TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Zucker et al. 1988 *Artherosclerosis* 73:13.	Randomized, crossover.	6 weeks	3.2 g EPA 2.2 g DHA (MaxEPA) v safflower oil.	9 normal, 16 hyperlipoproteinemics.	↓ TGs, VLDL; ↑ LDL in type IV hyperlipoproteinemics; NS Chol, TG, LDL, HDL among normals.	Safflower oil was used a control oil. The stu design was double blir but many of the subjec reported identifying th FO by its characterist aftertaste. This is one the very few article r ported FO aftertaste in double blind study.

Abbreviations used: NS, not statistically significantly different; Chol, cholesterol; VLDL, very low-density lipoprtein cholesterol; LDL, low-density lipoprote cholesterol; HDL, high-density lipoprotein cholesterol, TGs, triglycerides; apoA, apoprotein A (a protein in high-density lipoprtoein); apoB; apoprotein B (a protein low-density lipoprotein); apoE, apoprotein E (a protein in many lipoproteins, most notably VLDL and HDL; CHD, coronary heart disease; FO, fish oil; TX thromboxane; TPA, tissue plasminogen activator; PAI, plasminogen activator inhibitor; v, versus; /d per day.

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21 CFR Part 101

[Docket No. 91N-0094]

RIN 0905-AB67

Food Labeling: Health Claims; Calcium and Osteoporosis

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to authorize the use on food labels and in labeling of health claims relating to the association between calcium and osteoporosis. FDA has reviewed the available scientific data under the provisions of the Nutrition Labeling and Education Act of 1990. Based on its review, FDA has tentatively concluded that there is significant scientific agreement among qualified experts that this data supports that calcium intake has a significant impact on bone health. The agency proposes that for a product to be eligible to bear such a claim, one serving of the product must contain a minimum of 20 percent of the Recommended Daily Intake (RDI) for calcium or 180 milligrams (mg) in an assimilable form.

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the Nutrition Labeling and Education Act of 1990.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Mona S. Calvo, Center for Food Safety and Applied Nutrition (HFF-265), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-485-9564.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Nutrition Labeling and Education Act of 1990

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (Pub L. 101-535) (the 1990 amendments), which amend the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorize the Secretary of Health and Human Services (the Secretary) to issue regulations authorizing nutrient content or health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)).

Published elsewhere in this issue of the **Federal Register** is a proposed rule to establish general requirements for health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs or other nutritional substances (referred to generally as "substances") to a disease or health-related condition on food labels and in labeling. In this companion document, FDA has tentatively determined that such claims would be justified only for substances in dietary supplements as well as in conventional foods if the agency determines based on the totality of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles) that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The 1990 amendments also require (section 3(b)(1)(a)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x)) that, within 12 months of their enactment, the Secretary shall issue proposed regulations to implemen section 403(r) of the act (21 U.S.C. 343(r)), and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including calcium and osteoporosis, meet the requirements of the act. In this document, the agency will consider whether a label or labeling claim on food or food products, including conventional foods and dietary supplements, on the relationship between calcium and osteoporosis would be justified under the standard proposed in the companion document entitled "Food Labeling: General Requirements for Health Claims for Food."

FDA has followed the general concepts and criteria proposed in the companion document in considering whether to propose to authorize the use on the labels and labeling of food of health claims for calcium and osteoporosis. In the companion document, FDA has proposed that, in evaluating whether support exists for a health claim, it will consider the levels and safety of a nutrient within the context of its use in the daily diet. Before a health claim for a particular nutrient will be authorized, it is necessary that the nutrient be safe and lawful for use in food at the level found to have an effect on a disease or health condition.

The topic of calcium and osteoporosis involves a substance which has recognized uses both as a component of food and of drugs. The agency has looked at all data relevant to this topic whether the data involved tests at dietary levels or at therapeutic levels. The agency thought this necessary to

ensure the completeness of its review. However, the agency emphasizes that this proposal is only about whether a claim has been justified for calcium and food. A component of food must be safe in the context of the daily diet. On the other hand, drugs may be used even if they present questions of safety to the general population, and even to the population being treated, on the basis that there is a benefit from its use that outweighs the potential risk.

B. Definition and Disease Prevalence, Morbidity, Mortality, and Health Costs

Osteoporosis is a disease characterized by low bone mass, where the internal structure of the bone has been eroded to the extent that even slight trauma will cause the bone to fracture easily (Ref. 7). An estimated 75 million people are afflicted with osteoporosis in the United States, Europe, and Japan (Ref. 7). These estimates include one in three women over 65 years and more than half the elderly men and women over 75 years.

Osteoporosis causes more than 1.3 million fractures per year in the United States, typically involving the spine, wrist, hip and ribs (Ref. 109). Because life expectancy in the United States will soon average in the eighties, osteoporosis is expected to affect an even larger proportion of our population (Ref. 20). By age 80, approximately 40 percent of all women will have sustained a wedge-type fracture of the spine, a common source of pain, disability, and deformity, resulting in progressive loss of height with age (Ref. 109).

Fractures of the hip, however, have the greatest health and economic impact. In 1985, approximately 250,000 hip fractures occurred in the United States, primarily in persons over age 45 (Refs. 20 and 101). An estimated 12 to 20 percent of the hip fracture victims die within the year following the fracture (Ref. 83). Among those that do survive, a significant proportion never regain their prefracture independence and require varying degrees of nursing and often permanent custodial care (Ref. 7).

Estimates of the annual financial costs of osteoporosis in the United States, based primarily on the cost of hospitalization and acute and long-term care services were $6.1 billion dollars in 1984 (Ref. 5) and are currently thought to exceed $10 billion dollars (Ref. 8).

C. Risk Factors and Populations at Risk

The most important risk factors for osteoporosis and associated bone fractures are age, gender, race (Caucasian or Asian), and hormonal status (Refs. 1, 2, 3, 5, 7, 10, 83, and 109). For women, hormonal changes associated with menopause (natural or premature cessation of the menstrual cycle) places them at increased risk (Ref. 118). In addition, evidence exists identifying low dietary calcium, cigarette smoking, and alcohol intake as factors in the development of osteoporosis (Refs. 2, 8, and 109). In general, factors that impair maximum bone formation early in life and those that underlie excess postmenopausal and age-associated bone loss later in life will predispose persons to osteoporosis.

D. Calcium's Nutrient and Physiologic Function

The human body contains approximately 1,000 grams (g) of calcium, 99 percent of which is found in the skeleton and a small but very important 1 percent is found in the plasma and soft tissues (Ref. 21). Calcium is an essential nutrient. In terms of its physiological function, calcium is probably one of the most critical minerals in the body. Within bone, calcium provides structure and support. The bone's exchangeable calcium pool allows for calcium storage that can be readily released in times of need. When this pool is exhausted, bone can be resorbed, that is, physically broken down to release needed calcium (Ref. 100). Within plasma and cells, calcium functions in bone mineralization, blood clotting, membrane stability and permeability, nerve conduction, muscle contraction, cellular secretion, regulation of ion transport, enzymatic activity, and cell growth and differentiation (Refs. 21 and 100). Plasma calcium levels are maintained within a very narrow range through the interaction of three hormones whose actions raise or lower the calcium levels appropriately in order to maintain proper physiologic function (Ref. 100).

While bone can serve as a temporary source of calcium during acute physiologic need, the body is dependent on dietary intake as the ultimate source of calcium to replete the skeletal reserves (Ref. 87). When increased demand for calcium results in excessive resorption of calcium from bone, the structural support function of bone is compromised, and the bone breaks easily (Refs. 21 and 30).

Because of its essential function in the maintenance of plasma calcium within such narrow limits, bone is constantly turning over and remodeling and thus remains a dynamic tissue throughout life. The process of bone remodeling consists of the tightly coupled actions of bone resorption and bone formation. It is thought that through changes in bone remodeling activity, factors such as dietary calcium, exercise and hormonal activity modulate the rate of bone loss or gain (Refs. 34 and 64).

The need for calcium throughout life varies with bone remodeling activity and is reflected in the dietary guidelines for calcium intake, which suggest highest intake during adolescence and early adult life when the greatest net growth of bone occurs (Ref. 3). Many experts argue that because of the increase in the bone resorption component of the remodeling activity that occurs at menopause in women, there is also a need for greater calcium intake at this stage of life (Refs. 23 and 67).

E. Importance of Peak Bone Mass and Its Relation to Calcium

Peak bone mass, the total quantity of bone present at skeletal maturity, may have the greatest bearing on whether or not a person is at risk of developing osteoporosis later in life. Most bone experts support the idea that the best way to reduce the risk of osteoporosis is to maximize the amount of bone formed at skeletal maturity which occurs by approximately age 35 (Refs. 2, 10, 16, 64, and 91). Experts agree that two factors, adequate calcium intake and physical activity, are critical to maximizing the amount of bone formed at skeletal maturity (Refs. 67, 91, 109, and 118). It is also widely held that if calcium intake is not adequate during childhood, adolescence, and early adulthood, full skeletal potential may not be attained (Refs. 16, 37 and 64).

Throughout life, bone is constantly changing and remodeling, but the components of bone remodeling, that is the rates of bone resorption and formation, differ at different stages of the life cycle. At puberty, bone formation occurs at an accelerated rate which results in an increase in both the length and density (mass) of bone (Ref. 118). While little to no further growth in length is experienced after the pubescent growth spurt, bone continues to grow in width and in mass adding approximately 10 percent or more mass over the next 10 to 15 years (Refs. 63 and 118). This later phase is known as the period of consolidation and continues until about 35 years of age, at which time a person is considered to be at peak bone mass or skeletal maturity (Refs. 10 and 118).

At midlife, between the ages of about 35 to 45, bone continues to remodel, but bone mass is maintained without change (balanced rate of resorption and formation). Thereafter, bone is lost at a constant rate of 0.3 to 0.5 percent per

year in both men and women (greater rate of bone resorption) (Ref. 20). Prior to and after menopause, women lose bone at a faster rate (2 to 5 percent per year) than men, but eventually return (between about 60 and 70 years of age) to the same rate of bone loss as men (Ref. 20). During the menopause, a decrease in the female hormone estrogen is the factor underlying this rapid rate of bone loss (Refs. 20, 90, and 118).

The postulated mechanism underlying the relationship of adequate calcium intake and optimal peak bone mass to the reduced risk of osteoporosis relates to the assumption that since all persons lose bone with age, those with higher bone mass at maturity take longer to reach the critically reduced mass at which fractures occur with minimal trauma (Ref. 20). Genetic factors probably have the greatest influence on setting the upper limit of an individual's peak bone mass (Ref. 64). One explanation why men have a lower incidence of osteoporosis than women is that men are genetically programmed to have a higher peak bone mass (Ref. 74).

Racial differences observed in the incidence of osteoporosis are also thought to be related to differences in genetically determined upper limits of bone mass. For example, Caucasian women, particularly those of northern European ancestry, experience the highest incidence of osteoporosis related bone fracture, while American women of African heritage have greater bone density and significantly lower (approximately 50 percent) fracture rates (Refs. 28, 4, 118, and 136). Experts suggest that the greater initial bone density (peak bone mass) observed in African Americans explains why they have fewer osteoporotic fractures than Caucasians and Asians (Ref. 28, 41, 69, and 118). Nevertheless, weight bearing exercise and diet can also influence the maximal amount of bone achieved, and unlike genetic factors, diet and exercise can be easily manipulated (Refs. 10, 78, 102, and 109).

F. Role of Calcium After Peak Bone Mass

Bone density later in life depends on both the amount of bone made during growth (peak bone mass) and the subsequent rate of bone loss after maturity. The impact of dietary calcium on bone loss that occurs between ages 35 to 45 or after peak bone mass is achieved but before menopause, is unclear, because limited data are available characterizing the rate of bone loss that occurs. Maintenance of an adequate calcium intake during the onset of menopause at about 45 to 50 years of age is important and may help to slow the rapid loss of bone at this time (Refs. 47 and 102). However, because the rapid rate of bone loss that occurs early in menopause is largely the result of the hormonal changes associated with the onset of menopause, a high dietary calcium intake alone will not effectively slow the rate of loss during this period of early hormone withdrawal in women (Refs. 7, 52, 109, and 120). Failure of men to experience this period of accelerated bone loss resulting from hormonal withdrawal is another explanation for the sex difference observed in the incidence of osteoporosis (Refs. 20 and 118).

G. Summary of Mechanism of Action of Calcium

Current scientific thought suggests that there are two mechanisms through which calcium intake may influence bone remodeling and ultimately, the risk of osteoporosis and related bone fracture. The first mechanism involves maximizing the amount of bone that is formed at skeletal maturity and the second involves slowing the rate of bone loss with age. Both mechanisms would allow an individual to maintain a higher bone mass later in life, thereby reaching the critical fracture threshold much later in life.

H. Regulatory History

1. Calcium

Calcium-containing food ingredients are used in food for a number of functional effects. In preparing this proposal, the agency identified those ingredients currently in use and their functions, conditions of use, and limits on the level for which they can be added to food (Ref. 33). For the uses of these ingredients in food to be lawful, they must be either generally recognized as safe (GRAS), or affirmed as GRAS by FDA, listed in the food additive regulations, or subject to a prior sanction. Of the 36 or more calcium-containing ingredients identified by the agency as currently in use, only the following 10 compounds have been demonstrated to FDA's satisfaction to be safe and lawful for use in a dietary supplement, or as a nutrient supplement by FDA: calcium carbonate, calcium citrate, calcium glycerophosphate, calcium oxide, calcium pantothenate, calcium phosphate, calcium pyrophosphate, calcium chloride, calcium lactate, and calcium sulfate.

FDA also allows the addition of calcium-containing compounds to certain foods for the purpose of fortification, under standards of identity. Examples of the foods in which calcium fortification (in mg per pound (mg/lb)) is allowed, and the permitted levels of fortification in mg per pound (mg/lb), include: 136.115 *Enriched bread,* permits the addition of 600 mg/lb; 137.260 *Enriched flour,* may contain 960 mg/lb; 137.260 *Enriched corn meal,* may contain up to 750 mg/lb; 137.350 *Enriched rice,* may contain up to 1,000 mg/lb; 139.115 *Enriched macaroni,* 139.155 *Enriched vegetable noodle product,* and 139.165 *Enriched noodle products,* may contain up to 625 mg/lb respectively; 139.120 *Milk macaroni,* calcium-containing milk solids content not less than 3.8 percent of the weight of the finished product; 139.121 *Nonfat milk macaroni products,* finished product contains up to 25 percent calcium-containing, nonfat milk solids; 163.130 *Milk chocolate;* 163.135 *Buttermilk chocolate;* 163.140 *Skim milk chocolate;* and 163.145 *Mixed dairy product chocolates,* contain not less than 3.66 percent and up to 12 percent by weight calcium-containing milk solids.

2. Health Claims

In the **Federal Register** of August 4, 1987 (52 FR 28843), FDA published a proposal to amend the food labeling regulations to codify and clarify the agency's policy on the appropriate use of health claims on food labeling. The comments received on this proposal strongly opposed the use of the health claims. In the **Federal Register** of August 8, 1989 (54 FR 32610), FDA published an advance notice of proposed rulemaking that asked for public comment on how to reasonably permit the use of health claims on food labels that link food components to reduction of risk of chronic disease. In the **Federal Register** of February 13, 1990 (55 FR 5176), FDA withdrew the 1987 proposal and reproposed a regulation outlining how the agency would allow health claims. Calcium and osteoporosis were among the specific diet and disease relationships mentioned in these documents. However, on November 8, 1990, as stated above, Congress passed the 1990 amendments. This action is being taken in response to those provisions.

I. Evidence Considered in Reaching the Decision

The agency has reviewed all relevan scientific evidence on calcium and osteoporosis. This evidence included several recent Federal government reports: "The Surgeon General's Report on Nutrition and Health" (Ref. 1); the National Institutes of Health's (NIH) "Osteoporosis Report of the 1984

Consensus Development Conference on Osteoporosis" (Ref. 6); the NIH 1984 and 1986 "Osteoporosis—Cause, Treatment, Prevention" (Ref. 5); FDA "Proceedings of the National Conference on Women's Health Series—Special Topic Conference on Osteoporosis" (Ref. 10); the Department of Health and Human Service's (DHHS) "Healthy People 2000: National Health Promotion and Disease Prevention Objectives" (Ref. 11); the 1990 International Conference sponsored in part by NIH, "Consensus Development Conference: Prophylaxis and Treatment of Osteoporosis" (Ref. 7); and the DHHS "Osteoporosis: Research, Education, and Health Promotion" (Ref. 8).

Other authoritative documents used included: the National Academy of Science's (NAS) "Diet and Health: Implications for Reducing Chronic Disease Risk" (Ref. 2); the NAS "Recommended Dietary Allowances" (Ref. 3); the World Health Organization's (WHO) "Diet, Nutrition, and the Prevention of Chronic Diseases" (Ref. 9); the Life Science's Research Organization (LSRO) "Calcium and Osteoporosis Report" (Ref. 13); and the NAS "Nutrition During Pregnancy Report" (Ref. 12).

The agency considered the conclusions reached by these documents in light of the findings of human studies and new review articles in the scientific literature published subsequent to these documents. To assure that its review of relevant evidence was complete, FDA requested in the **Federal Register** of March 28, 1991 (56 FR 12932), scientific data and information on the 10 specific topic areas identified in the 1990 amendments. The topic of calcium and osteoporosis was among the 10 subjects on which the agency requested information.

J. Comments in Response to FDA Request for Data and Information

In response to FDA's March 28, 1991 request for information other than that available in the authoritative documents cited in the **Federal Register**, the agency received comments from 17 sources. These sources included seven manufacturers of calcium supplements or calcium containing food products, three products or commodity interest groups, two consumer-public health interest groups, two academic institutions, two private citizens, and representatives of the Canadian government. These comments are described briefly here and will be considered, as appropriate, throughout the text of this document.

The majority of the comments supported a health claim proposal relative to calcium and osteoporosis, with only two comments, from a private citizen and from the Canadian government, opposing. A comment from a consumer advocate group urged FDA to be cautious and consider the consumer first and foremost when making its decision. Comments from an academic institution and from supplement manufacturers provided information purporting to demonstrate the effectiveness of a particular type of calcium supplement or food additive (fortificant) because of claimed superior bioavailability. The majority of the comments provided references or reviews of the calcium and osteoporosis relationship all of which were taken into consideration in preparing the science review.

II. Science Review

A. Federal Government and Other Reports

FDA identified seven documents in the **Federal Register** of March 28, 1991, that reviewed or made recommendations relative to the calcium-osteoporosis health relationship (Refs. 1 through 6, and 10). In addition, FDA considered the published conclusions of several recent government-sponsored conferences and reports and authoritative reviews (Refs. 7, 8, 9, 11, 12 and 13).

Comparing the conclusions from the first consensus conference on osteoporosis sponsored by NIH in 1984 (Refs. 5 and 6) to the most recent NIH-sponsored consensus conference held in October 1990 (Ref. 7), there is an evolution in thought concerning the importance of calcium intake to osteoporosis.

Changes in the recommended levels of calcium intake, and also changes in target population emphasis have in large part mirrored important clinical and epidemiological findings over the last decade. Initial emphasis was on a higher calcium intake for adults, with particular focus on postmenopausal women (Refs. 5 and 6). The 1984 NIH report suggested that all adults should consume more than the 1980 Recommended Daily Allowance (RDA) of 800 mg of calcium: "Adult women and probably adult men should have a total daily intake of 1,000 mg of calcium and women past menopause, not on estrogen therapy, need 1,500 mg daily" (Ref. 5).

NIH republished this document in 1986 (Ref. 5) with the following caveat: "It has not yet been proven by convincing scientific evidence that a high calcium intake will prevent osteoporosis." This qualification reflected the results of studies that failed to show that calcium intakes above the RDA or high calcium intake slowed bone loss in postmenopausal women (Refs. 109, 119 and 120).

The current focus presented at the 1990 "Consensus Development Conference: Prophylaxis and Treatment of Osteoporosis" shifts the emphasis on calcium intakes from older to younger individuals who are still actively laying down bone and recognizes that dietary calcium intakes below 1,000 mg per day of dietary calcium are adequate for adults (Ref. 7). The panel concluded that adequate calcium intake at all stages of life was a prerequisite for normal bone growth and attainment of peak bone mass. However, it also concluded that a high calcium intake is not as effective as a combination of adequate dietary calcium and estrogen therapy in blunting the accelerated bone loss during menopause. The panel also recognized that inadequate calcium intake is a risk factor for osteoprosis, citing a minimum intake of 800 mg calcium per day for all adults, and that "higher amounts are required in childhood, adolescence, pregnancy, lactation, and old age."

While the authoritative documents may present varying guidelines for adequate calcium intake, ranging from 800 to 1,500 mg per day for adults, they are unanimous in their recommendation that preventive efforts focus on maximizing peak bone mass (Refs. 1 through 3, 5, 6, 8 through 13). All of these documents emphasize that calcium intake is only one factor in this multifactorial disease, and that the exact nature of the association between calcium and osteoporosis is still unclear. The documents also agree that low calcium intake is a risk factor in the development of osteoporosis and may contribute to a lower peak bone mass or accelerate the rate of bone loss with aging (Refs. 1 through 3, 5, 6, 8 through 13). In addition, all these documents emphasize that during the interval of rapid bone loss that occurs early in menopause, both an adequate dietary intake in calcium and estrogen therapy are required and recognize the need for men and women to maintain adequate calcium intake later in life (Refs. 1 through 3, 5, 6, 8, through 13).

The 1987 FDA conference recognized that calcium is a threshold nutrient, i.e., deleterious effects may occur below a certain, unknown level of intake (Ref. 10). The NAS report on "Diet and Health: Implications for Reducing Chronic Disease Risk" emphasized, however, that potential benefits of calcium intakes above the RDA's to

prevent osteoporosis are not well documented (Ref. 2).

The recommendations for a particular level of dietary calcium intake are a key point of difference among the documents that set guidelines (Refs. 2, 3, 5, 7, and 11). "Recommended Dietary Allowances," published by NAS recommended an extra allowance of calcium to permit full mineral deposition through age 24, rather than through age 18, as in the 1980 edition of the calcium RDA (Ref. 3). The NAS made this change "to ensure a calcium intake that allows the development of each individual's genetically programmed peak bone mass during the formative years" (Refs. 2 and 3). Earlier recommendations of 1,000 to 1,500 mg calcium per day for peri- and postmenopausal women (Ref. 5) did not prevail, and the 1989 RDA for all adults of more than 25 years of age remained at 800 mg per day. This level for adults was recommended in the 1990 consensus conference, with higher, unstated levels for childhood, adolescence, pregnancy, lactation and old age (Ref. 7).

In summary, these documents show general agreement that, despite the lack of conclusive evidence, the data are sufficiently compelling to suggest that maintaining an adequate calcium intake during adolescent and early adult life may help to maximize peak bone mass and ultimately to reduce the risk of osteoporosis. Adequate calcium intake during the peri- and postmenopausal period in women and in elderly men is important, but alone, high calcium intakes will not prevent the accelerated rate of bone loss which normally occurs in peri- and early post menopause.

B. Recent Scientific Review of the Literature

1. Evidence Reviewed

A number of important studies have been published since the publication of the major authoritative and government documents described in the previous section. A thorough review of the literature from 1988 to March of 1991 revealed a number of review, commentary, and research papers dealing with various aspects of this subject. The criteria that the agency used to select studies required them to:

(1) Present primary, clinical data carried out in normal, healthy, nonpregnant, or nonlactating adolescents or adults;

(2) Be available in English;

(3) Include direct measures of bone status such as bone mineral density; and

(4) Include a measure or estimate of calcium intake or level of calcium supplementation.

The first criterion selected is consistent with the goals of the health claim in that it will be applied to a healthy normal population and is not to be a therapeutic claim. The second criterion is for convenience and was compelled by the timeframes imposed by the 1990 amendments. The third is consistent with the goal of the health claim in that it represents a direct measure of the health status of bone. The fourth criterion represents measurement of the nutrient for which evidence is sought to link adequate intake to the reduced risk of osteoporotic bone fracture.

FDA found that some of the papers identified in the literature search were not pertinent because they were carried out in subjects that were either not considered normal for their sex and age as a result of recent bone fractures or due to the diagnosis of osteoporosis or some other endocrine or dietary disorder (Refs. 14, 39, 40, 43, 56, 57, 84, 85, and 126). FDA did not consider others because subjects were inappropriately young (infants) (Refs. 81, 112 and 117), or the study failed to include a direct measure of bone status or calcium intake (Refs. 38, 62 and 135).

Furthermore, animal studies were not included in this review because "there is no completely satisfactory animal model of age-related or postmenopausal osteoporosis" (Ref. 2). While the extrapolation of animal studies to the human condition may not be appropriate, the results of studies in all animal models repeatedly show that low calcium intake causes reduced bone mass and osteoporosis (Refs. 46, 76, 77, and 127).

2. Criteria Used in Evaluating Studies

The criteria used in evaluating human epidemiological and clinical studies included:

(1) Reliability and accuracy of the methods used in food intake analysis and in assessing subjects, calcium intake for the day of study, lifetime, or their habitual intake, that is, the usual amount of calcium consumed;

(2) Choice of control subjects (e.g., age, sex, and race matched or matched for years since menopause);

(3) Representativeness of subjects;

(4) Control of confounding factors, particularly the level of activity or physical exercise must be controlled;

(5) The sensitivity of the endpoints measured, particularly with reference to the type of bone measured (cortical bone versus cancellous bone) or the bone site measured, (the rate of bone loss differs between types of bone and bone sites);

(6) Presence of recall bias and interviewer bias; and

(7) Degree of compliance and how compliance was assessed.

FDA evaluated the weaknesses and strengths of individual studies (see "Assessment" column of the Table). It then assessed the strength of the overa combined evidence (e.g., clinical intervention studies and epidemiologic studies) taking into account the strengt of the association, the consistency of findings, specificity of the association, evidence for a biological mechanism, and presence or absence of a dose-response relationship. FDA's conclusions reflect the strength, consistency, and preponderance of data

3. Evaluation of Evidence

FDA's evaluation of the totality of the recent human studies meeting the criteria outlined above is presented in Table 1. In addition, FDA considered a number of recent thorough reviews of this subject written by well-recognized experts which are not included in the Table (Refs. 16, 18, 20, 21, 22, 23, 26, 45, 49, 67, 69, 92, 103, 104, and 133).

To update and evaluate the impact of new findings on the earlier conclusions established by the authoritative and consensus documents, FDA sought to answer three questions:

First, do any of the studies present evidence documenting the role of calcium in achieving peak bone mass? The most frequently cited study supporting the importance of adequate calcium intake to the attainment of peak bone mass studied bone status and rate of hip fracture (cross-sectionally or at one point in time) in two areas of rural Yugoslavia (Ref. 96). The two communities were similar in several factors that could influence bone health and fracture rates (similar age, racial profiles, and levels of physical activity), but differed significantly in their usual calcium intake (about 400 versus 1,000 mg per day). Bone mass was significantly greater in both men and women by the age of 30 in the community with the higher calcium intake. More importantly, the incidence of hip fracture was significantly lower in the high calcium intake community with the higher peak bone mass. Experts concluded from this study that high life-long calcium intakes did not prevent bone loss since differences in bone mass as a function of age were constant in both groups, but it did increase peak cortical bone mass and significantly reduced the incidence of hip fracture later in life.

All the recent studies that examined subjects over a wide range of ages either

cross-sectionally (at one point in time) or longitudinally (several points over time) contributed some evidence relating to peak bone mass (Refs. 18, 25, 48, 60, 78, 82, 94, 97, 98, 99, 111, 123, and 125). Matkovic et al., (Ref. 97) demonstrated a trend toward an increase in bone density measured in two different skeletal sites in young teenagers who consumed higher levels of calcium over a period of 2 years relative to an age-matched control group. The controls consumed their usual, self-determined, or what is termed "habitual" calcium intake. However, the difference in bone mineral density between the high and low calcium groups was not statistically significant. This failure to show statistical significance could have been attributable to the small number of subjects studied (28 total). In another clinical trial, Baran et al., (Ref. 25) demonstrated no change in bone loss in women (30 to 42 years old) consuming 1,300 to 1,500 mg of calcium per day over 3 years, as compared to a control group that did not consume added dairy products and that showed a significant 2.9 percent loss of bone.

In a large supplementation study in women 35 to 65 years of age, Smith et al., (Ref. 123) demonstrated that daily supplementation of 1,500 mg calcium per day over 4 years in premenopausal women significantly reduced the loss of bone mineral relative to controls. Several cross-sectional studies in premenopausal women showed significantly higher bone density in women consuming higher calcium intakes (Refs. 60, 78, 94, and 111), yet others have failed to demonstrate a significant positive correlation between bone density and calcium intake (Refs. 19, 48, 86, 98, 99, and 125). In one study in men (Ref. 82), calcium intake was found to be an excellent predictor of bone density of the spine.

A critical concern in evaluating the effectiveness of dietary calcium intakes on bone density is that calcium intakes at the time of interview do not always correlate well with bone density measures that reflect a lifetime of a variety of influences. This lack of correlation between intake and bone density is particularly true for postmenopausal women (Refs. 94 and 124). However, in two studies where lifetime or historical calcium intake (intake estimated at age 20) was determined, there was strong positive correlation between high lifetime calcium (>500 mg per day) intake and bone mineral density of the mid and distal radius (Ref. 60) and the lumbar spine (Ref. 111). Cauley et al. (1988) showed that postmenopausal women who reported high lifetime intakes of calcium had significantly greater bone density than those who reported lower lifetime intakes (Ref. 36). Reliability of calcium intake estimates, either current, habitual, or lifetime estimates, is also a concern because these data are usually the weakest factor in these studies.

While the results of the more recent studies do not provide definitive evidence linking high calcium intake to achievement of maximum peak bone mass, they do provide evidence demonstrating a trend for increased bone mass in a carefully controlled, clinical trial (Ref. 97), and evidence of a strong positive correlation to bone density when lifetime calcium intakes were estimated (Refs. 36, 60 and 111). Moreover, the results of some of these studies demonstrate that a high calcium intake is beneficial in reducing the rate of bone loss in premenopausal women shortly after peak bone mass is achieved (Refs. 25, 78, and 111). A large intervention trial that utilized subjects over a wide range of ages showed a positive correlation between calcium intake and bone mass (Ref. 123). However, the results did not indicate whether this occurred through a maximization of peak bone mass or through a slowing effect on the rate of bone loss after skeletal maturity. Thus, the recent data, although not definitive, are sufficiently compelling to support the link between adequate calcium intake and achievement of peak bone mass.

The second question asked in reviewing these studies is whether added calcium or high calcium intake reduces the risk of fracture, or slows the rate of bone loss in younger or older subjects. Variation in results from the older studies underscores the lack of conclusive evidence that high calcium intake delays the development of osteoporosis. As stated in the NAS report on "Diet and Health Report: Implications for Reducing Chronic Disease Risk" (Ref. 2):

> Many published reports have shown either no relationship or only a modest relationship between dietary calcium and cortical bone mass, * * * evidence that calcium supplementation prevents trabecular bone loss associated with menopause is at best weak. There is strong evidence that calcium supplementation has a modest influence in preventing cortical bone loss, but * * * evidence relating calcium supplementation to fracture prevalence is scanty.

The lack of consistency in results in these older studies is the result in part of the various confounders that are also, regrettably, present in some of the more recent studies. Higher calcium intakes were shown to slow the rate of loss in premenopausal women consuming more dairy foods (Ref. 25) and in those consuming calcium supplements (Ref. 123). In postmenopausal women, calcium supplementation had no effect on spinal bone loss early in their menopause, but for women late in their menopause, the rate of bone loss was significantly reduced with calcium supplementation if initial habitual calcium intakes were lower than 400 mg per day (Ref. 47). This finding presents strong evidence supporting what others have shown—that spinal bone (predominantly cancellous bone at this site) loss in early postmenopause is less responsive to calcium supplementation than cortical bone of the hip or radius (Ref. 126). Stevenson et al., (Ref. 124) also found that dietary intake of calcium did not influence the rate of bone loss after 12 months of supplementation in women studied during the first 5 years of menopause.

In a large study examining women 35 to 65 years of age, calcium supplementation of postmenopausal women was shown to counteract a large portion of the annual bone loss that is attributable to menopause (Ref. 123). Others found that the rate of bone loss after 9 months of calcium supplementation (about 1,700 mg per day) in postmenopausal women was lower than in untreated controls, but the difference did not reach statistical significance (Ref. 113). In this study, when comparisons were made only between women within 10 years of the onset of menopause, there was a significant reduction in the rate of bone loss with calcium supplementation from dairy products. Others showed no relation between habitual calcium intake in postmenopausal women and bone mineral density of the radius in a cross-sectional study (Ref. 128) or of the radius, femoral neck or spine in a longitudinal study (Ref. 131). Habitual calcium intake exceeding 800 mg per day was not effective in preventing cortical bone loss in early menopause (Ref. 132).

It is apparent that a large part of the inconsistency observed in studies involving postmenopausal women may be the result of the overwhelming influence of the hormonal change early in menopause versus that of late menopause. With the exception of Polley et al., (Ref. 113), these findings suggest that subjects studied in early menopause are less responsive to increased calcium intake, but that women in late menopause are responsive. These findings suggest the

possibility that adaptational influences come into play later in menopause.

Another factor that may contribute to the inconsistency of study results is the differential response of the various skeletal sites measured. Fujita, et al., (Ref. 55) showed an increase in forearm bone density (primarily cortical bone at this site), but no change in spinal bone (mostly cancellous bone at this site), with calcium supplementation of subjects greater than 70 years of age (late menopause) for 2 years. Holbrook et al., (Ref. 72) found that the age-adjusted risk of hip fracture was associated with low estimates of dietary calcium intake in a large population of men and women aged 50 to 79 at the start of the 14-year study.

The results of the recent clinical trial of Nelson et al., (Ref. 102) underscores this point concerning the differential responses between cortical and cancellous bone to increased calcium intake. In this study, results showed a 1.1 percent loss of bone density in the femoral neck (cortical bone) in postmenopausal women consuming a moderate calcium intake, and a significant 2 percent gain in femoral neck bone density in women consuming a high calcium intake. However, calcium intake had no measurable effect on bone mineral density of the spine (cancellous bone) in this 12-month study.

Thus, as reported for earlier studies, inconsistencies also exist in the results of recent studies examining the effect of calcium intake on slowing the rate of bone loss. However, recognition of the facts that bone sites respond differently to high calcium intake, and that their responsiveness to calcium varies with time after menopause, requires that any evaluation of these studies place less weight on those that found no effect of calcium on spinal bone density in early menopause because of what is thought to be the overriding effect of estrogen withdrawal. Given the current understanding, evidence becomes more compelling in support of the hypothesis that adequate calcium intake slows the rate of bone loss in general in perimenopausal women (Refs. 25, 78, 111, and 123) and in predominantly cortical bone sites in women late in menopause (Refs. 36, 47, 55, 102, and 113).

The third question considered was whether or not any of the studies showed a threshold effect for the level of calcium intake associated with changes in bone mass. The concept that calcium is a threshold nutrient was discussed in the FDA sponsored conference on osteoporosis in 1987 (Ref. 10). Concern focused on the lower threshold suggesting that low dietary calcium is a permissive element rather than a causative element in the development of osteoporosis (Ref. 65). Only recently have the upper limits of the effect of calcium intake been explored.

Kanders et al. (Ref. 78), in their cross-sectional study, showed that bone mineral density of the spine did not increase with calcium intakes above 800 to 1,000 mg per day, which implies an upper limit of calcium intake on optimizing peak bone mass in premenopausal women. Halioua and Anderson (Ref. 60) observed similar results at levels above 800 mg of calcium per day in postmenopausal women. These studies support the concept of an upper level of calcium intake beyond which no benefit to bone status can be observed.

The more important aspect of the threshold concept is the lower level, the level of calcium intake below which bone health is impaired. The findings of Dawson Hughes et al. (Ref. 47), suggest that for women in their late menopause this level is probably around 400 mg per day. This question clearly needs further research and careful definition.

Another important consideration is the speculation presented by Kanders and her coauthors (Ref. 78) concerning their findings that bone mineral density of the spine can be influenced by both physical activity and optimal calcium nutrition during the period of consolidation in young adult women. The authors speculate that if their findings of an increase in spinal bone mass were applied longitudinally (over time), one may be able to delay the development of osteoporosis and related bone fractures for an estimated 10 years (Ref. 78).

To summarize these new findings, some aspects of the relationship between calcium and osteoporosis remain unclear, but with the growing understanding of how other factors confound these results, it is becoming increasingly evident that calcium intake has a significant impact on bone health. Study results must be interpreted in light of new findings concerning the sensitivity of specific bone sites to diet, the limitations of the effect of diet during early menopause, and the inherent weaknesses of measuring or estimating habitual, current, lifetime or historical calcium intake, the independent variables in the recent studies reviewed here. This issue of accurate determinations of calcium intake is discussed at length in the LSRO report on "Calcium and Osteoporosis" (Ref. 13), where the authors emphasized that the weakest point in determining the relationship between calcium intake and changes in bone mass rests with the inadequacies of determining this independent variable, notably an accurate and reliable estimate of calcium intake. It is now apparent that calcium's effect on retarding bone loss in postmenopausal women may be influenced by habitual calcium intake, where persons with lower habitual intakes show the greatest response (Ref. 47). Thus, recent findings were generally consistent and strengthened the conclusions and guidelines set forth in the government and authoritative documents.

III. Decision to Accept Health Claim

A. Public Health Context

Osteoporosis is a major health concern of the elderly, particularly women, since 25 to 30 percent of all postmenopausal women are affected (Ref. 18). The etiology of this disease is multifactorial with sex and race being the strongest influences (Ref. 118). Low calcium intake has been identified as a risk factor, although controversy exists concerning the extent of its effect (Refs. 65, 79, and 80). Many experts argue that a lifetime low calcium intake, that is at levels below the level of obligatory loss (calcium that the body must lose every day in fecal secretions and urine), which is usually 150 to 300 mg per day but which some have defined as 300 to 400 mg per day, may result in low peak bone mass and above average loss of bone mass in adults (Refs. 8 and 87).

B. Dietary Calcium Intake

National food intake surveys (Refs. 3, 54, and 105) provide evidence identifying calcium from dietary sources as a problem nutrient in a subpopulation at risk for osteoporosis, namely women between 11 through 35 years of age. These surveys show that men have a greater intake of calcium than women largely as the result of greater total caloric consumption by men rather than as a result of differences in types of foods consumed. These surveys suggest that as early as 9 years of age, mean calcium intake for women is well below the RDA and remains low from early to late adulthood. These dietary data alone, however, are insufficient to establish calcium status of women 9 years and older with low dietary calcium intakes.

C. Sources of Calcium

For the general population, diet is the primary source of calcium (Ref. 63). However, for some individuals, calcium in vitamin/mineral supplements or contained in drinking water or in certain chronically used medicines are

significant sources of their total daily calcium intake (Ref. 63). Calcium is not uniformly distributed in the food supply. Milk and milk products are among the richest sources of calcium and have been shown in recent surveys to contribute approximately 40 percent of the total dietary calcium ingested by adult men and women and nearly 65 percent of the daily calcium in children (Ref. 54).

D. Guidelines for Calcium Intake

The National Academy of Sciences set the RDA for men and women 19 years of age and older at 800 mg per day in 1980. However, acknowledging that greater calcium intake is needed during the period of consolidation to maximize peak bone mass, NAS redefined the adult age range to include men and women 25 years and older in the 1989 revision (Ref. 3). Because of differences in physiologic need, it set the RDA for adolescents 11 to 24 years of age at 1,200 mg per day; for children (1 to 10 years) at 800 mg per day; at 540 mg for infants (0.5 to 1 years); and at 360 mg per day for neonates (Ref. 3). By definition, the RDA for any nutrient contains a large margin of safety, representing adequacy for 95 percent of the healthy normal population (Ref. 3).

E. Safety of Calcium Guidelines

Calcium toxicity is not generally recognized as a problem in the United States population because normal healthy people have intrinsic control mechanisms that prevent excessive serum levels (Refs. 22, 63, and 73). The main control occurs at the level of absorption because calcium absorption becomes less efficient as calcium intake increases. The usual side-effects that are the hallmark of calcium toxicity include hypercalcemia (elevation of calcium in the blood) which has neurologic and neuromuscular effects, excessive calcium loss in urine, formation of kidney stones, and deposition of this mineral in soft tissue.

In 1979, an expert panel reviewed the data on the safety and effectiveness of various vitamin and mineral products and concluded that "calcium intakes ranging from 1,000 to 2,500 mg daily do not result in hypercalcemia in normal individuals" (Ref. 53). Calcium toxicity is, however, a concern for individuals who for some physiologic reason hyperabsorb calcium from the gut or from filtered urine. Most common among these individuals are those with a family history of kidney stones. For the normal healthy population, the guidelines for calcium intake (RDA) are considered well within the limits of safety.

F. Rationale Leading to the Decision to Accept Health Claim

FDA has proposed no specific provisions pertaining to the agency's assessment of conformance with the standard. Instead FDA envisions that to satisfy the scientific standard, a health claim must be supported by a sound body of scientific evidence that establishes the relationship between a dietary component and a particular disease or health related condition. The data must persuade FDA that the proposed claim is valid, and that the benefits featured in the claim pertain to the general U.S. population or to a significant segment of the U.S. population. Thus, the body of scientific data must be strong. A few unconfirmed studies, preliminary or incompletely documented data, or significantly contradictory findings do not constitute a sound body of evidence.

The standard requires that significant agreement exist among qualified experts that the claim is valid. "Qualified experts" include individuals whose training and experience have produced a general or specific scientific expertise in the diet/health topic being considered for a specific claim. FDA is not proposing to define "significant agreement" among experts because each situation may differ with the nature of the health benefit. The agency believes that any specific definition of such agreement might prove arbitrary when viewed in the light of the multiplicity of potential health benefits and the widely variable nature of expertise required to evaluate the significance of these benefits. Instead, FDA intends to use the discretion granted it by the 1990 amendments to assess the degree of agreement on a case-by-case basis. Nevertheless, FDA will take the full range of opinions among qualified scientific experts on a specific claim into account in determining whether significant agreement exists.

FDA does not prescribe a specific set, type, or number of studies as being sufficient to support a health claim for the procedure to assess conformance with the scientific standard. The agency will consider all relevant data on a topic, including clinical studies (human studies conducted in a controlled clinical setting), epidemiological data (data from uncontrolled human populations), and animal studies. However, the type, quality, and relevance of a study from which data are derived have an important bearing on how much weight is placed upon the data. Because of the many unknowns about the direct effect of a dietary substance on health or disease relative to the effects of other environmental and genetic variables, and given the limitations on the ability to accurately quantify dietary intake for some substances, indirect approaches are usually required to assess the scientific weight of a set of data.

The overriding principle will be to determine whether there are consistent results from different types of well-conducted human studies by different investigators in different populations. The strengths and weaknesses of each individual study will be evaluated. When experiments with animal models are appropriate, consistency of results between human and animal studies will also be considered. Such results will be interpreted in the light of any available evidence on the biological mechanism of the substance-disease relationship, evidence of a dose-response relationship, and similarity of the test substance with the nutrient or food component of interest. The significance of the disease from a U.S. public health standpoint will be also evaluated. In sum, FDA intends that its judgments concerning the overall quality of available data, the appropriateness of the study design, the consistency across different types of studies and laboratories, and the conclusions derived from the total body of evidence will be based on the generally recognized scientific procedures and principles that are most appropriate to the issues being addressed.

FDA has reviewed the conclusions in the Federal government and other documents (Refs. 1 through 13) and in recent review articles on calcium intake and osteoporosis (Refs. 16, 18, 20, 21, 22, 23, 26, 45, 49, 67, 69, 92, 103, 104, and 133). It also examined the totality of pertinent human studies published since the NAS report on "Diet and Health: Implications for Reducing Chronic Disease Risk" (Refs. 18, 25, 36, 47, 48, 55, 72, 78, 82, 86, 94, 97, 98, 99, 102, 111, 113, 123, 124, 125, 128, 131, and 132). In addition, the agency considered all comments received in response to the notice of request for scientific data in the **Federal Register** of March 28, 1991, on the link between calcium intake and osteoporosis. Based on the overwhelming concurrence among the experts in this area, FDA proposes to allow a health claim on the label of products that meet the regulatory specifications set forth in proposed § 101.72. The health claim will relay the message that an adequate intake of calcium throughout life may delay the development of osteoporosis and ultimately reduce the risk of bone fracture in some individuals later in life.

The tentative decision to allow the proposed claim is based on significant agreement among experts in the field concerning three important conclusions. First, experts conclude that maintenance of adequate calcium intake during all stages of life is important to normal bone health and to optimal peak bone mass, and that optimizing bone mass at skeletal maturity (at about 35 years of age) may help to delay the onset or reduce the risk of osteoporosis and related bone fracture. To produce definitive evidence directly linking calcium intake to optimized bone mass and ultimately to reduced risk of osteoporosis and the delayed onset of bone fracture would require a 50- to 60-year-long study. However, there is overwhelming agreement among experts and among the authoritative documents reviewing this subject that adequate calcium intakes are important in optimizing bone health and therefore in reducing the risk of osteoporosis. With a higher peak bone mass, individuals have a lower risk of reaching the critical fracture threshold. Review of recent data did not refute this conclusion; it strengthened it, demonstrating a trend toward increased bone mass with higher calcium intake.

Secondly, for older adults, experts have concluded that maintenance of adequate dietary calcium is crucial to slowing the rate of bone loss, notably during the first decade following menopause. However, for the postmenopausal women, calcium alone will not significantly slow the rapid rate of bone loss that occurs shortly after menopause. The recent literature also supports this conclusion with rigorously controlled intervention studies or studies with more accurate measures of estimated calcium intake. These recent studies demonstrate the bone loss-slowing effects of calcium on bone sites known to be responsive to this nutrient and in women late in menopause, when the overriding effect of estrogen withdrawal does not mask the beneficial effect of adequate dietary calcium.

Thirdly, bone experts have concluded that the recommended calcium intake levels are safe and there is a growing recognition that RDA guidelines are adequate and can be reached within the context of the total daily diet. Current evidence supports the concept that a threshold nutrient intake level exists for calcium, below which bone health is jeopardized, and the concept of an upper limit of intake, above which bone derives no further benefit (Refs. 10, 47, 64, 78).

Maintaining an adequate calcium intake is a concern in certain segments of the United States population. Estimates of daily calcium intake for men and women determined in the most recent nationwide surveys show that for men, mean calcium intake closely approximates the guideline for intake throughout their life span (Refs. 35 and 105). However, both surveys show that the average calcium intake for women falls well below the 1980 RDA guideline and remains below the RDA with increasing age. This low calcium intake in conjunction with high rates of osteoporosis in the elderly, female, U.S. population is of greatest concern in adolescent and young adult women, an age group with the highest calcium requirement and who comprise the population at greatest risk of developing osteoporosis (Refs. 2 and 3). Others at risk of osteoporosis because of low calcium intake include those individuals, notably women and elderly men, whose calcium intakes may be less than the amount of calcium that is naturally required to be lost each day in urine or in gastrointestinal secretions or sweat (Ref. 8). No individual should consume less calcium than they naturally lose in a day which is normally about 200 mg or in the range of 150 to 300 mg, but may range between 300 to 400 mg per day (Refs. 3, 8, 66, and 88). A decision to allow a health claim would help the public to meet one of the dietary goals established in the federally sponsored "Healthy People 2,000: National Health Promotion and Disease Prevention Objectives" (Ref. 11), since the labels will facilitate the recognition of calcium-rich products.

The newer evidence is supportive of, and does not contradict the scientific consensus reached earlier. However, from the findings of the documents and studies cited above, the role of calcium in reducing the risk of osteoporosis is most relevant for those subpopulations at greatest risk because of sex, race, or family history.

IV. Description and Rationale for Components of Health Claim

A. Relationship Between Calcium and Osteoporosis

Based on the totality of the evidence and significant scientific agreement among experts qualified by training and experience to evaluate such claims, FDA has tentatively determined that there is adequate scientific evidence that consumption of an adequate calcium intake throughout life may optimize peak bone mass during adolescence and early adulthood and help to slow the rate of bone loss later in life. By maximizing the amount of bone present in old age through higher peak mass and subsequent slower rate of loss, one may reduce the risk of osteoporosis and related bone fractures.

In proposed § 101.72(a), FDA describes the relationship between calcium and osteoporosis. Experts have identified low or inadequate calcium intakes as one of many risk factors in the development of osteoporosis (Refs. 21, 63, 95, and 118). Inadequate calcium intake is thought to contribute to low peak bone mass (Ref. 10). Peak bone mass is the total quantity of bone present at skeletal maturity which experts believe has the greatest bearing on whether a person will be at risk of developing osteoporosis and related bone fractures later in life (Refs. 21, 64 and 118). The rate of bone loss after skeletal maturity also influences the amount to bone present at old age and also influences an individual's risk of developing osteoporosis (Refs. 21 and 118).

Experts conclude that an adequate calcium intake maintained throughout life, particularly during adolescence an early adulthood, will help to achieve one's genetically programmed upper limit of bone density (Refs. 2, 3 and 64). The rationale linking adequate calcium intake and optimal peak bone mass to the reduced risk of osteoporotic fracture relates to the fact that all individuals lose bone as they age. However, those individuals with more bone present at maturity take longer to reach the critical reduction in bone mass at which bone fractures with little trauma (Ref. 20).

Bone density later in life depends on both the amount of bone made during growth (peak bone mass) and the subsequent rate of bone loss after maturity. Maintenance of an adequate calcium intake later in life has been shown to be important in reducing the rate of bone loss particularly in the elderly (Refs. 63 and 118) and in women during the first decade following menopause (Refs. 47, 63, 67, 102 and 118).

In proposed § 101.72(d)(3), FDA requires that the health claim state the mechanism of optimizing peak bone mass during adolescence and early adulthood and the mechanism of helping to slow the rate of bone loss at menopause in women and in the elderly by adequate consumption of calcium. These mechanisms link calcium intake to the disease state of osteoporosis. In the label statement, FDA proposes to allow the concept of achieving peak bone mass to be conveyed to the public with a simpler phrase such as "build and maintain good bone health."

B. Significance of Calcium

In proposed § 101.72(b), FDA is describing the significance of calcium in affecting osteoporosis. The agency has tentatively identified those factors that describe the multifactorial nature of osteoporosis and has identified those risk factors that identify subpopulations of individuals who would most benefit from a lifelong, adequate calcium consumption. In proposed §§ 101.72(b) and 101.72(d)(2), FDA tentatively proposes to require specific identification of those individuals within the general population at greatest risk of developing osteoporosis and for whom the proposed health claim would have greatest benefit. These individuals include Caucasian and possibly Asian women and adolescent girls between 11 and 35 years of age, men and women with family histories of osteoporosis, menopausal women (who may be identified as middle-aged women in the label statement), and elderly men and women.

Proposed § 101.72(d)(2) also tentatively requires that the health claim not convey the misconception that the risk of osteoporosis is equally applicable across the general United States population. Many individuals in the U.S. population are at much lower risk for the development of osteoporosis than the target populations described above. This fact was presented to the public as early as 1984, when NIH identified those individuals at greatest risk of osteoporosis in their publication, "Osteoporosis: Cause, Treatment, Prevention" (Ref. 5). Being Caucasian was cited as the third greatest risk factor following being a woman and early menopause (Ref. 5). The document further stated that "white women are at higher risk than black women and white men are at higher risk than black men and oriental women are also thought to be at greater risk for the disease, but there is not enough data to confirm this" (Ref. 5).

African Americans have a significantly lower incidence of osteoporosis-related bone fracture than Caucasian Americans (Refs. 28, 41, 118, and 136). This lower incidence of osteoporosis in African Americans is attributed to a significantly higher peak bone mass than Caucasian Americans (Ref. 28). Asian Americans are reported to have lower bone mineral content of the radius than age-matched Caucasians (Refs. 21 and 134). However, recent findings show that hip fracture rates among Asian Americans are approximately half that of Caucasians (Ref. 121). Data on time trends in the incidence of hip fractures are available for Caucasians and to a limited extent Asian populations (Ref. 136). These data indicate an increase in the incidence of hip fractures in Asian women and men. Information on the bone density and fracture incidence among Hispanics in America is limited but reported to be lower than Caucasians (Ref. 136).

The vast majority of studies examining calcium intake and bone status exclusively use Caucasian subjects (Ref. 13), largely because the incidence of the disease is higher in Caucasians. In addition, surveys indicate that other races such as African Americans have a much lower calcium intake purportedly because of their inability to digest the milk sugar, lactose (lactose intolerance) (Refs. 50, 51 and 63). In light of the facts that African Americans have genetically higher peak bone mass, significantly lower incidence of osteoporosis-related bone fracture, lower calcium intakes, and significantly higher incidence of lactose intolerance, they are at much lower risk of developing osteoporosis and presumably would not benefit by increasing their calcium intake. Moreover, with milk and milk-related products contributing the greatest portion of dietary calcium to daily calcium intake (Ref. 54), trying to consume because of dietary calcium may result in greater incidence of discomfort due to lactose intolerance. A similar statement could be made for other racial groups such as Hispanic Americans, although far less data is available concerning the incidence of osteoporosis-related bone loss in this population, but they have been identified as having low calcium intakes and lactose intolerance (Refs. 51, 63 and 137).

FDA does not want to mislead those individuals within the population for whom there is no apparent benefit to bone health from consuming relatively higher levels of calcium over a lifetime. However, this is a difficult concept to present on a label claim without confusing the general population. Thus, the agency solicits comment on alternative ways of presenting this information and tentatively proposes in § 101.72(d)(2) that the claim shall not convey the misconception that the risk of osteoporosis is equally applicable to the general United States population, and that the subpopulation clearly at greatest risk is identified. This subpopulation includes Caucasian females but may also include Asian females. The agency has proposed that the subject of appropriate population targeting for the calcium and osteoporosis health claim, and how to most clearly present this information to the public, as an objective of the focus groups assembled to examine the impact and interpretation of the new labeling.

Men have greater peak bone mass than women across all races, and in addition men do not undergo the rapid rate of bone loss that women experience at the onset of menopause (Refs. 74 and 136). These factors contribute to men having a significantly greater bone mass in later years than women. These differences in the rate of loss of bone and in the total bone mass at maturity help to explain the significantly lower incidence of osteoporosis in men compared to women (Refs. 20 and 118)

Calcium intake is not the only recognized risk factor in the development of osteoporosis. Other factors include a person's sex, race, hormonal status, family history, body stature, level of exercise, general diet, and specific life style choices, such as smoking and excess alcohol consumption. Experts have identified those individuals at greatest risk of developing osteoporosis as being older, Caucasian or Asian, female and menopausal (natural or premature), thin and slight in stature with a relatively sedentary lifestyle (Refs. 10, 83, 109 and 118). Cigarette smoking and high alcohol intake also increases individual risk for the development of osteoporosis (Refs. 64 and 83).

In proposed § 101.72(d)(1), FDA tentatively proposes to require that the claim make clear that calcium is not the only recognized risk factor in the multifactorial bone disease, osteoporosis, by identifying specific other risk factors including sex, race, family history, and the need for adequate exercise and a well-balanced diet. Because osteoporosis is multifactorial, FDA believes that it is not possible to quantitate the amount of reduced risk of osteoporosis that results from adequate calcium intake throughout life. Therefore, FDA is proposing in § 101.72(d)(4) to require that a claim not quantative the degree of reduced risk.

In proposed § 101.72(d)(5), FDA is providing that a claim shall state that a total dietary intake of calcium of greater than 200 percent of the RDI (1,800 mg) has no known additional benefit. This provision reflects the findings discussed above that calcium intakes of 800 to 1,000 mg of calcium a day appear to be the upper level of calcium intake beyond which no benefit to bone status has been observed (Refs. 60 and 78). The agency has tentatively set this level at 1,800 mg a day to reflect that higher

amounts of calcium are needed in old age (Ref. 7).

C. Proposed Qualifying Levels of Calcium

In proposed § 101.72(c)(2), FDA is proposing to identify the calcium content levels needed to qualify for a health claim. In the companion document on general requirements for health claims, published elsewhere in this issue of the **Federal Register**, FDA has tentatively concluded that for nutrients for which increases in intake are associated with a desirable health outcome, FDA's proposed criterion for a "high" amount of a nutrient shall be the basis for determining the minimum amount of the nutrient that must be in a food for the food to be eligible to bear a health claim. This criterion is described in the proposal on nutrient content claims, published elsewhere in this issue of the **Federal Register.** For calcium, a product must contain a minimum of 20 percent of the proposed RDI for calcium (see companion document on Mandatory Nutrition Labeling published elsewhere in this issue of the **Federal Register**) or 180 mg of calcium per reference amount customarily consumed and per labeled serving to meet this criterion. This amount may either be naturally occurring in foods or may be added to a food or a supplement.

In proposed § 101.72(c)(1), FDA is requiring that a product satisfy all the requirements of § 101.44. Among these requirements is that if a calcium-containing ingredient is added to a food or supplement, the use of that ingredient must be demonstrated by the proponent of the claim to be safe and lawful under the applicable food safety provisions of the act. This showing can be made in a number of ways, including a showing that the use of the substance is:

(1) GRAS as listed in 21 CFR part 182, or in accord with the general principles stated in 21 CFR 170.30, provided that the use of the ingredient remains at individual consumption levels consistent with its use prior to January 1, 1958; or

(2) Affirmed as GRAS in 21 CFR part 184, approved for use as a food additive, or subject to a sanction or approval granted by FDA or the U.S. Department of Agriculture (USDA) prior to September 6, 1958.

In addition, FDA is proposing in § 101.72(c)(3) that the calcium content of the product, either added or natural, be assimilable as required in the calcium and iron enrichment of cereal-grain products (21 CFR part 137). Benefits of calcium intake from foods and supplements can only be obtained if the calcium is available for metabolic use by the body. There is strong evidence that dietary intake of protein, fiber, phosphorus, and certain naturally occurring and added substances such as oxalate, phytate, and fiber interfere with calcium absorption or metabolism (Refs. 15, 63, 69, and 71).

FDA is concerned about the bioavailability (ability to assimilate) of the calcium contained in products that make a health claim. It would be misleading to put a health claim for a substance on a food if consumption of that food will not provide the substance. Spinach illustrates the concern that products contain bioavailable calcium. While spinach is rich in calcium, it is not an appropriate candidate for a health claim on its label because of its established poor calcium bioavailability (Ref. 70). FDA recognizes the difficulty of assessing mineral bioavailability in humans where inter-individual variation is a significant confounding factor. For this reason, FDA requests comments on how calcium bioavailability can be assessed without bias in products under review for health claim eligibility. More specifically, the agency requests comments that would flag other foods or food components that are good sources of calcium but have poor bioavailability. These solicited comments should also consider products that are processed in such a way that the processing alters the bioavailability. For example, yeast enzymatic cleavage of phytase during the leavening of bread alters calcium bioavailability (Ref. 15). The agency also requests comments on how to address the issue of bioavailability for calcium supplements (Refs. 66, 69, 108 and 122).

D. Proposed Disqualifying Components of Products

Calcium bioavailability means both absorption and tissue utilization of calcium. Therefore, the presence of food or supplement components that cause increased urinary or fecal excretion, or impair the utilization of calcium by bone, would disqualify a product for a calcium-osteoporosis claim. Thus, FDA is proposing in § 101.72(c)(4) to disqualify calcium supplements from a health claim if they fail to meet the United States Pharmacopeia standards for disintegration (Refs. 122, 129 and 130) and dissolution (Refs. 122, 129 and 130). These products should not contain any substance, such as a salt of orotic acid, that is known to be harmful and to have adverse effects on calcium metabolism or on nutrient status (Refs. 42, 61 and 75).

High levels of dietary phosphorus and protein significantly adversely affect the metabolism and obligatory loss of calcium, respectively (Refs. 2, 3 and 17). The agency, however, is not proposing to disqualify high protein products from bearing a calcium claim. Like calcium, protein is not ubiquitously distributed in our food supply and is richest in specific food sources (Refs. 27 and 110). Some of these protein rich foods, such as milk or milk products, contribute more than half the calcium and protein intake of some individuals, notably children. Thus, relatively few foods are sources of calcium and protein, forcing consumers to be selective to meet the nutritional needs for both calcium and protein. It would be misleading to disqualify a product that is both rich in calcium and protein based on the protein's effect on urinary excretion of calcium without knowledge of what contribution this product made to the consumer's total protein intake.

While only a few foods are rich in calcium and protein, nearly all foods contain phosphorus as either a natural component or as an ingredient added during processing (Refs. 17, 31 and 58). Thus, unlike for calcium, consumers do not have to be selective to meet their daily phosphorus needs. In contrast to the low calcium intakes that have been reported for the majority of American women, phosphorus consumption is high for both men and women (Ref. 31). National nutrition surveys indicate that the diets of teenagers and young adults are relatively high in phosphorus and low in calcium (mean daily intake of 500 to 600 mg per day of calcium and greater than 1,000 mg per day of phosphorus) (Ref. 105).

According to NRC's 1989 report "Recommended Daily Allowances," the desired calcium to phosphorus ratio of the United States diet is 1:1, but the ratio of actual food consumption patterns differs with age (Ref. 3). Infant consumption patterns produce a ratio of 2.3:1 for human milk, that decreases with age to 1:1.3 for adults but may be as low as 1:4 for individuals with low intake of dairy foods or green vegetables (Ref. 3). Protein rich foods such as milk, meat, poultry, fish, cheese, and cereal grains contribute the majority of phosphorus in the American diet, but highly processed and convenience foods can contribute 20 to 30 percent of the daily phosphorus as food additives (Ref. 58). Evidence shows that phosphorus intake may be underestimated as much as 15 to 20 percent, because the phosphorus supplied by numerous food additives in processed foods are not always accounted for in tables of food composition (Ref. 106).

FDA is proposing that high levels of phosphorus (naturally occurring or added) in conventional foods or supplements that result in calcium to

phosphorus ratios lower than 1:1 will disqualify the product from bearing a calcium/osteoporosis health claim. FDA's tentative decision to identify phosphorus as a disqualifying nutrient is based on the ubiquitous distribution of this mineral in the food supply, the low ratio of calcium to phosphorus that typifies current intake patterns, and current evidence demonstrating that high levels of dietary phosphorus coupled with low dietary calcium adversely influence hormonal factors that regulate calcium and bone metabolism (Refs. 17, 21, 29, 32, 46, 93, 114, and 116). Recent studies in humans show that high intakes of phosphorus compared to calcium typically observed in the United States diet will produce changes in serum calcium and bone regulating hormones that may adversely affect peak bone mass (Refs. 17, 21, 31, 32, 114, 115 and 116). This evidence is supported by findings from a variety of animal models demonstrating that diets high in phosphorus and relatively low in calcium result in changes in calcium regulating hormones that adversely affect bone formation and stimulate bone resorption, and ultimately bone loss (Ref. 46).

To qualify for the health claim, FDA tentatively proposes in § 101.72(c)(5) that a product should not contain more phosphorus than calcium on a weight per weight basis. For those products that contain just 20 percent of the proposed RDI for calcium (about 180 mg of calcium), the product must contain no more than 20 percent of the RDI for phosphorus (about 180 mg) in a single serving or recommended daily supplement intake to be eligible to bear a health claim. This level is consistent with the 1:1 ratio of calcium to phosphorus set by the RDA for calcium and phosphorus (Ref. 3) and previous nutritional quality guidelines promulgated by FDA. This proposed disqualifying level of phosphorus is consistent with the nutritional guidelines set forth in § 104.47(d)(4): "When technologically practicable, product components and ingredients shall be selected to obtain the desirable calcium to phosphorus ratio of 1:1."

Other nutrients, such as sodium, also have adverse effects on calcium metabolism when high dietary levels are consumed (Refs. 59 and 135). However, sodium and other nutrients in high levels may disqualify a product from the claim because of their association with diseases other than osteoporosis. FDA has proposed disqualifying levels for fat, saturated fat, cholesterol, and sodium in proposed § 101.14. In proposed § 101.72(c)(1), as stated above, FDA proposes that all requirements for health claims as defined in proposed § 101.14 must be met for a product to bear a claim relating calcium intake to osteoporosis. Disqualifying nutrient levels are discussed in the proposal on general principles for health claims published elsewhere in this issue of the **Federal Register.**

Given the proposed conditions and requirements for a product to bear a health claim relating calcium intake to reduced risk of osteoporosis discussed above, some typical foods that would qualify for this claim include servings of: lowfat yogurt, 1 and 2 percent fat milk, skim milk, cultured buttermilk, 2 percent lowfat chocolate milk and tofu (Ref. 44). As discussed in the preamble to the proposal on general principles for health claims, FDA finds no basis to provide an exception to the disqualifying levels to permit a calcium and osteoporosis claim on whole milk.

To assist manufacturers in formulating a health claim, FDA is providing a model message in the proposed regulation.

V. Appendix to the Preamble—Consumer Summary on Dietary Calcium and Osteoporosis

The following appendix is a proposed consumer summary on dietary calcium and osteoporosis. FDA solicits comments on this document as explained in the proposal on general requirements for health claims published elsewhere in this isue of the **Federal Register.**

Appendix—Consumer Summary on Dietary Calcium and Osteoporosis

Dietary Calcium and Osteoporosis

Under the provisions of the recent Nutrition Labeling and Education Act, manufacturers may put clear information on the food label about the relationship between a nutrient, such as calcium, and a disease or health-related condition. To prevent consumers from being misled, the Food and Drug Administration (FDA) allows only truthful label statements about diet and health relationships that are firmly supported by current scientific evidence. There is agreement that the evidence is strong enough to allow a health claim about the relationship between dietary calcium and osteoporosis.

Many consumers have said that health claims on food labels could be useful to them in making improvements in their diets. However, label space is often limited. Therefore, this pamphlet provides information about the diet and health claims that supplements what you may see on food labels.

In addition to dietary calcium and osteoporosis, FDA is allowing health claims about the relationship between sodium and hypertension, saturated fat and cholesterol and cardiovascular disease, fat and cancer, and _____. For information about these other diet and health relationships, write to: [TO BE INSERTED].

What is Osteoporosis?

Osteoporosis is a disease condition in which reduced bone mass causes the bones to fracture easily. The disease occurs in both sexes but is more common among older women.

Why is There Concern About Osteoporosis?

Osteoporosis is a public health concern because from 15 to 20 million Americans are affected. Osteoporosis reduces the mobility and quality of life of the people affected. The disease is responsible for about 50,000 deaths annually, and substantial health care costs are associated with it.

One-third of women 65 years and older have spinal vertebrae fractures, the most common break associated with osteoporosis. Vertebral fractures are often undetected, and few women identify the height loss that results as due to osteoporosis. Many elderly men and women suffer hip fractures as a result of osteoporosis, which few people associate with this disease.

Osteoporosis contributes to some 1.3 million bone fractures per year in persons 45 years and older. Spinal fractures are painful, but hip fractures may have more serious effects and usually result in hospitalization.

What is the Cause of Osteoporosis?

Osteoporosis is a complex disease, and why it develops in some people is not entirely understood at this time. The factors that make a person most at risk for developing the disease are increased age and being a female (particularly when loss of the hormone estrogen occurs) of the Caucasian or Asian race. However, several lifestyle factors over which people have greater control are also believed to be associated with a decreased risk of its development. These include consuming an adequate amount of dietary calcium and getting enough exercise, especially during the bone-forming years; eating a balanced diet; not smoking cigarettes; and either not drinking alcohol or doing so in moderation.

The exact nature of the association between calcium and osteoporosis is under active research. Scientific experts

agree that consuming an adequate amount of calcium in your diet throughout life is important to bone health.

The maximum amount of bone that a person can build is determined by heredity. Bone continues to be added to the skeleton until about 35 years of age, at which time skeletal maturity occurs. Scientists agree that adequate dietary calcium during the bone-forming years is important to building an optimal amount of bone (called "peak" bone mass). Building optimal bone mass through a balanced diet, including adequate calcium, until skeletal maturity occurs may help to delay the onset of or limit the chance of developing osteoporosis later in life.

Bone experts also agree that, for adults in midlife or older years, maintaining adequate dietary calcium is crucial to slowing down the rate of bone loss that naturally occurs at that time. Getting enough dietary calcium is especially important during the first decade following menopause. However, for women at the onset of menopause, dietary calcium alone will not sufficiently slow the rate of bone loss, which is especially rapid early in menopause. At menopause, estrogen replacement therapy is the most effective means to reduce the rate of bone loss, and the risk for fractures.

Low calcium intakes are of greatest concern in adolescent and young women who have high calcium requirements. Young women who do not meet their calcium need during these age periods are most at risk of developing osteoporosis later in life. Postmenopausal women and elderly men also are at special risk of developing osteoporosis.

Do Most People Get Enough Calcium in What They Eat?

Because of concern that some people are consuming too little calcium, the U.S. Public Health Service has set a national health goal for people to eat food sources of calcium regularly. People from 12 to 25 years of age are encouraged to eat 3 or more servings a day of foods that are sources of calcium. This advice is appropriate for pregnant and lactating women because of their higher calcium needs. All adults 25 years and older are encouraged to consume 2 or more servings of calcium-rich foods daily.

How Do You Learn Which Foods Are Sources of Calcium

A good way to learn about food sources of calcium is to read nutrition labels. Most foods now have nutrition information on their labels.

The amount of calcium in a serving of food is listed on the nutrition label as a percentage of the Reference Daily Intake (RDI). The RDI for calcium is 900 milligrams (mg) for adults and children over 4 years of age. The RDI is not an amount recommended for you personally. It is a general reference number to help you determine how the amount of calcium in a serving of food relates to an average amount for a day.

More specific information for individuals comes from the National Academy of Sciences which recommends amounts of calcium for several age groups. For infants and children younger than 11 years, the recommended daily amounts range from 400 to 800 mg. The recommended daily amount of calcium for ages 11 through 24 years for both sexes, when maximum bone growth occurs, is 1,200 mg. The recommended daily amount for 25 years and older is 800 mg. For pregnant or lactating women, 1,200 mg of calcium a day is recommended. These recommended amounts can be reached easily by choosing foods each day that are good sources of calcium.

The richest sources of calcium are milk and other dairy products, which provide much of the calcium in U.S. diets. Some people cannot or only poorly digest the sugar (lactose) in milk, and are said to have "lactose intolerance." Most people with lactose intolerance, however, are able to consume small amounts of milk and other products containing lactose without distress. Also low-lactose and reduced-lactose dairy products are available.

Some foods containing relatively small amounts of calcium but that are eaten frequently during the day, for example, bread, are also good sources of calcium. Other nonfood sources, such as drinking water and some medications, such as antacids containing calcium carbonate, may also contribute to the level of calcium that you consume.

What Do Label Claims About Calcium Mean?

Besides the amount of calcium on the nutrition label, you may see claims about calcium in other places on the package of some products. There are two kinds of these label claims—content claims and health claims.

Content claims are those made about the *amount of calcium* the food contains. For example, a label may say "high in calcium" or "source of calcium." FDA allows a food that contains 20 percent or more of the RDI per serving to be labeled as a "high" in calcium, while a food containing from 10 percent to 20 percent of the RDI per serving can be labeled as a "source" of calcium.

Some foods that are high in or sources of calcium may contain one or more nutrients that increase the risk of a diet-related disease. For example, a high sodium intake is linked to high blood pressure in some people. To alert consumers, a claim about calcium content cannot be made on the label of such foods without indicating the presence of the other nutrient. A label might say, for example, "High in calcium; see nutrition label for information about sodium and other nutrients."

Health claims are those made about the relationship between calcium and osteoporosis. A health claim can be made only on foods that contain 20 percent or more of the RDI of calcium per serving and do not contain another nutrient (or nutrients) that increase the risk of a diet-related disease or health condition. Here are some examples of the kinds of foods on which you may see such claims: low fat milk, skim milk including dry skim milk, buttermilk made from skim milk, chocolate drinks and yogurt made from skim or low fat milk, reduced-calorie chocolate and cocoa dairy drink mixes, orange breakfast drinks, and tofu.

What About Dietary Supplements of Calcium?

The first important approach to getting enough calcium is to choose a healthful diet that has food sources of calcium. If for some reason (such as food intolerance or an increased calcium need during pregnancy or lactation), it's difficult to eat foods with enough calcium, a supplement to the diet may be appropriate. Supplements that exceed the recommended levels are unnecessary, however, and provide no further benefit to bone health. For further guidance, a personal physician or dietitian may be consulted.

Other Risk Factors for Osteoporosis

In addition to eating food sources of calcium regularly, improving some other habits may help to reduce the risk of osteoporosis. Regularly performing moderate weight-bearing exercise, such as walking, can help to increase bone mass during the bone-forming years. In addition, choosing not to smoke and limiting alcoholic beverages are healthful ways to reduce your chances of developing the disease.

Older people benefit from regular exercise that strengthens their muscles and helps lessen the danger of falls that may result in broken bones. A safe environment, such as removal of scatter

rugs, is also important for elderly people.

Facts to Keep in Mind

- It's the total combination of foods that you eat regularly—both the kinds and the amounts—that's important in terms of good nutrition. Eating a particular food or foods isn't a magic key that will assure that you have a more healthful diet.
- Eating a healthful diet, in itself, doesn't guarantee good health. However, a healthful diet is an important part of a healthy lifestyle that includes, for example, regular physical exercise, not smoking, not drinking alcoholic beverages in excess, and not abusing drugs.
- In addition to what you eat, many factors may be related to your own chance of developing a particular disease, for example, your heredity, your environment, and the health care that you get. Our knowledge about most diet-health relationships is incomplete and will improve as scientific knowledge increases. However, enough is known today about some of these relationships to encourage changes in dietary practices believed to be beneficial.

VI. References

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VII. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) that this action is of a type that does not individually or cumulatively have significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Economic Impact

The food labeling reform initiative, taken as a whole, will have associated costs in excess of the $100 million threshold that defines a major rule. Therefore, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354), FDA has developed one comprehensive regulatory impact analysis (RIA) that presents the costs and benefits of all of the food labeling provisions taken together. The RIA is published elsewhere in this issue of the **Federal Register**. The agency requests comments on the RIA.

IX. Effective Date

FDA is proposing to make these regulations effective 6 months after the publication of a final rule based on this proposal.

X. Comments

Interested persons may, on or before February 25, 1992, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of the Food and Drugs, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 is revised to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355, 371).

2. Section 101.72 is added to subpart E to read as follows:

§ 101.72 Health claims: calcium and osteoporosis.

(a) *Relationship between calcium and osteoporosis.* An inadequate calcium intake contributes to low peak bone mass and has been identified as one numerous many risk factors in the development of osteoporosis. Peak bone mass is the total quantity of bone present at maturity that experts believe has the greatest bearing on whether or not a person will be at risk of developing osteoporosis and related bone fractures later in life. Another factor that influences total bone mass and susceptibility to osteoporosis is the rate of bone loss after skeletal maturity. An adequate intake of calcium is thought to exert a positive effect during adolescence and early adulthood in optimizing the amount of bone that is laid down. However, the upper limit of peak bone mass is genetically determined. The mechanism through which an adequate calcium intake and optimal peak bone mass are thought to reduce the risk of osteoporosis relates to the fact that all persons lose bone with age, hence those with higher bone mass at maturity take longer to reach the critically reduced mass at which bones can fracture easily. The rate of bone loss after skeletal maturity also influences the amount of bone present at old age and can influence an individual's risk of developing osteoporosis. Maintenance of an adequate intake of calcium later in life is thought to be important in reducing the rate of bone loss particularly in the elderly and in women during the first decade following menopause.

(b) *Significance of calcium.* Calcium intake is not the only recognized risk factor in the development of osteoporosis multifactorial bone disease. Other factors including a person's sex, race, hormonal status, family history, body stature, level of exercise, general diet, and specific life style choices such as smoking and excess alcohol consumption affect the risk of osteoporosis.

(1) Heredity and being female are two key factors identifying those individuals at risk for the development of osteoporosis. Hereditary factors include race, notably Caucasian and possibly Asians are characterized by lower peak bone mass at maturity, and have a significantly higher incidence of bone fracture with increasing age, than African Americans.

(2) Maintenance of an adequate intake of calcium throughout life is particularly important for a subpopulation of individuals at greatest risk of developing osteoporosis and for whom adequate dietary calcium intake may have the most important beneficial effects on bone health. This target subpopulation includes adolescent and young adult Caucasian and possibly Asian American women. In addition, those individuals with known family histories of osteoporosis are also at greater risk of developing this bone disease later in life.

(c) *Health claim conditions.* A food label or labeling may contain a health claim stating that consumption of an adequate calcium intake throughout life helps to optimize peak bone mass during adolescence and early adulthood and to slow the rate of bone loss later in life and, by maximizing the amount of bone present in later years through these mechanisms, may reduce the risk of osteoporosis and related bone fracture provided that the following conditions are met by the product:

(1) All requirements for health claims as defined in § 101.14 are met;

(2) A serving of food or a total daily recommended supplement intake meets or exceeds the requirements for a "high" level of calcium as described in § 101.54;

(3) The calcium content of the product is assimilable;

(4) Dietary supplements shall meet the United States Pharmacopeia standards for disintegration and dissolution; and

(5) A serving or total daily recommended supplement intake does not contain more phosphorus than calcium on a weight per weight basis.

(d) *Health claim requirements.* Health claims relating adequate calcium intake to the possible reduction in the risk of osteoporosis may be used on the label and in the labeling provided that such statements comply with the following requirements:

(1) The claim shall make clear that adequate calcium intake throughout life is not the only recognized risk factor in this multifactorial bone disease by listing the specific factors, including a persons's sex, race, age, and family history, that place them at risk of developing osteoporosis and stating that an adequate level of exercise and a well-balanced diet are also needed;

(2) The claim shall not convey the misconception that the risk of osteoporosis is equally applicable to the general United States population. The claim shall clearly identify the populations at particular risk for the development of osteoporosis. These include white (or the term "Caucasian") women and may include Asian women in their bone forming years (approximately 11 to 35 years of age or the phrase "during teen or early adult years" may be used). These may also include menopausal (or the term "middle-aged") women, persons with a family history of the disease, and elderly (or the term "older") men and women;

(3) The health claim shall state that adequate calcium intake throughout life is linked to reduced risk of osteoporosis through the mechanism of optimizing peak bone mass during adolescence and early adulthood. The phrase "build and maintain good bone health" may be used to convey the concept of optimizing peak bone mass. When reference is made to persons with a family history of the disease, menopausal women, and elderly men and women, the claim may also state that adequate calcium intake is linked to reduced risk of osteoporosis through the mechanism of slowing the rate of bone loss;

(4) The claim shall not quantitate the degree of reduced risk of osteoporosis that may result from maintaining an adequate calcium intake throughout life; and

(5) The health claim shall state that a total dietary intake greater than 200 percent of the recommended daily intake (1,800 milligrams (mg) of calcium) has no further known benefit to bone health.

Sample Health Claim

Osteoporosis affects older persons, especially middle-aged, white women and those whose families tend to have fragile bones in later years. A lifetime of regular exercise and eating a healthful diet that includes enough calcium, expecially during teen and early adult years, builds and maintains good bone health; and may reduce the risk of osteoporosis later in life. Adequate calcium intake is important, but intakes above about 1,800 mg are not likely to provide any additional benefit.

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

Note: The following table will not appear in the annual Code of Federal Regulations.

BILLING CODE 4160-01-M

TABLE 1

Calcium and Osteoporosis: Effects of Calcium on Bone Status

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Angus R. M., et al., 1988 (Ref. 18)	Cross-sectional study To determine influence of diet on bone mass in proximal femur, intake of 14 nutrients measured, and bone mineral density quantitated by dual photon absorptiometry (DPA) Bone mineral density also measured in spine and bone mineral content in forearm by single photon absorptiometry	159 White women, aged 23 to 75 years Volunteers, Australia Study Participants asked to record their food and fluid intake for 4 consecutive days by weighing all items on a portable digital scale	None	None	Mean calcium intakes for premenopausal and postmenopausal women were 759 and 717 mg/day, respectively	Usual dietary habits Mean calcium intake calculated from 4-day weighed food record	None	This was a study of multiple nutrients	No significant correlation was found between current calcium intake and bone mass at any site	Results suggested that bone mass is influenced by dietary factors other than calcium Appropriate use of multiple logistic regression
Baran, et al., 1990 (Ref. 25)	Randomized prospective clinical trial Measured: bone density of the lumbar spine by dual photon absorption Blood chemistries measured every 4 weeks included lipid profiles and parathyroid hormone	59 started (37 finished) women (30 to 42 years old premenopausal Control n = 22, Average increase in calcium intake = 610 mg/day	3 years (36 months)	Dairy foods	500 to 600 mg/day as dairy foods	3-day dietary histories repeated Instruction on calcium intake of dairy foods Compliance confirmed with 24-hour urine calcium measure Urged to use low fat dairy products Habitual calcium intake:? Control = 892 mg/day treatment = 962 mg/day increased to 1300 to 1500 mg/day	All groups were age and weight matched with no difference in habitual calcium intake or initial bone densities Direct questions and HDL-Cholesterol profiles showed no group differences in exercise patterns, thus it was no considered a confounder	None	No change in vertebral bone density over 3-year duration in women consuming the dairy supplemented diet, but the untreated controls showed a significant decline (-2.9%) that differed from the treated group at 30 and 36 months No changes in any parameter of lipid profile or calcium homeostasis other than a significant increase in urinary calcium excretion was observed in the treated group	Unlike earlier studies, this is the first to confirm calcium intakes Suggests that dietary modification via supplementation with dairy products during the period of consolidation could retard vertebral bone loss and decreased the incidence of osteoporosis A very important study, despite high attrition rate of 37%

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Cauley, J. A., et al., 1988 (Ref. 36)	Purpose: To examine the interactions between normal levels and calcium with cortical bone Researchers combined factors for the development of peak skeletal mass (milk consumption during childhood and adolescence) with factors that may be related to the maintenance (serum hormone levels and dietary intakes of calcium) of bone integrity after menopause Hormones studied: Estrone Testosterone Androstenedione Calcium intake in childhood, adolescence, and adulthood was assessed retrospectively from responses to questions concerning frequency of milk consumption at various stages of life	174 postmenopausal women (healthy) All participants were in a 3-year randomized clinical trial designed to evaluate of walking in postmenopausal bone loss	3 years	Habitual and life time calcium intake	None	Calcium intake by food frequency method: 25th percentile: 407 mg/day 50th percentile: 684 mg/day 75th percentile: 942 mg/day Mean daily calcium intake 768 mg/day	None of the participants was receiving estrogen therapy at baseline	Bone measures were assessed with a computed tomographic scanner in the dominant radius at a site three tenths of the distance from the wrist to the elbow approximately one month after the annual clinic visit Current calcium intake was estimated at year 1 and year 3 by a food frequency questionnaire in which women recorded the frequency of consumption of various foods known to be common sources of calcium At year 1, calcium intake was also assessed by 3-day food records that were documented by nutritionist and coded according to the USDA handbook	Little relationship found between androgen hormones and radial bone density Estrone levels were independently related to radial bone density Examination of the relationship of calcium intake to bone revealed a protective effect solely in women who reported high "lifetime" calcium intakes Considering calcium and estrone together revealed an additive relationship between the 2 factors, in that women with high estrone and high calcium levels had significantly greater bone density than women with less calcium and or estrone	Results suggest that a lifetime of adequate calcium intake coupled with adequate levels of serum estrogens could maximize bone density after menopause

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Dawson, Hughes, et al., 1990 (Ref. 44)	Intervention placebo: Controlled Double blind Randomized Measured: Bone mineral density of spine and femoral neck by DPA Biochemical markers of calcium homeostasis	301 healthy postmenopausal women Early postmenopausal n = 67 average = 54.5 years year pm = 3.2 Sub-Groups High Calcium, n = 124 Low Calcium, n = 112 Late postmenopausal n = 169 average = 59.9 years	24 months	Placebo micro crystalline cellulose calcium carbonate Calcium citratemalate (CCM) Depending on habitual calcium intake, women were randomized to 3 treatments Thus, 6 treatment groups total	500 mg/day 500 mg elemental calcium 500 mg elemental calcium all tablets	Assessed by questionnaire initially and every 6 months By design half selected had habitual calcium intakes of: (1) < 400 mg/day (2) 400 to 650 mg/day	None	Effectiveness of calcium supplementation was affected by years since menopause Therefore data analyzed separately for: (1) Menopause in last 5 or fewer years (accelerated rate of a bone loss) (2) Menopause more than 5 years ago Time of day of supplementing (before bedtime) may have produce different effects between calcium carbonate and CCM, since calcium carbonate is absorbed better when consumed with a meal	Women in early menopause lost bone from spine and this rapid rate of loss was not affected by calcium supplementation (500 mg calcium) from any source Women in late menopause, the rate of bone loss was less rapid in those with higher habitual calcium intakes and there were no differences in bone density among treatment groups at any site All late postmenopausal women had significant bone loss from the spine, except those with a lower habitual calcium intake who received CCM For those on a low dietary calcium diet, CCM significantly decreased the rate of bone mineral loss from the spine, femoral neck, and radius Calcium carbonate decreased bone loss only at femoral neck and radius.	Study presents strong evidence that bone loss in early postmenopause is unresponsive to calcium supplementation Women in late menopause, whose habitual calcium intake is less than 400 mg may reduce their bone loss by increasing their calcium intake to 800 mg/day.

Table 1 continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Desai, S., et al., 1987 (Ref. 48)	Cross-sectional Measured: Bone mineral density by DPA of the lumbar vertebrae Estimates of calcium intake made from 3-day diet histories via computer software package	60 normal premenopausal 30 to 40 years of age Average age = 35	None	Habitual calcium intake assessed from 3-day diet history Average = 868 mg/day Range: 278 to 2064 mg calcium/day	None	None	Subjects had no other factors known to alter calcium or bone metabolism	None	Bone density at any site did not correlate with calcium intake, age or calorie intake	Dietary data from a 3-day record is not sufficient estimate of habitual calcium intake No measurement of physical activity which may have been an important confounder in this age group
Fujita, T., et al., 1990 (Ref. 55)	Clinical trial: Non placebo Controlled Not blinded Not randomized Japanese study Measured: Radial bone mineral density by single photon absorptiometry and spinal trabecular bone density by quantitative computed tomography	12 test subjects Asian female > 70 year age, normal except for osteopenia expected for age 20 controls age matched All subjects in geriatric hospital All subjects in late menopause	24 months	Oyster shell electrolysate (OSE)	900 g of calcium as OSE	Hospital diet consumed by all subjects Contained about 600 mg/day calcium	No record control of physical activity	Differences in physical activity may have confounded the results It remains unclear	Radial bone mineral density increased significantly in subjects consuming the OSE calcium and decreased significantly in the untreated controls No change in spinal bone density in either calcium treated or untreated controls Concluded that in late menopause hed positive response of cortical but not cancellous bone to calcium supplementation	Study flawed by large percentage of attrition attributed to their age (>70)

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Halioua, et al., 1989 (Ref. 60)	Cross-sectional Measured: bone mineral content and bone mineral density of the nondominant arm at the distal and mid (2/3) radius by single-photon absorptiometry	181 premenopausal women aged 20 to 50 mean age, 3 to 5 years All Caucasian	None	Habitual diet Calcium intakes for current, past, and lifetime classified as; Low, (<500 mg/day) Intermediate (>500 mg and <800 mg/day) High (>800 mg/day)	Diet assessment included current, past and lifetime calcium intake Used a quantitative food frequency questionnaire based on a 1 week intake Validated on a subset of 20 women on a 3-day dietary intake record (r = 0.52 Between the 3 methods) Similar quantitative food frequency questionnaire used to determine past and both current and past intakes were used to estimate lifetime calcium intake Appears to be a carefully conducted procedure conducted by a trained professional		Physical activity assessment, used a questionnaire to establish: Current activity Past activity Lifetime activity with each classified as: sedentary, moderate or active	All menopausal women, or women with abnormal menstrual cycle excluded	An intermediate or high lifetime calcium intake was associated with significantly higher bone mineral density and content at both distal and midradius when data was adjusted for physical activity Similar findings were observed when data was adjusted for calcium intake Thus, lifetime high calcium, and active level of exercise was associated with highest radial bone densit;	Any estimate of past or lifetime calcium intake is inherently weak, but effort was made to validate against current intake estimate Findings suggest that both adequate calcium intake and regular exercise during adolescence enhance peak bone mass

Table 1.—continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Holbrook T., et al., 1988 (Ref. 72)	Prospective cohort	957 white upper middle class subjects, aged 50 to 79 years (416 men, 531 women) sub-sample of cohort of 6,155 including all hyperlipidem (a 15% random sample)	14 years	Dietary calcium usual intake estimated from 24-hour diet recall taken in 1973 to 1975 and quantified in 1985	Range of estimated calcium intake: not given	Use 24-hour recall, weak method for estimate of calcium intake	Alcohol, age, obesity, sex, smoking, exercise, estrogen replacement	None	Hip fractures were usually proportional to calcium intake in both sexes therefore positive effect associated with calcium 33 hip fractures (male 15 and female 18) mean calcium intake: mg/day Men with fracture = 305.9 Men without fracture = 384 9 Females with fracture = 319.8 Females without fracture = 401.3	Weakest point of study was method of estimating calcium intake from 24-hour recall, particularly since the data were collected 10 years prior to analysis Study was weakened by small sample size Unresolved issue as to whether calcium effect is preventive after 50 years of age or is the therapeutic end result of habitual higher calcium intake, thus affecting peak bone mass

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Kanders, B., et al., 1988 (Ref. 78)	Non randomized Cross-sectional Measured: Bone mineral mass by SPA 1/3 radius site Bone mineral density of the lumbar spine by DPA Physical activity measurement via Minnesota Leisure Time Activity Questionnaire Daily walking by a 7-day pedometer recording Nutritional assessment by 24-hour dietary recall with food models and a prospective 6-day record to yield a weighted 1-day intake All women were within 20% of ideal body weight	60 women eumenorrheic, healthy normal age 25 to 34 years old	None	Lifestyle variation with regard to habitual calcium intake	None	Mean calcium: 871 mg/day Range: 286 to 2,128 Only one subject avoided dairy products 17 were taking calcium supplement users for 3 years	Exercise monitored: Energy Expended: Average Kcal/day = 960 Range: 286 to 2,128 Examined statistically as: <970 kcal/day >970 kcal/day	None	Highly significant correlation between bone mineral density of the lumbar spine and overall level of physical activity Radial bone density showed no correlation to physical activity and only a modest relations to calcium intake which was statistically significant Statistical comparison made after the group was divided at the RDA for calcium of 800 mg/day both vertebral and radial mineral were significantly greater in those with high calcium intake The mean spinal bone mineral density was highly significantly different between women with the highest calcium intake and physical activity level, relative to those who were relatively inactive and on a lower calcium intake. -Bone mineral density of the spine did not increase with calcium intakes above 800 - 1000 mg/day, implying a calcium threshold effect.	General conclusion that Bone mineral density of the spine can be influenced by both mechanical stress of physical activity and optimal calcium nutrition during the period of skeletal maturation (consolidation) Data implies an optimal calcium intake between 800 to 1000 mg of calcium

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Kelly, P. J., et al., 1990 (Ref. 82)	Cross-sectional Measured: Bone mineral density of radius by single photon absorptiometry and lumbar spine and hip by DPA to assess relation between bone mineral density and: Dietary calcium intake Anthropometric features Age Serum sex hormone level	48 normal men (age 21 to 79, median 44)	None	Dietary calcium assessed from questionnaire validated against 4-day dietary record	Range: 0.3 to 1.7 g/day (from figure 1)	Not specified	None	None	Dietary calcium intake was significant predictor of bone mineral density of axial bones, explaining 24% and 42% of the variance at the lumbar spine and femoral neck, respectively This effect was independent of weight In contrast with the axial skeleton, bone mineral density at each forearm site was predicted by weight and an index of free testosterone but not dietary calcium intake	Strengths: Appropriate application of stepwise logistic regression Limitations: Specific diet of study participants not described Level of physical exertion not discussed, may present as confounder
Lacey, M., et al., 1991 (Ref. 86)	Cross-sectional Measured: Mid-radial bone mineral content and bone density by single photon densitometry	178 Japanese women living in Japan 89 premenopausal women (35 to 40 years) 89 postmenopausal women (55 to 60 years)	None	Habitual dietary intake	None	Habitual diet assessment carried out on 3-day food diary interpreted by American interviewer using Japanese computerized nutrient data base A quantitated food frequency questionnaire was used to assess calcium intake between 14 to 22 years of age	None	Physical activity Medical history and anthropometric measurements were taken to determine influence on bone status	Current calcium intake was not associated with bone indices on either pre- or postmenopausal women Vegetable intake and current milk intake were positively correlated with mid-radial indices An important finding since both are calcium rich foods	Assessment of past calcium intake in these very elderly ladies was confounded by probate food restrictions imposed during WWII when many of these women would have faced food restriction

TABLE 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Lutz, J., et al., 1990 (Ref. 96)	Cross-sectional Measured: Bone mineral content of the lumbar spine and right proximal femur (femoral neck and trochanter) by dual-photon absorptiometry	37 with mother-daughter pairs aged 52 + 7 years and 25 + 4 years Mothers premenopausal n = 20 postmenopausal n = 17	None	3-day dietary intakes assessed dietary contribution notably calcium Mean calcium intakes: mother = 1102 mg/day daughters = 818 mg/day 13 mother had <800 mg/day 7 daughters had <800 mg/day	None	None	Supplemental calcium intake by mothers (n = 21) averaged 580 mg/day by daughters (n = 13) averaged 340 mg/day This may have confounded the study Another confounder may be the heterogeneity of the subjects with respect to their age and menopausal status Exclusion criteria in selecting pairs included estrogen use or other factors that would affect bone	23 mothers and 19 daughters were taking vitamin/mineral supplements	Total calcium intake was significantly correlated with 3 bone mineral density sites for the daughters, but not for the mothers	3-day dietary records are not sufficient to get an accurate estimate of calcium intake Study may be flawed by over interpretation of the findings concerning calcium intake The method used was not competent to estimate habitual calcium intake
Matkovic, et al., 1990 (Ref. 97)	Calcium intervention Longitudinal trial Measured: Calcium balance Radiogrammetry of the hand Single photon absorptiometry of distal radius DPA of the lumbar spine	30 adolescent females healthy 14 years old at onset eumenorrheic 18 of these participated in the balance study	2 year	Habitual dietary calcium or-- Supplemental calcium from either milk or calcium carbonate	Subjects stratified into 2 groups: Control n = 9 <850 mg calcium/day Initially with a continued Average intake of 750 mg calcium/day Calcium supplemented Milk group n = 10 <10,900 ml of milk/day Calcium carbonate group n = 12 took 4, 250 mg calcium tablets/day Average calcium/day = 1049 mg Stratification was based on prestudy calcium intake	Determined from 3-day food record Initially and at 6, 12, 18 and 24 weeks	None	For statistical analysis the high calcium groups were pooled since baseline values, bone mass, nutrition ecc. were the same	While trend toward an increase in bone density in those girls consuming the higher calcium intake was observed over 2 years in the distal forearm and spine, this difference did not reach statistical significance both groups showed a significant increase in bone mass and more significantly bone density Girls retained 800 to 570 mg calcium/day suggesting that inadequate calcium intake may translate into inadequate retention and a reduction in peak bone mass	No adjustment was made for physical activity differences between the two groups which may have a confounding effect Very difficult study design to follow--too concluded Due to the small "n" in this study of 9 for the control and 10 for the calcium supplement group a type II error is possible

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Mazess, R., et al., 1991 (Ref. 98)	Longitudinal observation over a 2-year period Dual-photon absorptiometry of lumbar spine and Single-photon absorptiometry of the standard one-third radius and distal radius sites	200 to 300 White premenopausal women aged 20 to 39 All were ambulatory and free of current or previous chronic disease or medications known to affect bone	2 years	Normal diet, content assessed from several; 24-hour reporting periods over the two years using preceded Nutrient Adequacy Reporting System	Dietary calcium intake 989 + 351 mg/day	Normal diet	No specific treatments	Study of effects of age, dietary intake, physical activity, smoking and birth-control pills on bone mineral density	There was no association of calcium intake with bone mineral density or changes in bone mineral density Current calcium intake was not a significant influence on bone and mineral density in this age group No apparent additive interaction of activity and calcium intake on bone mineral density Body weight was a better predictor of bone mineral density than was any other factor No association of bone mineral density or bone mineral density changes with calcium	Appropriate analysis of data using linear and multiple regression Calcium intake and methods were weak, used less reliable method of 24-hour recall

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
McCulloch R., et al., 1990 (Ref. 99)	Cross-sectional Random selection Measured: Cancellous bone density of the os calcis using computed tomography	101 healthy normal females 20 to 35 years old	None	Childhood milk consumption Current dietary calcium intake Avocational Physical activity Various Lifestyle variables, e.g., smoking Range of Current Calcium Intake: 150 to 1560 mg/day	None	Dietary information determined from a questionnaire as was assessment of childhood physical activity Questionnaire was readministered 10 weeks later and discrepancies resolved Current levels of physical activity and calcium intake also evaluated by a 2-week and 1-week recall check test Limited explanation given for this check test	Exclusion criteria included: menstrual disfunction, kidney disease; etc.	None	There was a nonsignificant correlation between calcium intake and bone density of the os calcis There was no significant difference in bone density of the os calcis of subjects grouped according to self classifications high, moderate or low childhood milk consumers	Questionable competency of the dietary calcium intake validation estimates offered Diet and calcium intake analysis, a very weak point of this study

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Nelson, M., et al., 1991 (Ref. 102)	Prospective clinical trial, Double-blind, placebo controlled, Randomized for dietary, variable, Assigned according to preference to exercise training or sedentary Measured: Trabecular bone density of Lumbar spine (L1-L3) by computed tomography (QCT) Femoral-neck (nondominant) and Lumbar spine (L2-L4) bone mineral density by DPA Bone mineral density of the shaft of the nondominant radius (1/3 distance) by single photon absorptiometry Total body calcium by delayed gamma neutron-activation Various measurements of muscle strength, aerobic capacity and body fluid analysis for hormones electrolytes.	36 postmenopausal Caucasian women All > 2 y postmenopause Average = 10.8 year Average age = 60.2 All < 130% ideal body weight	12 months	Milk with high calcium content 831 mg calcium/day Moderate calcium milk drink-placebo artificial milk 41 mg calcium/day	None	Usual diet, instructed all subjects to consume 800 mg calcium/day through inclusion of 4 servings of dairy products per day	Exercise which included walking 1 mile per day 4 times/week for 52 weeks or Sedentary no scheduled routine exercise but were allowed weekend recreation 4 Groups designated as: Exercise, moderate dietary calcium n = 9 Sedentary, moderate dietary calcium n = 9 Sedentary, high dietary calcium n = 9	Possible differences in dietary content of Vitamin D, protein and phosphorus Groups differed initially only by parity: Exercise group = 4.3 Sedentary = 2.6*.	Bone mineral density of the spine, measured by QAT decreased 7% in sedentary group and increased in exercise group by 0.5% (p = 0.028) but calcium intake had no significant effect Femoral neck bone mineral density measured by DPA decreased 1.1% in moderate calcium group and increased 2% in high calcium group (p = 0.014) and no significant effect of exercise No change in hormone or urinary metabolism observed with any treatment	Well controlled and well designed study examining more than usual endpoints Important finding was that due to varying proportion and rates of bone turnover of cancellous and cortical bone at various skeletal sites, exercise and dietary calcium may preferentially modify bone mineral at these different sites Findings confirm previous studies showing calcium to affect cortical bone but not cancellous bone Limit power of study since each group contained only 9 subjects

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Picard, D., et al., 1988 (Ref. 111)	Cross-sectional Observational Measured: Bone mineral content of the spine by DPA and of the forearm by single photon absorptiometry	183 women, aged 40 to 50 average age = 43.8 years all normal healthy with regular menses	None	Range of historical intake: High > 1000 mg/day n = 38 Medium 500 to 1000 mg/day n = 75 Low < 500 mg/day n = 70	Historic and habitual calcium intake: Average calcium intake at age 20 = 576 mg/day	Diet history taken to determine intake at age 20 3-day food recall to verify calcium intake	Estimates of caffeine, alcohol intake, cigarette smoking, exercise, estrogen use, and parity were also made	Homogeneous population of French Canadian women, geographic and racial differences were minimized	Significant positive correlations were noted between the bone mass measurement at the spine and forearm and weight, height and calcium intake at age 20 Significant differences were observed between the low and high calcium intake groups for the mean adjusted bone mineral content at both sites Concluded: Chronic calcium intake has a significant effect on lumbar bone mass indices in premenopausal women	Study did not indicate whether the effect of calcium intake was on the formation of maximal peak bone mass or on slowing the rate of bone loss at midlife Has all the predicted limitations inherent in a cross-sectional study examining histories, dietary intake

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Polley, K. J., et al., 1987 (Ref 113)	Prospective intervention with consecutive and concurrent controls Random assignment to treatment Measured forearm mineral content by single photon absorptiometry	Postmenopausal women <65 years old 3 treatment groups 210 completed 52 strict controls, 122 not able to take supplements, 136 treated	Initial 9-month control period 9-months of the treatment (total duration 18 months)	Group 1: Reduced sodium Group 2: Increased dairy foods 1250 mg/day Group 3: diet + 1000 mg calcium as sandolcal total diet content: 1700 mg Untreated controls None	Group 1: None Group 2: 450 mg calcium, dairy Group 3: 1000 mg effervescent tablets of calcium gluconate, lactate and carbonate Untreated controls None	Group 1: 709 mg calcium Group 2: 711 mg calcium Group 3: 714 mg calcium Average for treated 711 mg calcium Untreated controls 717 mg calcium	Group 2: Subdivided into dairy products + salt restriction Dairy products only	Diet Sodium Content Group 1: 1827 mg/day Group 2: Restricted 1803 mg/day 2103 Group 3: (+ calcium) 2422 mg/day	Bone mineral content No significant differences in forearm mineral content for any treatment or subgroup, initially Rate of Bone Loss The difference between pretreatment and after 9-months of calcium was significantly reduced Calcium treated women had a greater reduction in the rate of bone loss, but it was not statistically different from the untreated strict controls Comparison of women within 10 year of menopause showed a significantly different (reduced) rate of bone loss in both the calcium supplement and dairy product only group, relative to untreated control.	Poor or questionable compliance, especially in control group Confusing design with too many variables Unexplained significant reduction in rate of bone loss in strict controls between period 1 and 2 Questionable inclusion of noncompliant subjects in control groups

Table 1--continued

Reference* (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Smith, E. L., et al., 1989 (Ref. 123)	Double blind study of effects of calcium carbonate supplement on bone loss Random assignment to treatment or control groups Bone mineral content and width measured bilaterally on the radius, ulna and humerus Single-photon absorptiometry used	169 women aged 35 to 65 years Subjects recruited from general population of Madison, WI	4 years	OS-Cal 500 (Marion Labs) Each tablet contained 500 mg elemental calcium in form of calcium carbonate	1500 mg calcium/day was desired goal Less was actually achieved	Usual diet for each participant	None	Subjects excluded from study if they had a history or current diagnosis of osteoporosis, malignancy, and any other condition known to have major effects on calcium metabolism	Bone mineral content and bone content/width loss rates were consistently lower in treatment than in control subjects Loss was significantly reduced in the left and right humerus and right radius In premenopausal women, only left humerus bone mineral content loss was significantly reduced by calcium supplementation In postmenopausal women, bone mineral content and bone mineral content/width bone loss was reduced in all 12 of the bone variables measured, 5 at $p<0.01$, and 2 at $P< 0.05$	Calcium supplementation counteracted a large portion of the additional bone loss attributable to menopause in this population

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Stevenson J. C., et al., 1988 (Ref. 124)	Cross-sectional 16 women placebo group applied inactive gel 5 grams daily throughout the study to the skin of the abdomen and upper thighs and took 3 inactive tablets daily for the first 12 days of each calendar month 38 women in treatment group took either synthetic human calcitonin or percutaneous estradiol together with oral progesterone for 12 days each month, or both	59 healthy postmenopausal women most of whom were within 5 years of menopause Volunteers Median age 55 years (37 to 64)	12 months	Calcitonin: Ciba-Geigy Estradiol: Basins-Iscovesco	Synthetic human calciton-20 IU 3 times/week by s.c. injection Estradiol 5 grams daily Progesterone 300 mg/day	Dietary intake of calcium assessed by questionnaire and interview Dietary intake of calcium before treatment 530 mg (lower quaritle) and 1564 mg (upper quaritle)	See study design	None of the women taking any other drug known to affect calcium metabolism	No correlation was found between current intake of calcium and either total calcium in the body or the density of trabecular of cortical bone in the forearm or vertebral trabecular bone Dietary intake of calcium did not influence the rate of postmenopausal bone loss in the 54 women who completed 12 months of active or placebo treatment Even when extremes of calcium intake were examined, no difference was found in bone measurements between the women with the highest and lowest intake	Results of this study suggest that the bone density of women in the early menopause is not influenced by current dietary intake of calcium Weak dietary data, determining calcium intake

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Stevenson J. C., et al., 1989 (Ref. 125)	Cross-sectional study of bone density measurements of vertebral and proximal femur using DPA Possible predictors and risk factors for bone density were assessed in study participants	284 White healthy women-volunteers ages 21 to 68 Included 112 premenopausal women	Cross-sectional study	Dietary calcium intake assessed	Dietary calcium estimated mean calcium intake for premenopausal women was 598 g/day, while for postmenopausal women it was 619 g/day	An estimate of dietary calcium intake was derived form the current consumption of diary products	None	None of study participants was taking any drugs known to influence bone or calcium metabolism	Peak adult bone density had been attained soon after the end of linear skeletal growth Thereafter, there was some decline with age in the proximal, femur, but the major fall in bone density in all sites was related to the menopause Other factors decreasing bone density, and thus increasing risk for osteoporosis (low body weight, alcohol and cigarette consumption, nulliparity, lack of previous use of oral contraceptives, and lack of regular exercise) seemed to be important None, however could predict satisfactorily women at future risk for osteoporosis.	Values obtained for bone density were similar to those obtained from equivalent studies performed in women in the United States In agreement with others, no evidence obtained of skeletal consolidation in the third or fourth decade Weak assessment of dietary calcium intake; no validation

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Tylavsky F., et al., 1988 (Ref. 128)	Cross-sectional Used multiple regression model to assess effects of current calcium, P, and protein intake on bone indices Measured: Bone mineral content and bone density at the mid and distal radius using single photon densitometry	287 omnivorous postmenopausal women 88 lacto-ovo-vegetarian postmenopausal women All Caucasians	None	Habitual intake from omnivorous and lacto-ovo vegetarians (16-year minimum duration of lacto-ovo-vegetarian diet)	Quantitive food frequency questionnaire used to estimate usual and past calcium intakes Administered by a trained interviewer Validated against 3-day food record	Current calcium intake: Average omnivores: 902 + 21 mg calcium/day Lacto-ovo-vegetarian: 823 + 48 mg calcium/day	Factors known to affect bone density excluded subjects from study, e.g., long-term immobilization, hyperparathyroidism etc.	Smoking, alcohol use, parity and lactational experience was also determined and differed between the omnivorous and lacto-ovo-vegetarians The 2 groups also varied significantly by their age, weight, body mass in diet, lean body mass and parity Groups did not differ in number of subjects using estrogen, aluminum antacids or magnesium Omnivorous women had a greater use of thiazide diuretics that conserve calcium which may have masked true differences in bone densities	Bone indices were in general positively influenced by body mass index, and dietary protein intake and negatively influenced by age and dietary phosphorus Current calcium intake had no positive effects on bone indices	Question the accuracy of the quantitative food frequency questionnaire, however, authors did validate it against a 3-day food record for 20 adult women

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Van Beresteijn, E., et al., 1990 (Ref. 132)	Longitudinal study Measured: Bone mineral content of distal third nondominant radius Serum electrolytes and calcitropic hormone levels	194 perimenopausal women 63 pre- and 94 post-menopausal After the 3rd year, all women were postmenopause	8 year follow-up study	Habitual calcium intake 3 Groups: < 800 mg/day (n = 28) 800 to 135 mg/day (n = 95) 1350 mg/day (n = 31)	Dietary calcium intake determined by cross-check dietary history method	Habitual calcium intake was estimated from the mean of 7 annual histories	None	No estimates of physical activity were made which may serve as a confounding factor Women with significantly lower habitual calcium intakes also had significantly lower intakes of total protein energy and phosphorus, a potential confounder.	Cortical bone mineral content/bone width decreased over time in all groups The rate of bone loss did not differ significantly between groups Bone mineral content/Bone width or bone loss correlated with age or habitual dietary calcium intake Concluded: Habitual calcium intake exceeding 800 mg/day was not effective in preventing cortical bone loss in early menopause	Weak estimate of annual calcium intake

Table 1--continued

Reference (author, date)	Study Design	Number and Description of Subjects	Duration of Study	Source and Identity of Test Material	Dosage of Test Material Used	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Van Beresteijn, E., et al., 1990 (Ref. 131)	Complicated: Longitudinal Nonrandomized Cross-sectional Observational Measured: Bone loss at the radius determined by single photon absorptiometry One-time measurement of bone mineral content of spine and femoral neck by DPA Rate of bone loss at radius extrapolated to spine and femoral neck	60 normal healthy postmenopausal women 3 to 10 years post menopause average = 7.7 years average age = 61	Longitudinal component, 8 years	Habitual calcium intake	Range of calcium intake: 560 to 2,580 mg/day average calcium intake = 1132 + 401 mg/day	Habitual calcium intake estimated as a mean of 8 annual dietary intake estimates, 75% diary derived in Dutch population Used Cross-check dietary history method	None	No activity assessment, may be a confounding factor	With Univariate analysis, neither cortical bone (radius or femoral neck) or cancellous (spine) was correlated to habitual calcium intake Body mass index had a protective effect on cortical bone but not trabecular bone Concluded: In early postmenopause, bone mineral content of the appendicular and axial skeleton are not related to calcium intake Longitudinal measurements of cortical bone mass are of limited value in predicting bone density of spine	Study results do not rule out possibility that high calcium intake in early postmenopausal phase may decrease the rate of loss of cancellous bone mass Question the appropriateness of combining longitudinal and cross-sectional data and extrapolating from one data set to another Weak dietary calcium estimates

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