

VICTOR HERBERT, M.D. J.D.
130 WEST KINGSBRIDGE ROAD
BRONX, NEW YORK 10468-3922

TELEPHONES: (718) 384-5799; (718) 579-1645
OR (718) 584-9000, EXT. 6113, 6114
FAX: (718) 582-9120; FTS: 884-6113, 6114 E-MAIL: NUTRISTAR@AOL.COM

PROFESSOR OF MEDICINE AND CHAIR
COMMITTEE TO STRENGTHEN NUTRITION
MOUNT SINAI SCHOOL OF MEDICINE
NEW YORK, NEW YORK

DIRECTOR, NUTRITION RESEARCH CENTER
CHIEF, MOUNT SINAI HEMATOLOGY & NUTRITION RESEARCH
LABORATORY AT VETERANS AFFAIRS MEDICAL CENTER
BRONX, NEW YORK

August 26, 1996

FDA Docket No. 96P-0349/CP 1, filed September 26, 1996

Dockets Management Branch

ATTN: Jennie Butler

Food & Drug Administration

Department of Health & Human Services, Room 1-23

12420 Parklawn Drive

Rockville, MD 20857

By mail and FAX to 301-594-3215

The undersigned submits this petition to the Commissioner of Food and Drugs to issue an order in the form of administrative action.

A. Action requested

That the FDA require a minimum of 25 μg crystalline vitamin B₁₂ fortification per 100 g food wherever there is food fortification with pteroylglutamic acid (PGA; synthetic folic acid).

B. Statement of grounds

Implementation of the above action will prevent nerve damage from folate-masked pernicious anemia (PA) in fertile Afro-American females¹⁻² and millions of Americans over age 50.³ Such damage will be produced by the mandated-by-FDA (effective January 1, 1998) fortification of grains with folic acid, if simultaneous fortification with vitamin B₁₂ is not also mandated.

The minimal daily absorbed requirement of vitamin B₁₂ to sustain normality is only 0.1 μg .⁴ In PA, a disorder characterized by absent secretion of gastric intrinsic factor (IF) (and the presence of circulating antibody to IF) and therefore the loss of the physiologic machinery for absorption of food vitamin B₁₂, about 1% of any oral crystalline vitamin B₁₂ dose will be absorbed via non-physiologic mass action.⁵⁻⁶ Thus, an average of 0.25 μg B₁₂ will be absorbed from an oral dose of 25 μg of crystalline vitamin B₁₂ by persons who no longer secrete IF.

Since about half of an orally ingested 25 μg crystalline B₁₂ is destroyed in the stomach when co-ingested with supplements of iron and vitamin C,⁷ which often is the case in the US, leaving only half of the 25 μg of ingested B₁₂ to reach the small bowel for 1% diffusion absorption, we recommend 25 μg rather than 10 μg B₁₂ be the minimum added per 100 g flour.

There are two etiologic mechanisms for gastric atrophy eventuating in PA.³ One is genetic, i.e., gradual gastric atrophy develops in all humans in a genetically programmed way (half from each biological parent), starting sometime between age 50 and age 120, with most acquiring it between age 50 and age 90.³ Genetically predisposed gastric atrophy proceeds irregularly to total gastric atrophy; no current therapy prevents this. Acquired gastric atrophy results from gastric insult, as by iron deficiency or *helicobacter pylori*. Before reaching total gastric atrophy, acquired gastric atrophy may be partially to completely reversed by appropriate therapy.

Since an average of 1% of orally fed crystalline B₁₂ is absorbed by mass action in the absence of intrinsic factor, and only 0.1 µg absorbed B₁₂ will sustain normality with respect to vitamin B₁₂, it would superficially appear that the minimal amount of B₁₂ to be added to flour is 10 µg (to assure absorption of 0.1 µg). However, most bread is fortified with iron, and over 40% of Americans take a daily vitamin C supplement. We have shown that when iron and vitamin C hit the stomach with vitamin B₁₂ and folic acid, within 30 minutes, they destroy about 40% of the B₁₂ (and about one-sixth the folic acid).⁷ Thus, in these many millions of Americans, when the vitamin B₁₂ hits the absorptive surface of the small bowel, only about half of the B₁₂ has survived. Thus, 25 µg of B₁₂ taken orally by these people translates into only about 13 µg of B₁₂ surviving passage through the stomach to be then absorbed. Thus, the minimum safe daily oral dose becomes 25 µg of vitamin B₁₂.

Grain fortification with iron is a holdover from an FDA ruling which was appropriate a quarter century ago, but is now obsolete.⁷ A quarter century ago, about 10% of Americans, almost exclusively infants, menstruating women, and children, were iron deficient; today, only ~6% are in negative iron balance, with about half having only harmless iron storage depletion, and the other half having iron deficiency, ranging from biochemical deficiency to clinical deficiency.⁸ Equally importantly, it was totally unknown a quarter century ago, but has recently become widely known, that heterozygous hemochromatosis, with its moderate iron overload, is present in ~12% of all Americans, ~30% of Afro-Americans, and homozygous hemochromatosis, producing body organ iron storage so high that it causes sterility, heart failure, chronic fatigue, impotence, cirrhosis, arthritis, diabetes, cancer, and, ultimately, death,^{8,9} is present in about 1 in 200 Americans. In fact, in February, 1996, the Centers for Disease Control (CDC) convened an Iron Overload Workshop, which concluded that every American should have his/her blood tested for iron overload (heterozygous and homozygous) and those found to have such overload should be appropriately treated by phlebotomy, so that the homozygotes would have their organ damage arrested at its current stage and the heterozygotes would not continue to accumulate iron to the point where they develop organ damage. Details of this Workshop are available from Sharon McDonnell, MD, MPH, at the CDC.

There is an intermediate stage in progressive gastric atrophy where there is loss of gastric acid and enzymes, but not yet of IF. In this intermediate stage, food B₁₂ is not split from its food peptide bonds and therefore is not absorbed. In that intermediate stage, crystalline B₁₂ is absorbed physiologically as long as IF continues to be secreted. To prevent B₁₂

deficiency in this intermediate stage, only 1 to 5 μg daily of fortification B₁₂ is needed,³ provided the B₁₂ is not added to raw liquid protein food (such as raw eggs) which will bind it irreversibly in the absence of gastric acid and enzymes.

The bread and cereal industry has objected to adding sufficient B₁₂ to bread and cereal as to turn the product pink, alleging that pink baked goods would be rejected by consumers. Following a recipe for white bread printed on page 209 of *Betty Crocker's Cook Book* © 1978, using Pillsbury® All-Purpose Flour, we found no change from the pristine white color of the bread with no B₁₂ added when we added (prior to baking) 25 μg , 100 μg or 500 μg of vitamin B₁₂ per 100 grams of final baked bread. When we added 1000 μg of vitamin B₁₂ per 100 grams of bread, the bread, as sliced, was not quite as pristine white as with 500 or less μg of B₁₂, but there was no visible pink color whatsoever.

The Pillsbury® All-Purpose Flour we used was bleached, enriched, and pre-sifted. It contained bleached wheat flour, malted barley flour (improved yeast baking), niacin, iron, thiamin mononitrate and riboflavin. Each 31 grams contained 8% of the Daily Value for niacin, 8% of the Daily Value for iron, 15% of the Daily Value for thiamin, and 8% of the Daily Value for riboflavin.

The scientific basis of the above **Statement of grounds** is contained in the following articles in the scientific literature (and the references at the end of each article):

1. Herbert V: Folate and neural tube defects. *Nutrition Today* 1992; 27(6):30-33.
2. Herbert V. Folate supplements should be appropriately labeled to protect consumers. *Pediatrics* 1994;93(4):694-5.
3. Herbert V. Vitamin B-12. In: Ziegler EE, Filer LJ, Eds. *Present Knowledge in Nutrition* (7th Edition), Chapter 20. Washington, DC, International Life Sciences Institute (ILSI) Press, 1996:191-205 (ISBN 0-944398-72-3).
4. Sullivan LW,* Herbert V. Studies on the minimum daily requirement for vitamin B₁₂. Hematopoietic responses to 0.1 microgram of cyanocobalamin or coenzyme B12, and comparison of their relative potency. *N Engl J Med* 1965;272:340-346.
5. Ellenbogen L, Herbert V, Williams WL. Effect of D-sorbitol on absorption of vitamin B₁₂ by pernicious anemia patients. *Proc Soc Exper Biol Med* 1958;99:257-259.
6. Herbert V, Estren S, Brody E, Wasserman LR. Oral treatment of pernicious anemia. *Lancet* 1958;ii:801.
7. Herbert V. Anti-hyperhomocysteinemic supplemental folic acid and vitamin B₁₂ are significantly destroyed in gastric juice if co-ingested with supplemental vitamin C and iron. *Blood* 1996; (November supplement), in press.
8. Herbert V: Everyone should be tested for iron disorders. *J Am Dietetic Assoc* 1992; 92:1502-1509.
9. Herbert V, Shaw S, Jayatilleke E. Vitamin C-driven free radical generation from iron. *J Nutr* 1996;126(Suppl 4):1213S-1220S


*Subsequently Secretary, Department of Health & Human Services (DHHS), under President George Bush.

C. Impact

Implementation of the above action will prevent nerve damage from folate-masked pernicious anemia (PA) in fertile Afro-American females^{1,2} and millions of Americans over age 50.³ It will have the additional enormous public health advantage of preventing many millions of Americans from ever getting pernicious anemia in the first place, with its enormous cost in morbidity, mortality, and billions of health care dollars.³ It will also, with the folic acid, prevent millions of Americans from getting vasculotoxic hyperhomocysteinemia, with its enormous cost in heart attack, stroke, and other vasculotoxic morbidity, mortality, and billions of health care dollars.^{3,7}

The FDA should require that all pills containing folate should also contain vitamin B₁₂, but no other vitamins or minerals, since, when the pill dissolves in the stomach, the iron and vitamin C will destroy a substantial amount of the vitamin B₁₂ and folate.

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.



Signature: Victor Herbert, M.D., J.D.



Jean Bigaouette, M.A., R.D.

Name of petitioner: Victor Herbert, M.D., J.D.
Mailing address: 130 West Kingsbridge Road
Bronx, NY 10468-3922
Telephone: 718-364-5799;
718-579-1645

Jean Bigaouette, M.A., R.D.
460 Krumkill Road
Albany, NY 12203-5946
518-482-8704

cc: FDA Commissioner David Kessler, MD, JD
FDA Associate Commissioner Stuart Nightingale, MD
Director, FDA Office of Plant & Dairy Foods & Beverages, John E. Vanderveen, PhD
FDA Office of Special Nutritionals, Elizabeth A. Yetley, PhD
FDA Office of Special Nutritionals, Lori Love, MD, PhD
CDC's Godfrey Oakley, MD
CDC's Sharon McDonnell, MD, MPH

c:\...Vda-kessler\B12fortpet82696