.

DR. PATTEN: Yes. And this is my reason for saying yes. I am told that those cases of masking that have occurred and been identified have occurred at cases where there were 1,000 micrograms or more of folic acid being administered. My safety issue is the woman who is getting the supplemented contraceptive, getting 200 micrograms in her diet, and taking a multivit.

We've been told that there are approximately 600,000 people of reproductive age who conceivably have pernicious anemia assuming that half of those are women. Not right? 60,000. Sorry. Assume half of them are women. Here is the thing I'm thinking of. We're trying to prevent perhaps 1,000 neural tube defects using this approach. Are we putting at risk a thousand or more women who may have pernicious anemia masked? That would be my question. That's why I say yes. There's a safety issue.

DR. GUIDICE: Okay. Thank you.

Dr. Darney.

DR. DARNEY: Well, I want to retort by saying no because we were just told that if you ate a Big Mac and drank a quart of orange juice, you could mask your pernicious anemia. Yet, we're talking about people who will be under the care of a doctor who will say, "If you take these birth control pills with folate, you really don't need to take a supplement."

DR. GUIDICE: Or eat a Big Mac.

Dr. Green.

DR. GREEN: I say yes. I do want to point out that I don't think that there's any way that one can set up an equivalency between risk to potential infants of neural tube defects and women who may have megaloblastic anemia masked, so it's not that issue at all. It's merely that 1,000 micrograms is the dose recommended by IOM as the upper limit for safety and, as such, the answer to the specific question, "Are there safety issues?" is affirmative. I vote yes.

DR. GUIDICE: Thank you.

Dr. Crockett.

DR. CROCKETT: If we're specifically talking about the 400 microgram level, which I believe you included in the question, my answer is no. However,

I'm not convinced that the company has identified the optimum dosing and there may be safety issues at higher doses that are not known yet.

DR. GUIDICE: Thank you.

DR. RICE: No.

DR. WENSTROM: No.

DR. EMERSON: No.

DR. SHANE: No at 400, provided they are not taking supplements as well. Last time my yes was converted to a no.

DR. GUIDICE: I say no with some of the above caveats.

DR. GREENE: No, I'm not worried.

DR. TAMURA: Yes, I am worried. The reason why is that I don't know whether the person who is going to prescribe the folic acid-containing oral contraceptives has enough time to ask questions to phatients. The reason why I'm saying this is when my wife was pregnant she had a slightly above normal range of hematocrit and the nurse practitioner came in and said, "Your wife needs iron." I said, "Why?" She couldn't answer, and we didn't give iron to my wife. That's what's happening. So yes.

DR. GUIDICE: Thank you.

Dr. Rosenberg.

DR. ROSENBERG: Well, are there safety issues? I would have to say yes. If the predominant vote of the previous question was, "Don't define the population," and we're talking about everyone, then clearly we are going to have considerable numbers of people who are getting more than a milligram a day of crystalline folic acid from a combination of their oral contraceptive and other supplements and the 200 or 300 crystalline folic acid that they are also getting from other sources. So if we don't define a subpopulation, then I think we have safety issues.

DR. GUIDICE: Thank you.

Dr. Dickey.

DR. DICKEY: I think I have to agree yes. I don't think we have the data to answer the question, to be perfectly honest with you. I don't want us to lose track, as most of our conversation has been about the masking of pernicious anemia, if there remain some other safety issues that need to be addressed, such as people taking medications that may have some antifolate inhibitors there or activity there. At 400 micrograms, probably not with the data we've heard today, but I have to say the data has been anything but clear.

DR. GUIDICE: Dr. Lewis.

DR. LEWIS: No.

DR. LIPSHULTZ: Yes.

DR. MACONES: No.

DR. STANFORD: I'm going to go with Dr. Dickey. It's unknown with the current data.

DR. GUIDICE: Thank you. We've already answered -- we've had quite a long discussion on this and since we have half an hour to answer the last two questions, I think we have probably given the agency enough information for 3(a)
and 3(b) as well so I would like to go on to No. 5.

COMMITTEE PARTICIPANT: What was that vote?

DR. GUIDICE: The result? What is the total? Dr. Crockett, what was your vote? Was it a yes or a no?

DR. CROCKETT: No.

DR. GUIDICE: It was a no. Okay. So the result of the vote was 11 no and 7 yes.

Question No. 5: Is an oral contraceptive pill a reasonable delivery vehicle if additional folic acid supplementation is likely to provide public health advances in preventing further neural tube defects?"

Then (a): If so, would 400 micrograms be a reasonable dose? And if 400 micrograms is not

appropriate, what dose of folic acid should be provided?

Please note that we are asked to vote on the question and section (a). I think we have actually had the discussion in (b) but if there is additional discussion needed, we can certainly devote some time to that. Is there any discussion about the overall question, No. 5?

DR. ROSENBERG: Did we skip 4?

DR. GUIDICE: Yes, we did. The reason for that is that we have already had so much discussion. In fact, it was almost included -- it was included in the last question as an implicit assumption of 400 micrograms, so I thought we would go straight to the next 400 microgram question.

Does the Committee need to discuss whether or not -- essentially this is really the concept of the entire meeting, whether this is a reasonable vehicle in which to supplement or provide additional folic acid supplementation to women of reproductive age.

Dr. Dickey.

DR. DICKEY: I think that it is a reasonable vehicle but it is not a vehicle without its own problems. For example, for the unintended pregnancy

that occurs for a woman who is currently taking contraceptives, it should obviously address the problem.

There's reasonable data that says up to three months out you maintain a fair amount of increase in your folic acid, but there wasn't a lot of data about what happens at 4, 5, 6, etc. There was some implication that the education that goes along with using a supplemented oral contraceptive might, in fact, motivate a few people. I think it is a reasonable delivery vehicle but it's certainly not a panacea for the problem.

DR. GUIDICE: And the issue of continuation or persistence of folic acid X number of months out we still have yet to address in question No. 4.

Dr. Greene.

DR. GREENE: I would like to ask the representatives of the sponsor to polish up their crystal ball for us and tell us the degree to which the promotion of other steroid contraceptives that are not administered orally may undermine the potential public health benefit of oral contraceptives. In other words, as more women choose hormonal contraceptives delivered not orally, how is that going to affect this as a public health intervention.

DR. GUIDICE: Please identify yourself.

DR. CAFFERSON: My name is Michael Cafferson. The question comes in a few parts for me. Number one, since this is a concept and no products exist, and we're talking about orals today, one of the questions that comes up is would other delivery systems (a) be amenable and, if they were amenable, be of interest for development. The answer is I'm not certain of the first part, but we would certainly look at that. And would we be interested if they were amenable to what I hope will be found to be a reasonable concept? We would certainly probably be visiting with you again to talk about that possibility.

To be more specific in answering your question, if we take as the premise that other delivery systems do not now and won't have this option, I would say that my assumption is, number one, virtually all contraception and family planning decisions would be predicated on what women or a couple and a health care provider determine will be the most appropriate method of contraception.

Secondarily, if a product were selected, such as an oral contraceptive, then that subsequent discussion -- if we presume the subpopulation is those

women not taking other supplements -- then that discussion would happen.

It's hard for me to predict exactly what penetrants other than oral deliveries would have. There have been waxing and waning successes with different entrants. Implants would be one extreme, the still-on-the-rise patch another. And there are obviously many other potential delivery systems.

As has been said a number of times, none of us view this as the one and only way to reduce NTDs. It's one more contribution. So would other delivery systems reduce some of that potential population? Sure, but that's why this is only one of what I hope will be many more approaches to get to that magical all-NTDs-that-are-preventable-by-folic-acid being prevented.

DR. GUIDICE: Thank you. I'm just wondering if we need an awful lot of discussion about Question No. 5 or if we should go directly to a vote. Let's go straight to a vote then.

Dr. Stanford, starting on your side this time. This is, again, for proof of concept here.

DR. STANFORD: So all three questions or just -- I'm sorry. I'm a little unclear.

DR. GUIDICE: Just the first part.

DR. STANFORD: Okay. I think it is reasonable.

DR. MACONES: Yes.

DR. LIPSHULTZ: Yes.

DR. LEWIS: Yes.

DR. DICKEY: Yes.

DR. ROSENBERG: Yes, but I must return to the idea that it is yes particularly because of the possibilities of dealing with subpopulations.

DR. TAMURA: Yes, if we are living in an ideal world.

DR. GREENE: Yes.

DR. GUIDICE: Yes.

DR. SHANE: Yes.

DR. EMERSON: Yes.

DR. WENSTROM: Yes.

DR. RICE: Yes.

DR. CROCKETT: Yes.

DR. GREEN: Yes.

DR. DARNEY: Yes.

DR. PATTEN: Yes.

DR. HAGER: Yes.

DR. GUIDICE: Thank you. I think that was unanimous also.

Now for 5(a): Would 400 micrograms be a

reasonable dose? Dr. Crockett.

DR. CROCKETT: You know, I wanted to expound a little bit on the reasonable delivery thing. I want to compliment the drug company. I think it's brilliant, this idea of delivery in this manner, and I think they should be lauded for taking this active part in public health in trying to prevent birth defects in unborn children even before they are conceived. That's something rare.

So I preceded my comment because I'm not happy about how they have done their selection of their dosing. I believe that they have picked a relatively safe dose, but I'm not sure that it's the most efficacious dose, and I would definitely like to see some more dose testing and see if we could further reduce the incidence of neural tube defects and further impact the public health problem with increasing doses.

DR. GUIDICE: Thank you. I guess the real question is do we have enough data to recommend that 400 micrograms would be a reasonable dose.

Yes, Dr. Lewis.

DR. LEWIS: Well, in some way it would be nice to see another -- it would nice to see a dosing study given the current fortification policies and

different dietary intake that people have in the United States. It would be nice to see a dose-finding study.

DR. GUIDICE: Dr. Rice and then --

DR. RICE: And I still am remembering in the back of my mind that there's some studies that really have talked about the absorption of folic acid in different dosages of oral contraceptive pills. I mean, I think it is important that we have more information.

I think 400 micrograms is a reasonable place to start but I do think you've got to do some dose studies to know that you are getting the optimum. Then I still think there's some relevance to the fact of those other studies that show that as you increase the dose, you do see a decrease in neural tube defect.

I know about the folic levels. I got that part but I think there is still some relevance there. I think we need to be -- if we're going to do this, we might as well make sure that we're given the best dose to get the maximum benefit.

DR. GUIDICE: Dr. Darney.

DR. DARNEY: By dose finding, we don't mean looking at the ultimate outcome. Do we mean looking at what would be administered and looking at serum

ferritin or red blood cell concentrations? Is that what we mean by dose finding?

DR. LEWIS: Folate, not ferritin but, yeah. That's what I meant.

DR. GUIDICE: And that type of thing I think probably would be addressed in any subsequent discussions between the sponsor and the agency in terms of setting up a clinical trial if one is needed.

So does the Committee feel comfortable moving forward on voting on 4(a) because we have been asked to vote on that, although not on 4(b) because we've had the discussion.

Yes.

DR. HAGER: I would just like to ask if we could -- I know we've done a lot of dividing but is 400 micrograms a reasonable dose? I would say yes, it is. But is it an ideal dose, I would say no. I don't know. I would kind of like to vote that way if I could.

DR. GUIDICE: Yes, Dr. Tamura.

DR. TAMURA: Recently I reviewed four papers where investigators evaluated how much plasma folate declines over a period of three to eight weeks -- this is a very extreme case, worst scenario -- based on 160 micrograms of folate per day. It came out fairly

consistent data which range from 3.5 to 4.2 nanomols per liter per week. Which means 1.5 nanograms per mL.

Looking at the study published in the Journal of Nutrition in October indicating that folate intake from bread where fortification is mandated, 12 percent of women had less than 200 micrograms a day of intake. Also three percent of women -- they studied about 600 women -- got less than 100 micrograms a day.

If you give 400 micrograms with oral contraceptives for, let's say, a year or so and then stop, then the average waiting period for them to get pregnant would be about three months. I don't know what the initial value is but let's say it's going to be 50 nanomols per liter which is about 22 nanograms per mL because they are taking fairly large doses of folic acid, within eight weeks it will reduce to 22. Within 12 weeks it goes down to four nanograms per mL.

I'm not saying that the decline in plasma folate completely parallels the decline in tissue folate, but if we target the initial folate value or initial tissue stores as high as possible by these oral contraceptives, we will be safer to say that will be effective even after three months of discontinuation of oral contraceptives.

We are targeting low socioeconomic

populations. That's what everybody seems to agree. And they may have much lower folate intake than the general population. Therefore, I am a bit hesitant to say 400 micrograms would be really, really ideal. I think we need to have very careful assessment here how much we should give together with oral contraceptives. I'm talking about worst scenario, worst case scenario but we should consider that. I recommend to do some studies.

DR. GUIDICE: I think you are in agreement then with Dr. Hager who said that the 400 micrograms sound reasonable but we really don't know.

I would like to begin the vote, please, with Dr. Hager.

DR. HAGER: Reasonable, yes; ideal, no.

DR. GUIDICE: Dr. Patten.

DR. PATTEN: I will agree on reasonable, but I would never support using that level without definitive research being done.

DR. GUIDICE: Dr. Darney.

DR. DARNEY: Yes.

DR. CROCKETT: What Dr. Hager said.

DR. GUIDICE: And Dr. Green.

DR. GREEN: Reasonable, yes. On the second part, I would really like to say absent any

information I would prefer to -- and also given the earlier discussions about safety issues -- abstain from the vote on part (b), but to part (a), yes.

DR. CROCKETT: Sorry, Dr. Green. I would say reasonable, yes; ideal, no.

DR. RICE: I would say reasonable, yes; ideal, no. But I also want us to remember that if you have that long period of time, three to six months, that a women is trying to get pregnant and hasn't, remember she's probably going to have some recommendation to be on a supplement. Sorry, I shouldn't have added that to my vote.

DR. GUIDICE: We've not exactly been a yes- or no-only kind of vote today.

DR. WENSTROM: Yes, reasonable.

DR. GUIDICE: And ideal?

DR. WENSTROM: We can't answer that. Probably not.

DR. EMERSON: So reasonable, yes, and who knows on ideal.

DR. SHANE: Yes and maybe.

DR. GUIDICE: Yes and I don't know.

DR. GREENE: Yes, I think it's reasonable, and I'm sure that the sponsor would do dose range-finding studies as part of the application.

DR. TAMURA: For (a) I would say reasonable but, like I said, study is needed.

DR. ROSENBERG: Three hundred years into the Age of Reason, we're gathered here on a quantitative question and voting on what is reasonable. But having made that observation, yes, I think 400 is reasonable for a simple reason, and that is that I can tag it not to what feels reasonable but that there is at least a recommendation out there, which is 400 micrograms of crystalline folate, and this would deliver that. In that sense it's reasonable, but I would reiterate the need for some further study about what would be the most useful dose.

DR. DICKEY: Reasonable yes. Further study is needed before we know ideal.

DR. LEWIS: Ditto.

DR. LIPSHULTZ: Yes, same answer.

DR. MACONES: Yes.

DR. STANFORD: Yes.

DR. GUIDICE: Thank you. That leaves us the tally of 18 yes on the reasonable. I think we've had quite a bit of discussion on ideal subsequent.

Now the final question, and we have touched upon this. It's a little bit difficult to answer the question and to vote on it without much information

but the question is: Would the benefit of prior folic acid use persist if conception occurs after discontinuation of folic acid? Again, it's not stated how long after discontinuation. We've heard some data. There were some that was presented.

DR. DICKEY: I was going to say I think we've seen data presented that eight to 12 weeks there is some, though not at the same level obviously. It a decremental persistence so I think the answer has to be sure, it persist. We don't know how long and those questions need to be asked and answered so that you can appropriately counsel patients, prescribe, etc.

DR. GUIDICE: Dr. Greene.

DR. GREENE: Yes, but I would point out that what's been demonstrated is that folate levels in red cells persist but it hasn't been proven that protection against neural tube defects also persist for weeks after stopping the medication. The studies of red cell folate as relates to risk of neural tube defects have been all over the lot over the years.

DR. WENSTROM: I don't think we can answer this question without answering Question 5 because, as Dr. Tamura said, it's dose-related. The higher dose you're on, the longer it's going to take to wash out.

DR. GUIDICE: Dr. Green.

DR. GREEN: I would just like to point out that red cell folate does appear to be, for reasons that Dr. Shane gave earlier, the best indicator of continuing folate status. But it is historical in terms of what is in the red cells is what got there when that cohort of red cells overall was formed.

Consequently, we have no information to know what the target cell would be with respect to, say, neural tube defects, presumably the developing blastocyst. And, at that stage, red cell folate on average represents the legacy of an average of three months of folate studies.

DR. GUIDICE: I think also when you think of the population that is on oral contraceptives, say, with the supplementation, if there is an accidental pregnancy, then they would go off the OCP and then they would go on a multivitamin with folic acid, so it's unlikely that there would be a huge amount of time.

Secondly, the taking of the -- when those individuals who are planning a pregnancy stop their birth control pills and then decide, "Well, I'll wait a month or so," usually those women, if they are under the care of a physician or another health provider, would have some counseling with regard to

supplementation with folic acid.

One of the populations that is probably the most at risk are women who decide to stop the pill for whatever reason. Maybe not planning a pregnancy or even planning a pregnancy but don't go to anybody to talk about it and that's the population that is probably at the highest risk.

I think we do need some additional information. We've heard about the half-life of the red cell folate stores or the whole body stores which seem to be very long but I'm not sure that we've really heard enough information about the protective period when there's a washout of the folic acid being taken.

DR. SHANE: That's because no one knows. Even if you know how fast body stores go down, you don't know what level is optimum to prevent NTDs. It's not likely to be found out by one of these dosing studies that was suggested. That's just going to tell you how much is in plasma but there's no way to relate that as far as I know, if you go back to one of Jim Mills' studies, to relate that to NTD risk for actual NTDs.

It's like everything. It clearly will persist for a while and the level will get lower but

it seems if you have to go to a physician to get the prescription to get the pills with the vitamins in, then maybe that should be part of the requirement that physicians say that if you go off this to become pregnant, you should take vitamin pills instead of the mixture. Then they don't have to go back to the doctor to get the drugs.

DR. GUIDICE: And it may be also that, with more and more discussion, the entire population will have its consciousness raised about the importance of folic acid supplementation.

Dr. Emerson.

DR. EMERSON: I guess I was just being naive but I was always assuming that it was the plasma level that would have any effect on the fetus development, so that's what we would really want to be seeing for the long-term thing and we don't have that.

DR. SHANE: I can assure you that if you do a dosing study, the more you give, the higher the plasma level up to infinity essentially.

DR. EMERSON: But those stores that we have after you stop taking the folate, it starts coming out of those stores or whatever and maintains the plasma level at some value but we don't have that data. Right?

DR. SHANE: Part of it will come out of tissues. Most folate actually turns over by cleavage so most of the stuff that goes into a tissue and gets retained in the tissue doesn't come out again as an active form of folate.

DR. OAKLEY: The fetus has to have the plasma.

DR. SHANE: Well, the fetus clearly has to have the plasma, just like any other tissue. As far as I know, it's not really clear whether the folate has to go in very early in gestation or it keeps supplying the fetus during the first four weeks.

DR. EMERSON: So that would argue that, without knowing how the plasma behaves, we know absolutely nothing about whether there would be a continued affect.

DR. SHANE: You know how plasma behaves. It will go up and up.

DR. EMERSON: No, no, this is after you've stopped.

DR. SHANE: After you've stopped.

DR. EMERSON: The question is: After you've stopped receiving folate, what is the persistence of that effect? And we only have it on the red cells. We don't have it on plasma.

DR. GUIDICE: Thank you. So we have now -- I guess we need to do our formal vote on Question No. 4 and please give a simple yes or no. If you have a major caveat and it's ditto, you can say ditto around the table.

Dr. Stanford, this is your opportunity to massage the question somewhat.

Dr. Emerson has a comment.

DR. EMERSON: Just because I did want to look up what the thing was on the plasma since I was saying we didn't have that, but I do stand corrected that we do have it for eight weeks post-discontinuation where baseline was at 5, and then at four weeks of treatment it was 11.9 and then at eight weeks after discontinuation it was still at 9. I don't have a sample size on that.

DR. OAKLEY: About 200 young Dutch women.

DR. GUIDICE: Thank you. OK.

DR. STANFORD: Yes.

DR. MACONES: Yes.

DR. GUIDICE: The question is: Would the benefit of prior folic acid use persist if conception occurs after discontinuation of folic acid? And we're not voting on a dose because we don't know or for how long.

DR. LIPSHULTZ: Okay. So yes.

DR. LEWIS: Yes, and we don't know.

DR. ROSENBERG: Yes, even if conception doesn't occur.

DR. GREENE: No. I know of no data that suggest that neural tube defects are prevented after discontinuation of folate.

DR. GUIDICE: I'm just re-reading the question. I would say that I would have to abstain. I don't really know the answer to this.

DR. SHANE: Yes, for a limited period.

DR. EMERSON: I'll go with yes.

DR. RICE: Even though Dr. Greene is technically right, I'm going to still say yes.

DR. CROCKETT: Me too.

DR. GREEN: I say yes on available evidence.

DR. DARNEY: Yes.

DR. PATTEN: Yes.

DR. HAGER: No.

DR. GUIDICE: Can we have a tally on this, please? Twelve yeses, two noes, one abstention, and two of our members had to go catch airplanes.

Before we leave, I just want to ask the agency if there are any other questions that you would want us to be thinking about or answering for you. If

not, thank you. I would like to thank all the members of the Committee and all the participants in the open public session and also members of the sponsor. I hope we have given you the information that you need.

Tomorrow's meeting occurs in this room and begins at 8:00, so please come before then. Thank you.

(Whereupon, at 5:00 p.m. the meeting was adjourned.)