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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane/Room 1061
Rockville, MD 20852

Attention: Center for Food Safety and Applied Nutrition

We, as a group of concerned scientists, hereby submit a Citizens Petition, in accord with Par. 10.30, Code of Federal Regulations, Title 21, to amend certain regulations which currently mandate the addition of five (5) nutrients in the enrichment (or fortification) of cereal grain products in the U.S. Our aim in this petition is to add calcium to the current mandatory list, as the sixth item. Calcium addition is currently an optional ingredient, but not largely used in several classes of cereal grain products.

We have assembled into this petition what we believe to be excellent rationale and adequate data to justify the low cost modest addition of calcium to the U.S. diet, in order to achieve the much larger health benefits, and reduction in medical treatment costs of at least two common diseases, osteoporosis and colon cancer.

We would welcome any discussions, contacts, etc., deemed necessary or useful by the Food and Drug Administration to aid in its review.

Sincerely,

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6/29/05

TO: Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane/Room 1061
Rockville, MD 20852

FROM: Drs. Harold L. Newmark, Robert P. Heaney, Paul A. Lachance

Title: Petition for mandatory calcium addition to current cereal-grain enrichment

Specific Aims:

1. To add calcium to the current mandatory list of 5 nutrients included in cereal grain product enrichment (fortification) to ensure the nutritional health of the entire population.

2. To broaden the range of commonly consumed foods as dietary sources of intakes of calcium, at very low cost, in order to achieve a generalized modest increase of calcium intake beyond the variability of dietary intake of the present major calcium dietary sources (e.g. milk, dairy products, some enriched fruit juices, dietary supplements, etc.) which are not generally consumed by the entire population.

Table of Contents

I. Summary

We, as a group of concerned scientists, hereby submit a Citizens Petition, in accord with Par. 10.30, Code of Federal Regulations, Title 21, to amend certain regulations which currently mandate the addition of five nutrients in the enrichment (or fortification) of cereal grain products in the U.S. Our aim in this petition is to add calcium to the current mandatory list, as the sixth nutrient for enrichment to ensure nutritional health of the entire population. Calcium addition is currently an optional ingredient, but not largely used in several classes of cereal grain products. By including calcium into the mandatory list of ingredients for enrichment of cereal grain products we estimate a mean increase of calcium dietary intake in the U.S. of about 300 mg/day (200-400 mg/day probable range), partially reducing the current gap between estimated mean (daily) calcium intake (500-700 mg) and the range of adult adequate intake (A.I.) (1000-1300 mg) of the current Dietary Reference Intake (D.R.I.) of the National Academy of Science (N.A.S.), Food and Nutrition Board, Institute of Medicine, 1997. Such calcium addition could produce a significant reduction of the risk of osteoporosis, including reductions of bone fracture incidence, as well as a significant reduction of risk and incidence of colon cancer.

At low economic cost, estimated at less than 10 cents per person per year, this calcium addition to cereal grain enrichment could prevent about 30,000 new cases of colon cancer, and about 11,000 colon cancer deaths, annually, and several billion dollars of direct medical health costs involved in the care and treatment of osteoporosis and colon cancer. This modest calcium enrichment would add a major group of foods in the

U.S. diet as a significant calcium dietary source, applicable to all aspects of the populations at risk for developing osteoporosis and colon cancer, particularly useful for large population groups where the intake of high calcium foods such as milk and dairy products is inadequate, notably minorities, low-income groups, and those with lactose intolerance.

II. History of calcium fortification of cereal grain products

A. For over 50 years calcium has been an optimal added enrichment agent to selected cereal grain products in the U.S., under U.S. Public Law 480 (1954) and subsequent amendments (1966), largely used in low cost nutrified foods supplied to overcome dietary deficiencies in developing countries. This addition is, however, optional, except for some export flours and usually is not included in pre-mixes and pre-blends used to fortify domestic flour.

B. In 1974, the National Academy of Sciences/National Research Council (NAS/NRC), (see Ref. 1) Washington, D.C., proposed an expansion of the cereal grain product enrichment program; it included mandatory addition of calcium. That proposal prompted several studies at the American Institute of Baking (AIB) and other laboratories on functional (product quality) and nutrition-related work with calcium.

Calcium was one of six additional nutrients proposed by the NAS/NRC in 1974 to be added to cereal grain mandatory enrichment, which at that time consisted of only four items. Since 1974 the FDA has issued regulation for the mandatory addition only of folate, out of the originally proposed list of six nutritents. The remainder, including calcium, remain in "proposal" status in the U.S., (i.e. not acted on by the FDA).

C. In 1992, a group of scientists and physicians, including the signers of this petition, filed a Citizens Petition to amend the Code of Federal Regulations to change the optional addition of calcium and vitamin D to cereal grain products, to become a mandatory part of enrichment, in **Docket No 92R-0064/CPI**. After more than 8 years, this petition was denied in the year 2000, without any direct discussions with any of the scientists – petitioners involved.

D. Several other nations now include calcium addition (or nutrification) to cereal grain products. In Table 1 (below) is a list of countries that are claimed to fortify wheat flour with calcium, as adapted from a publication by Dr. J.C. Baurenfiend, together with the levels of calcium chosen for addition. Addition of calcium to wheat flour in the U.S. as we propose would add 960 mg/lb (2112 mg/kg) of calcium, close to the range of addition of some foreign countries.

Table 1. Nutrification of wheat flour by added calcium in foreign countries (mg/kg)

Country	Calcium	
	Min.	Max
Australia	1,000	–
Canada	1,100	1,400
Congo	1,000	1,500
Costa Rica	1,100	1,400
Denmark	2,000	–
Dominican Republic	1,100	1,400
Guatemala	1,700	–
Guyana	1,100	1,400
Japan	1,500	3,000
Panama	1,100	–
Peru	1,000	–
Philippines	1,100	1,400
Puerto Rico	1,100	–
United Kingdom	940	1,560
West Indies	1,100	1,400

Notes for Table 1:

Specifications also exist in some countries for addition of calcium to other cereal grain products such as white rice, maize meal, corn grits, pasta products, and breakfast cereals.

Nutrified food sent abroad from the USA under the USA-AID or Food for Peace (PL 480) have the following specifications: 500-1,107 mg (for 6% soy) or 750-1,364 mg (for 12% soy) calcium per lb.

Note: This table of values taken from the literature serves as a guide. Up-to-date values need to be confirmed with the regulatory agency of the specific country.

Adapted from: Baurenfiend, J.C. Nutrification of foods. In: Shils, M.E., Olsen, S.J., Shike, M. eds. Modern Nutrition in Health and Disease. 8th ed., Philadelphia: Lea and Febiger, 1994; Chapter 91, pp. 1579-1592.

III. Evidence of need for improving dietary calcium intake

A. General population.

For calcium, the gap between the AI (Adequate Intake, as established in 1997, by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRIs), Food and Nutrition Board, Institute of Medicine, National Academy of Science, (Ref. 2) or recommended intake, and the actual mean intake from the 1994 Continuing Survey of Food Intake by Individuals, is shown in (Ref. 3, Appendix 4) Figure 1. After age 10 y, the data indicate that the mean intake of calcium does not achieve the recommended values for either females or males. After age 50 y, the mean intakes of calcium in females and males are only ≈600 and ≈700 mg/d, respectively, and the combined mean intake is only slightly over one-half of the recommended intake. Given normal population variability from the mean, the data indicate that large segments of the U.S. population have inadequate dietary calcium intake.

Note: Nutritional intake data is sometimes expressed in terms of a median, representing the intake of the midpoint (50^{th} percentile of the population studied), rather than the mean, or average of the entire population. Probably, the use of the median actual calcium intake would indicate a larger discrepancy between actual and recommended calcium intakes, due to the larger population segments that have lower calcium intakes, while primarily health conscious groups take calcium supplements.

B. Population segments.

1. In a 1997 review by FDA scientists from the Center for Food Safety and Applied Nutrition, titled "Calcium Intake Levels in the United States: Issues and Considerations" (Ref. 4, Appendix 19), the authors found significant differences of calcium intake by gender with females further below recommendations than males, particularly during puberty and adolescence, ages 11-24, when bone growth is rapid. This results in much increased risk of osteoporosis in later life. Some minority and racial differences were also noted, leading to further risks of calcium intake inadequacy.

2. In a 2003 study of 3500 premenopausal women, 20-50 years of age, who were not pregnant or lactating, Arab et al, (Ref. 5, Appendix 20) found that "more than 75% of women irrespective of ethnic group had intakes of calcium lower than the new (1997) Adequate Intake."

3. In a 2004 study of dietary supplement use in the U.S., Radimer, et al. (Ref. 6, Appendix 21) reported that calcium dietary supplements, in contrast to other dietary supplements, appear to be consumed regularly by only a low percentage of the adult populations (20+ age), although a small percentage also used calcium containing antacids. Some used dietary supplements in the multivitamin/multimineral class but the calcium content of these tend to be low. These data, from the National Health and Nutrition

Examination Survey, United States, 1999-2000, indicate a low use of calcium supplements in this nationally representative cross sectional survey of almost 4500 people, as clearly shown in Table 2 of Ref. 6 (Appendix 21). These results are not surprising, since the significant higher cost of calcium supplementation supplied as dietary supplements (many fold higher than food enrichment or fortification), coupled with the cost of personal education and reminders for regular intake (advertising or other), present regular problems for dietary supplement use that are essentially eliminated by using food fortification or enrichment to deliver increased calcium to the population.

4. Calcium dietary supplement use, while growing slowly over the last 18 years, is still very low, and particularly for some minority groups (Hispanic, 6.1%, non-Hispanic African American, 4.99%), as presented by Millen, et al. (Ref. 7, Appendix 22) in their Table 3, which also indicates that individuals below the poverty index, and those with less education include a very low percentage using calcium dietary supplements (less than 7%) in the year 2000.

IV. Benefits of proposed calcium enrichment to reduce risk of osteoporosis.

Two NIH Consensus Development Conferences (1988 and 1994) (Refs. 8, 9), the 1993 FDA Calcium and Osteoporosis Health Claim on labels of qualified foods (Ref. 10), the 1997 DRIs for Calcium and Related Nutrients, Institute of Medicine (Ref. 2), the 2004 Surgeon General's Report on Osteoporosis (Ref. 11), and the Dietary Guidelines for Americans 2005 (Ref. 12) all reach an evidence-based conclusion that calcium intakes in the range of 1000-1500 mg/day are necessary to ensure optimal bone health for all adult Americans. Moreover, the recent Surgeon General's Report on Osteoporosis (Ref. 11) stated explicitly "Calcium has been singled out as a major public health concern today because it is critically important to bone health and the average American consumes levels of calcium that are far below the amount recommended for optimal bone health." We call to your attention that the earlier 1988 Surgeon General's Report on Nutrition (Ref. 13) had, 17 years ago, suggested calcium fortification of selected foods as an appropriate public health stratagem to help the public reach desired calcium intakes.

McCarron and Heaney in their analysis of cost savings associated with augmented calcium intake (Ref. 14) estimated five-year direct health cost reductions for nine diseases in excess of $200 billion, with cost savings specifically attributable to osteoporosis amounting to $14 billion (about $3 billion annually).

V. **Benefits of proposed calcium enrichment to reduce risk of colon cancer.**

Colon cancer development in the U.S. population at present is believed to be multi-factorial in origin. Some of these factors have been identified as dietary, including inadequate intake of calcium. An aim of this petition is to increase the dietary intake of calcium to reduce the risk of colon cancer. Increasing dietary calcium intake in the U.S. population would be a significant method of colon cancer prevention, which we estimate would reduce risk of colon cancer by 20% or more. However, since colon cancer development is multi-factorial, or results of interactions of several factors, no single agent or modality can be expected to completely prevent all risk. Rather, additional factors, including dietary ones, would need to be separately addressed in order to further the reduction of risk. An example is Vitamin D addition, which, when appropriately added to the U.S. diet, will probably further reduce risk.

We present the evidence from some pertinent recent reviews and publications that support the relationship between increased calcium intake and reduction of colon cancer risk:

A. Newmark, H.L., Heaney, R.P. and Lachance, P.A. Should calcium and vitamin D be added to the current enrichment program for cereal-grain products? *Am. J. Clin. Nutr.*, 80: 264-270, 2004. (Appendix 4)

This review represents our peer-reviewed publication of the rationale, data, efficacy, safety, cost and practicality of the addition of both calcium and Vitamin D to reduce the

risk of osteoporosis and colon cancer. Based on the data, we estimated (in this review), a conservative estimate of at least 20% reduction of disease and death rate of colon cancer and osteoporosis, resulting in large economic saving in medical care costs, and significant reduction of death from these diseases.

We urge the petition reviewers to read this review in detail carefully, as a summation of relevant studies up to 2004. While the review considers both calcium and Vitamin D, we believe that the studies and conclusions are based largely on calcium alone, and justify approval of mandatory addition of calcium at this time for cereal grain product enrichment.

B. Schatzkin, A., Peters, U. Editorial: Advancing the calcium-colorectal cancer hypothesis. *J. Natl. Cancer I*nst., 96: 893-894, 2004. (Appendix 5)

In this editorial, the authors, affiliated with Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, review several of the human studies of the effect of increased dietary calcium on reduction of colon cancer risk, since this was first hypothesized over two decades ago. In their view, the data have been growing rapidly, and they conclude as follows:

"With respect to the original biologic hypothesis, studies are now in place with the potential to provide a compelling – almost proven – case that a nutritional factor

(calcium) can alter the occurrence of malignant disease (colorectal cancer). That would be a tremendous advance."

C. Chia, V. and Newcomb, P.A. Calcium and Colorectal Cancer: Some Questions Remain. *Nutritional Reviews*, 62: 115-120, 2004. (Appendix 6)

The subject review (Appendix 6) states in the last paragraph: "Despite the many epidemiologie studies of calcium and colorectal cancer, calcium's effect has been difficult to establish. More recently, however, larger prospective studies and randomized controlled trials have provided the statistical power and precision to examine more fully this relationship. In general, these studies support a modest protective effect of about 20 to 30%." And "There is significant biologic plausibility for the relationship between calcium and colon cancer, and because calcium is associated with benefits to other organ systems, supplementation should be considered. This recommendation is more compelling given the large number of colorectal cancers per year (about 150,000) in men and women."

D. Baron, J.A., Beach, M., Mandel, J.S., et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N. Engl. J. Med.*, 340: 101-107, 1999. (Appendix 7)

Appendix 7 is an important paper demonstrating in a controlled, randomized, double-blinded trial that "supplemental dietary calcium is associated with a significant – though

modest – reduction in the risk of recurrent colorectal adenomas." Randomized, controlled studies of agents that successfully reduce colon adenoma recurrence risk in humans are rare in scientific literature. The risk reduction demonstrated by calcium over the 4 years of this study, about 20%, of a recognized precursor, or biomarker, of colon cancer risk, is thus very important.

E. Wu, K., Willett, W.C., Fuchs, C.S., Colditz, G.A., Giovannucci, E.L. Calcium intake and risk of colon cancer in women and men. *J. Natl. Cancer Inst.*, 94: 437-446, 2002. (Appendix 8)

Appendix 8 is an observational study by Wu, et al. which reported the finding from 2 large-scale, prospective studies in the United States: in almost 88,000 women (Nurses' Health Study) and >47,000 men (Health Professionals Follow-up Study). Higher calcium intake was associated with a significant reduction in the risk of distal colon cancer but not of proximal colon cancer. The authors found that, compared with subjects with a calcium intake $\leq$ 500 mg/d, those with an intake $\geq$ 700-800 mg/d had a 40-50% lower risk of distal colon cancer. The authors also cite the results of other studies that indicate a potential protective effect of moderately higher dietary calcium intake primarily against distal colon cancer. In the United States today, colon cancer cases in the left sided or distal colon [descending or sigmoid colon as described by Wu, et al.] constitute about two-thirds of all colon cancer cases. Thus, on the basis of the study by Wu, the net total reduction in colon cancer by higher dietary calcium intake can be estimated at $\approx$ 30% (i.e., a 40-50% reduction of two-thirds of all colon cancer cases). From the data, the

authors suggest that "even a modest increase in calcium intake may confer protection against distal colon cancer among those with low intakes." The authors conclude that, "considering the public health importance of colon cancer, even a modest protective effect of higher calcium intake on colon cancer could result in the prevention of a large number of colon cancer cases."

F. Terry, P., Baron, J.A., Bergkvist, L., Holmberg, L., Wolk, A. Dietary calcium and vitamin D intake and risk of colorectal cancer: a prospective cohort study in women. *Nutr. Cancer*, 43: 39-46, 2002. (Appendix 9)

In a large-scale, observational prospective study of > 61,000 women in Sweden who were followed for an average time of ≈ 11 y, Terry, et al. (Appendix 9) reported on the association between dietary calcium intake and the development of colorectal cancer. An inverse association was found: compared with women in the lowest intake quartile (median intake of 486 mg/d), those in the highest intake quartile (median intake of 914 mg/d) had a relative risk (RR) of colon cancer of 0.72 (P for trend = 0.02). Terry also indicated that "the inverse association may be strongest in relation to distal cancers and among older women." The results suggest a total reduction in colon cancer risk of ≈ 28%, which is similar to the ≈ 30% reduction calculated from the data of Wu. (Appendix 8)

G. Flood, A., Peters, U., Chatterjee, N., Lacey, J.V. Jr., Chairer, C., and Schatzkin, A., Calcium from diet and supplements is associated with reduced risk of colorectal

cancer in prospective cohort of women. *Cancer Epidemiol. Biomarkers Prev.*, 14, 2005. (Appendix 10)

The data and conclusions of Flood, et al (Appendix 10) indicate that a difference of <400 to >800 mg of calcium per day was associated with an approximately 25% reduction in risk of colorectal cancer, and this reduction in risk occurred regardless of the source of the calcium (i.e., diet or supplements).

H. Grau, M.V., Baron, J.A., Sandler, R.S., Haile, R.W., Beach, M.L., Church, T.R., Heber, D. Vitamin D, calcium supplementation, and colorectal adenomas: Results of a randomized trial. *J. Natl. Cancer Inst.*, 95: 1765-1771, 2003. (Appendix 11)

The study by Grau, et al. (Appendix 11) clearly demonstrates the important interaction of Vitamin D adequacy, as determined by serum levels of 25-hydroxy (25-OH) Vitamin D, in combination with calcium dietary supplementation to reduce the risk of colorectal adenoma recurrence. These data clearly suggest the potential for strong chemopreventive effect of combined increase in dietary intake of calcium and Vitamin D to reduce colorectal adenoma, risk of recurrence, and eventual cancer risk.

I. Wallace, K., Baron, J.A., Cole, B.F., Sandler, R.S., Karagas, M.R., Beach, M.A., Haile, R.W., Burke, C.A., Pearson, L.H., Mandel, J.S., Rothstein, R., Snover, D.C. Effect of calcium supplementation on the risk of large bowel polyps. *J. Natl. Cancer Inst.*, 96: 921-925, 2004. (Appendix 12)

Appendix 12 study suggests that increased calcium intake "may have a more pronounced antineoplastic effect on advanced colorectal lesions than on other types of polyps.

J. Peters, U., Chatterjee, N., McGlynn, K.A., Schoen, R.E., Church, T.R., Bresalier, R.S., Gaudet, M.M., Flood, A., Schatzkin, A., Hayes, R.B. Calcium intake and colorectal adenoma in a U.S. colorectal cancer early detection program. *Am. J. Clin. Nutri*, 80: 1358-1365, 2004. (Appendix 13)

Peters, et al. (Appendix 13) found a protective association between total calcium and colorectal adenoma, largely due to calcium supplement use, with a 27% decrease in adenoma risk. The protective associations of total and supplemental calcium were strongest for colon adenoma (descending and sigmoid colon).

K. McCullough, M.L., Robertson, A.S., Rodriguez, C., Jacobs, E.J., Chao, A., Jonas, C., Calle, E.E., Willett, W.C., Thun, M.J. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes and Control*, 14: 1-12, 2003. (Appendix 14)

Over 60,000 men and 66,000 women in the Cancer Prevention Study II Nutrition Cohort (American Cancer Society) had their dietary calcium intake estimated (in a questionnaire) in 1992-93. Follow-up through August 1997 indicated 421 incidents of

colorectal cancers in men and 262 in women. Total calcium intake, strongest for supplements, was associated with marginally lower colorectal cancer risk in men and women (RR=0.87, p trend=0.02 of quintiles). Vitamin D was associated with reduced risk of colorectal cancer only in men.

L. In summary, these pertinent reports and reviews indicate that a modest increase of dietary calcium intake of about 300 mg/day (200-400 mg daily), as we propose in this petition by mandatory fortification of cereal grain products would bring the mean total calcium intake in the U.S. from the currently estimated 500-700 mg/day to about 800-1000 mg/day, and would result in at least a 20% reduction in risk of colon adenomas and colon cancer.

As discussed in Ref. 3, (Appendix 4), at present in the United States, the incidence of colon and rectal cancer cases is ≈ 150,000/y, with ≈ 57,000 deaths annually. Although a precise dose-response estimate of dietary calcium intake in colon cancer prevention is not currently known, from the data of the large studies described above, particularly E, F and K, we suggest that a modest increase of ≈ 200-400 mg Ca in the daily diet may thus reduce both the incidence of and the death rate from colon cancer by ≈ 20%, which would possibly save ≈ 11,000 lives and prevent ≈ 30,000 cases annually. Cases of colon and rectum cancer represent slightly > 10% of all cancer cases in the United States. The National Institutes of Health estimates that overall direct medical costs (total of health expenditures) for cancer in 2002 were $60.9 billion. With cases of colon and rectum cancer constituting ≈ 10% of total cancer cases for both men and

women, it is reasonable to estimate that the direct medical costs associated with colon and rectum cancer were ≈ $6 billion in 2002. A reduction of 20% of these cancer cases, which we estimate would occur as a result of increasing the current dietary intake of calcium, could result in a reduction of these direct health costs by > $1 billion/y.

VI. Changes specifically requested in this petition.

This new petition is to add calcium to the mandatory items in cereal grain enrichment. Scientific reports, especially within the last 2 decades have established more extensive data that give strong credibility to the concept that increased dietary intake of calcium, with the total intake approaching the A.I. level for adults of 1000-1200 mg/day can significantly reduce the risk of osteoporosis and colon cancer.

A. Specifically, we request that selected parts of the U.S. code of Federal Regulations (CFR), in Sections 136, 137 and 139 be amended as follows.

Table 2. Selected parts of the U.S. Code of Federal Regulations (2001), Title 21, Sections 136, 137, and 139, that relate to calcium

Section and Paragraph nos.	Title	Current Statement on Calcium	Proposal (amended)
136.115	Enriched bread, rolls, and buns	May contain 600 mg Ca/lb	Shall contain 600 mg Ca/lb
137.165	Enriched flour	May contain 960 mg Ca/lb	Shall contain 960 mg Ca/lb
137.185	Enriched self-rising flour	Shall contain 960 mg Ca/lb	Shall contain 960 mg/Ca/lb
137.260	Enriched corn meals	May contain 500-750 mg Ca/lb	Shall contain 500-750 Ca/lb
137.305	Enriched farina	May contain ≥500 mg Ca/lb	Shall contain ≥500 mg/Ca/lb
137.115	Enriched macaroni products	May contain 500-625 mg Ca/lb	Shall contain 500-625 mg/Ca/lb
137.117	Enriched macaroni products with fortified protein	May contain 625 mg Ca/lb	Shall contain 625 mg Ca/lb

Note: 1 lb = 0.45 kg. This list includes the majority of enriched cereal grain products with the notable exception of rice, for which enrichment poses problems of higher mass with current enrichment technology.

VII. Technology and feasibility

A. Calcium enrichment of cereal grain products, with the exception of rice, has been sporadically utilized for special purposes for decades, under the current permissive optimal sections of the CFR, as discussed earlier. Addition of appropriate CFR approved food supplements of calcium poses no technical problems to the items listed in Table 1 above.

Calcium enrichment of wheat flour, probably the largest and most important vehicle, has been extensively studied in its effect on bread baking by the American Institute of Baking. This includes a variety of calcium (chemical) sources, tests at various levels in bread, organoleptic (taste) acceptability (essentially no change), biological availability (good), standards of consumer acceptance (very good) and analytical recovery. (See Ranhotra, G. et al "Research on calcium at the American Institute of Baking", Research Department Technical Bulletin Volume XXI, Issue 1, pages 1-6, January 1999, Appendix 15).

B. Our choice of cereal grain products for enrichment as a vehicle to increase calcium intake in the U.S. is guided by the following:

1. Approximately one fourth of the daily calorie intake in the U.S. is from cereal grain products, and the intake of total cereal grain products does not vary greatly by income or geographic region in the U.S. (Refs. 15-17).

2. Cereal grain product enrichment has been historically credited for (essentially) the eradication of pellagra by niacin enrichment in the U.S., as illustrated by Fig. 2 in Appendix 4. More recently, addition of folic acid (i.e. folate) to cereal grain enrichment has significantly reduced neural tube defects in newborns in the U.S. (Refs. 18-23).

3. Other foods, such as some fruit juices, are also now being used for calcium and Vitamin D nutrient enrichment to increase intake in the U.S. population. We applaud such increased diversity of food enrichment, and we strongly suggest that cereal grain products be added to the list, as a very reliable nutrient carrier, little prone to provide excess intake, safe and simple to use, low cost, and very broadly consumed and well distributed in the general population.

C. Sources of calcium addition. There are a variety of direct food substances affirmed as generally recognized as safe (Gras) in CFR, Title 21, for use as sources of calcium as indicated in Table 3.

Table 3.

184.1185	Calcium acetate
184.1187	Calcium alginate
184.1191	Calcium carbonate
184.1193	Calcium chloride
184.1199	Calcium gluconate
184.1205	Calcium hydroxide
184.1206	Calcium iodate
184.1207	Calcium lactate
184.1210	Calcium oxide
184.1221	Calcium propionate
184.1229	Calcium stearate
184.1230	Calcium sulfate
184.1409	Ground limestone (as a source of calcium carbonate when shown to be analytically sufficiently pure)

In part 182, substances generally recognized as safe, Subpart F, Dietary Supplements, a separate list of calcium sources approved for use as dietary supplements is given, as indicated in Table 4.

Table 4.

Subpart F – Dietary Supplements	
182.5191	Calcium carbonate
182.5195	Calcium citrate
182.5201	Calcium glycerophosphate
182.5210	Calcium oxide
182.5217	Calcium phosphate
182.5223	Calcium pyrophosphate

As we understand, all of the calcium sources listed in Tables 3 and 4 may be used for calcium enrichment of cereal grain products. However, we have strong reservations on the use of some of those sources, specifically calcium glycerophosphate, calcium phosphate and calcium pyrophosphate, as explained below:

1. Calcium phosphate (including monobasic, dibasic and tribasic) would also add appreciable phosphate to the human diet in the U.S., which is currently already high

from other phosphate sources (meat, processed meat, processed cheese, some soft drinks, etc.).

A good review of the potential adverse effects of the current U.S. high dietary intake of phosphate is presented in "Changing Phosphorus Content of the U.S. Diet: Potential for Adverse Effects on Bone," by Mona S. Calvo and Youngmee K. Park, J. Nutr., 126: 1168S-1180S, 1996 (Ref. 24).

2. Similar objections apply to calcium glycerophosphate and calcium pyrophosphate.

C. Most of the pharmaceutical-type dietary supplements of calcium use calcium carbonate as a chemical source. This includes calcium carbonate prepared by precipitation processes (CFR-Par 184.1191) and also selected sources of ground limestone (CFR-Par 184.1409), both sources meeting the specifications of the Food Chemical Codex. A recent review of updated current calcium carbonate production methods is: Tarquin, M., Altering the Calcium Landscape: Today's Chemist at work, American Chemical Society, July 2004, Pages 23-25. (Appendix 16)

VIII. **Cost**. An estimate of the cost of adding calcium (as carbonate) to cereal grain products is included in Newmark, et al. (Ref. 3, Appendix 4), and appears to be about $17 million annually, or less than 10 cents per person per year. This cost appears to be insignificant compared to the potential savings of the reduced medical treatment cost alone of a 20% reduction in colon cancer risk of over $1 billion annually, as well as a potential reduction of 11,000 colon cancer deaths per year. The cost savings specifically attributable to augmented calcium intake on osteoporosis is estimated at about $3 billion annually. (See section V, Ref. 14, Appendix 3).

The combined potential cost savings of a 20% reduction of colon cancer and osteoporosis is thus estimated to be over $4 billion annually, at a cost of calcium addition of only $17 million annually.

IX. **Safety** – The health risks of the mandatory addition of calcium to the currently enriched cereal-grain products appear to be negligible. The Food and Nutrition Board, Institute of Medicine of the National Academy of Sciences has established a tolerable upper intake level (UL) (Section V, Ref. 2) for daily calcium intake of 2500 mg/d for persons aged ≥ 1y. The concept and definition of UL, is as follows:

"UL, the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases."

Mandatory enrichment in the amounts currently listed in the Code of Federal Regulations would add about 200-400 mg Ca to the mean daily U.S. diet, or less than 16% of the UL for calcium.

The enrichment of cereal-grain products is highly unlikely to represent a risk of high sustained intake because of the highly dilute levels of enrichment in these foods and the practical difficulties and self-limiting intake of high or excess intake of these foods in individuals, especially over a prolonged period. Both the sources and quality of calcium that can be used for enrichment are carefully specified in the Code of Federal Regulations and the Food Chemical Codex.

In the older literature, a higher dietary calcium intake was considered to be a potential risk factor for kidney stones. However, both observational studies (Refs. 25-27)

and a controlled clinical trial (Ref. 28) showed that adequate dietary calcium decreases rather than increases the risk of kidney stones, probably by decreasing oxalate absorption and thereby lowering urinary oxalate concentrations as described by Newmark, et al. (Ref. 3, Appendix 4). In the gut, calcium combines with oxalate to form a salt that is poorly absorbed, which reduces the renal burden of oxalic acid and hence lowers the risk of stone formation (Refs. 2, 25, 26, 28). The recent report of Borghi et al. (Ref. 28) is particularly pertinent because it is a controlled trial and because the authors specifically measured urinary oxalate excretion. They showed a 50% reduction in the recurrence of kidney stones, as well as a reduction in urinary oxalate, with increased dietary calcium, in kidney stone prone subjects over a period of 5 years. More studies are needed to assess at a large-scale level the possible beneficial effects of moderately increased dietary calcium intake on reduction of the incidence of kidney stones, but the current scientific and medical consensus is that there is little or no increase in risk with moderately increased dietary calcium.

X. Impact Statement

The potential effect on the U.S. diet of the mandatory addition of currently allowable amounts of calcium to cereal-grain products (Table 2) can be approximately estimated. Some ready-to-eat cereals are currently marketed with some added calcium (e.g. General Mills products at 100 mg per serving and a newly marketed bread (Wonder Bread, new and improved) has added calcium. However, calcium addition is neither uniform nor universal and would benefit by standardization of fortification, at least on a minimum basis. Estimates of increased calcium intake can be made on the assumptions that mandatory enrichment would be practiced on all the products listed, and in the amounts listed, in the current Code of Federal Regulations, Title 21, except rice, for which enrichment poses unsolved technological problems. Data on year 2000 per capita annual consumption of cereal products were obtained from the U.S. Department of Agriculture, Economic Research Service (Ref. 29). In Table 5 the total proposed additions of calcium to the average U.S. daily diet may be estimated at about 400 mg, if the additions described in Table 1 were to become mandatory.

Table 5. Estimated increased daily dietary intake of calcium from major consumed cereal grain product foods if the current optional enrichment regulation were to become mandatory[1], based on USDA per capita consumption data.

	Year 2000 per capita consumption[2]		Calcium enrichment	
	Annual	Daily	Amount	Daily intake
	lb	lb	mg/lb	mg
Item				
Wheat flour & products	133.4	0.365	960	350
Corn meal	17.5	0.048	500-750	24-36 (≈30)
Pastas (macaroni, noodles	12.9	0.035	500-625	18-22 (≈20)
etc: semolina and				
durum flour)				
Total	–	0.45	–	400

Notes for Table 5:

1. Numbers in parentheses represent the approximate effects of using the middle value of the current optimal range for enrichment. 1 lb = 0.45 kg.

2. From U.S. Department of Agriculture, Economic Research Service. Food consumption (per capita) data system. Washington, D.C.: U.S. Government Printing Office, 2000 (Ref. 29).

The estimate in Table 4 may be higher than reality, since the data on "per capita consumption" from the USDA data system actually is based largely on cereal grain production data, rather than actual consumption, and does not allow for spoilage, waste, etc. in distribution and home use. The amount of such losses is difficult to ascertain with accuracy. This is shown by the total daily per capita consumption in Table 4 of 0.45 lb (0.2 Kg), representing about an 800 Kcal intake, which is overly high for mean U.S. dietary intake of cereal grain products, normally estimated at about 500 Kcal intake, based on 25% of a 2000 Kcal diet.

Another method of estimating potential impact of calcium enrichment of cereal grain products is based on the estimate by the National Research Council (Refs. 1, 15, 16) that approximately one-fourth (25%) of daily caloric intake in the U.S. is from cereal-grain products, mostly from wheat products. In Table 6, estimates are given for a low (2,000 Kcal) mean diet and a higher 2,700 mean diet for calcium dietary impact, using the proposed addition of 960 mg calcium per pound of wheat flour and products (about 2,000 mg Ca/Kg flour, or about 2.0 mg Ca per gm of flour).

Table 6. Estimated increased daily dietary intake of calcium from major consumed cereal grain product foods, based on current optional enrichment regulations, if made mandatory, based on estimated intake in a range of total caloric intake.

Kcal diet	Kcal 25% cereal grains	gm/day cereal grains	calcium/day added to diet
2000	500	125 g	250 mg
2700	675	169 g	338 mg

Notes for Table 6:

1. As discussed above, estimates of U.S. diet (Refs. 1, 15, 16) indicates that about one fourth (25%) is from cereal grain products, which are essentially 4 Kcal per gram, dry weight.

2. As discussed above, calcium addition is calculated as about 2 mg calcium per gram of cereal product dry weight (e.g. wheat flour).

By this method of impact estimate, calcium increase in the U.S. diet would be about 250-338 mg per day, which we believe may be broadened to 200-400 mg/day increase. It should be noted that Park and Calvo of the U.S. Food and Drug Administration estimated in 1995 that mandatory calcium fortification of cereal-grain products at levels similar to those in this petition would increase calcium intakes by 10-20% of the recommended dietary allowance (Ref. 30) and represents a significant increase for most persons whose intake is inadequate. This estimate is very close to our own.

In summary, we estimate that an increase of about 200-400 mg calcium per day in the U.S. mean diet would occur with mandatory calcium fortification of cereal grain products.

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