

recommendations for vitamin D supplementation or the use of dark (i.e. oily) fish may be prudent. [Study score = 2+]

As noted in the previous section on younger adults, Bischoff-Ferrari *et.al.* (2004a) reported significant positive associations between serum 25(OH)D concentrations and total hip BMD among 3,512 white, 1,167 Mexican American and 1,237 black participants in the NHANES III study who were ≥ 50 years of age. [Study score = 4]

A prospective study of 891 women (mean age 47.5 years at baseline and 53.9 at follow-up living near Aberdeen, Scotland was conducted by Macdonald *et.al.* (2004). Mean total calcium intake (food and supplements) was 1,070 mg/d at baseline and 1,032 mg/d at the end of the study. Analogous data for vitamin D were 4.5 and 5.5 $\mu\text{g}/\text{d}$. Energy adjusted calcium intake from diet alone was positively associated with BMD in the femoral neck ($p < 0.05$). This association remained significant ($p < 0.05$) after correction for age, height, weight, annual percentage weight change, physical activity level, change in physical activity since baseline, smoking, menopausal status and HT use. There was no significant association between calcium intake and spine BMD. Vitamin D was not associated with BMD in this study, but this lack of association may have been because intakes were adequate. [Study score = 2+]

2. Intervention studies

Dawson-Hughes *et.al.* (1991) conducted a one-year, randomized, placebo-controlled, double-blind study with 249 postmenopausal women (mean age = 61.7 years) to study

the effect of vitamin D supplementation on bone loss. The subjects (residents of the Boston area) were randomized to receive 10 μg (400 IU) of vitamin D or a placebo after stratification by dietary calcium intake and years since menopause. Both the vitamin D supplement and the placebo contained 127 mg elemental calcium as calcium phosphate, and all subjects received an additional 250 mg calcium as CCM. Dietary intakes were estimated by a FFQ. There were no differences between the experimental and control groups in age, years since menopause, weight, percent smokers, alcohol consumption or whole body or spine BMD. There was a borderline difference between the groups in the percent of women who had experienced menopause in the last six years ($p=0.07$). Total body and spine BMD increased in period 1 (June and July through December and January) and decreased in period 2 (December and January through June and July). The increases in BMD at these sites were not significantly different between treatment groups during period 1, but there was a significantly reduced loss of BMD at the spine ($p=0.03$) in the vitamin D supplemented group during period 2. The change in spine BMD for the entire year was significantly less ($p=0.04$) for the vitamin D-supplemented group. There were no differences in physical activity between the two groups, but calcium intake was approximately 10% higher (~ 810 mg/d vs. ~ 728 mg/d; $p<0.005$) in the vitamin D group. Vitamin D intake was also significantly higher in the experimental group ($p<0.05$).

Plasma 25(OH)D decreased in period 2 vs. period 1 for both the placebo (-20.7% ; $p<0.001$) and the vitamin D (-4.9% ; $p<0.005$) groups, but the magnitude of reduction was significantly lower in the vitamin D group for both periods ($p<0.001$).

Serum PTH increased during period 2 in the placebo group ($p<0.001$) but not in the vitamin D group. The authors concluded that vitamin D insufficiency contributes to

spinal bone loss in the winter in healthy postmenopausal women consuming 800 mg of calcium and 100 IU of vitamin D per day, and that increasing vitamin D intake to 500 IU/d reduces wintertime bone loss and improves overall density of the spine. [Study score = 1+]

Chapuy *et.al.* (1992) studied the effect of supplementation with a combination of calcium (1,200 mg from tricalcium phosphate) and vitamin D₃ (800 IU as cholecalciferol) for 18 months on fracture incidence and bone density among 3,270 healthy, ambulatory women (mean age 84 years). There were no differences between the experimental group (n = 1,634) and the placebo group (n = 1,636) at the beginning of the study in age, weight, percent of subjects who had fallen during the previous three months or calcium intake (511 mg/d and 154 mg/d in the experimental and control groups, respectively). The supplemented group was 1 cm taller than the placebo group (p=0.003). There were 43% fewer hip fractures in the treatment group of women who completed the study compared to the placebo group (p=0.043). Similarly, the treatment group experienced 32% fewer nonvertebral fractures (p=0.015) than controls. There was a significant increase in serum 25(OH)D in the supplemented group from 16 ng/ml (40 nmol/L) at baseline to 42 ng/ml (105 nmol/L) at 18 months (p<0.001). This increase was accompanied by a parallel decrease in serum PTH (from 54 to 30 ng/L; p<0.0001). There were no significant changes in 25(OH)D or PTH during the study in the control group. The supplemented group also maintained significantly more BMD in the femoral neck (p=0.036) total proximal femoral region (p<0.001) and the trochanter (p=0.044) compared to the placebo-treated controls. The authors concluded that 18 months of daily

supplementation with 1.2 g of elemental calcium and 800 IU of vitamin D was safe and decreased the incidence of hip fractures and other nonvertebral fractures among elderly women. A subsequent report from this population (Chapuy *et al.*, 1994) after 36 months of intervention found that calcium and vitamin D supplementation continued to reduce the risk of fractures. The RR for all non-vertebral fractures was 0.70 (95% CI, 0.51, 0.91 for) and a similar value (RR=0.70) for fracture of the hip (95% CI, 0.62, 0.78). [Study score = 1+]

The effect of calcium supplementation for two years on biochemical parameters and bone density among 122 healthy white women who had reached menopause more than three years earlier (mean age = 58 years) was studied by Reid *et al.* (1993) using a randomized, placebo-controlled, double-blind protocol. The experimental group received 1,000 mg calcium per day in the form of 5.24 g calcium lactate-gluconate and 0.8 g calcium carbonate, formulated as an effervescent tablet taken with water in a divided dose twice daily for two years. The placebo group received identical tablets containing sucrose. Calcium intake was estimated using four-day diet records obtained at baseline and at the end of the study. There were no significant differences between the two groups at baseline in age, years since menopause, weight, height, physical activity, smoking incidence, alcohol intake, mean calcium intake (760 mg/d in the experimental group and 730 mg/d in the control group), TBBMD or BMD at four sites. Calcium supplementation resulted in improved changes in BMD at all sites. TBBMC decreased in both groups ($p < 0.001$), but the decline was significantly greater in the placebo group ($p = 0.005$). There was no net change in BMD of the spine in the placebo group, but it increased in the

experimental group ($p < 0.001$) and there were significant differences between the two groups ($p = 0.04$). The authors concluded that calcium supplementation had beneficial effects on BMD in postmenopausal women who had calcium intakes above 400 mg/d at baseline, but that studies of longer duration are needed to determine whether the effects are cumulative. [Study score = 1+]

A randomized, placebo-controlled, double-blind study was conducted by Aloia *et al.* (1994) to study the effect of supplementation with 1,700 mg/d calcium (from calcium carbonate) with or without HT for 2.9 years among 118 healthy, white postmenopausal (mean age ~52 years). All subjects received 10 μ g (400 IU) of vitamin D per day. There were no significant differences for any variables measured between the three groups at baseline. Calcium intake at the start of the study ranged from 150 to 1,263 mg/d for the entire group. Mean calcium intake for the calcium-supplemented group was 492 mg/d (range 222 – 806 mg/d with 26% of subjects <400 mg/d). Mean calcium intake in the combination group was 545 mg/d. Calcium supplementation alone resulted in significantly less bone at the end of the study compared to the placebo group for the total body and femoral neck ($p < 0.05$). HT in combination with calcium supplementation resulted in additional benefits on BMD of the total body, Ward's triangle and trochanter ($p < 0.05$). The authors concluded that calcium supplementation alone significantly retards bone loss from the femoral neck and improves calcium balance in vitamin D replete recently postmenopausal women, and that calcium supplementation should be recommended as a strategic option in helping to prevent early postmenopausal bone loss. [Study score = 1+]

The effect of calcium supplementation for 18 months on BMD of healthy, vitamin D replete elderly (mean age = 72.1 years) subjects was reported by Chevalley *et.al.* (1994). Ninety-three ambulatory, healthy subjects (n=82 women) were randomized to receive 800 mg/d calcium carbonate, 800 mg/d calcium as osseino-mineral complex or a placebo. All subjects were given a single oral dose of 300,000 IU vitamin D at the beginning of the study. Another group of 63 elderly patients (mean age = 78.4) who had experienced a recent hip fracture were also randomized to one of the two calcium-supplemented groups, but these data will not be discussed because ethical considerations precluded the use of a placebo group among fracture patients. There were no significant differences at baseline between the three groups of non-fracture victims in any of the study parameters. Mean dietary calcium intake was 619 mg/d. Thirteen subjects (14%) failed to complete the 18-month study. There were no significant differences in the number of drop-outs between the three groups. Results for the two calcium-supplemented groups were combined. BMD of the femoral shaft was greater ($p<0.05$) among women in the treatment groups than in the control group at the end of the experiment. In addition, when mean changes in the femoral shaft and femoral neck BMD were averaged, regression analysis showed that values were greater ($p<0.05$) in the calcium-supplemented groups. Finally, a positive linear relationship ($p<0.05$) was observed between the mean changes in femoral shaft and femoral neck BMD and total calcium intakes (diet and supplements) in both men and women. These data support the premise that calcium supplementation improves bone health among vitamin D-replete subjects with low calcium intakes. [Study score = 1+]

Elders *et al.* (1994) examined the effect of calcium supplementation on bone loss among 295 pre- and postmenopausal women aged 46 to 55 years. The subjects were randomized into one of three groups: group 0 received a placebo, group I received 1,000 mg elemental calcium per day and group II received 2,000 mg supplemental calcium per day. The calcium was provided as effervescent tablets containing 5.23 g calcium lactogluconate and 0.9 g calcium carbonate (1,000 mg per tablet). At the end of the two-year study, 218 subjects agreed to continue for an additional year. There were no significant differences in age, height, weight, BMI or mean calcium intake (1,065 mg/d in group 0, 994 mg/d in group I and 1,052 mg/d in group II) at the beginning of the study. Significant bone loss in the spine occurred among pre- and early perimenopausal subjects in the control group ($p < 0.01$) but not in the supplemented group, and the difference was significant throughout the entire three-year study period ($p < 0.05$). There was no difference in the rate of bone loss between the two calcium supplementation groups. Among late perimenopausal and postmenopausal women, there was significant lumbar bone loss in all groups ($p < 0.001$). The rate of bone loss was significantly less in groups I and II during the first year of the study ($p < 0.01$), but not during the second two years. There was no significant difference in the rate of bone loss between the two supplemented groups. Significant metacarpal cortical bone loss also occurred in the control and treatment groups. The amount of bone loss was lower in the pre- and early perimenopausal women than in the late peri- and postmenopausal subjects ($p < 0.05$). Supplementation at both amounts of calcium resulted in less bone loss than in the control group ($p < 0.01$). Serum 25(OH)D and PTH did not change due to calcium supplementation. The authors concluded that calcium supplementation can play a role in

the preservation of the skeleton – especially before menopause. The high baseline calcium intakes of the women in this study may have diminished the effect of calcium supplementation, and the ability to discern significant differences among the different menopausal subsets was likely diminished by the small number of subjects in each cell (13-24). [Study score = 1+]

Strause *et.al.* (1994) conducted a randomized, placebo-controlled, double-blind study to determine the effect of supplementing the diet of 59 postmenopausal (mean age = 66 years) women for two years with 1,000 mg calcium/d with or without additional minerals on spinal BMD. The subjects were randomized into one of four groups: a mineral supplement group (15 mg/d zinc, 2.5 mg/d copper and 5.0 gm/d manganese); a calcium group (1,000 mg elemental calcium from CCM); a combination group that received both calcium and mineral supplements; or a placebo control group. There were no significant differences in any of the characteristics measured at the beginning of the study. Baseline calcium intake ranged from 524 mg/d in the calcium group to 622 mg/d in the trace mineral group ($p>0.05$). Two-way analysis of variance (ANOVA) showed that the main effect for calcium on BMD was significant ($p=0.045$), but only the combination group had higher ($p<0.01$) spinal BMD than the placebo group. The authors concluded that bone loss in calcium-supplemented, older postmenopausal women can be further arrested by concomitant increases in trace mineral intake. [Study score = 1+]

The effect of 900 mg/d calcium supplementation with heated oyster shell-seaweed calcium (HOSS Ca) or calcium carbonate for 18 months on BMD was studied among 58

hospitalized patients 65-96 years of age using a randomized, placebo-controlled, double-blind protocol (Fujita *et.al.*, 1995). Dietary calcium intake was approximately 600 mg/d and was provided by a standard Japanese hospital diet. Supplementation with HOSS Ca resulted in significantly greater BMD of the lumbar spine at six ($p=0.015$), 12 ($p=0.008$) and 18 months ($p=0.014$) compared to the placebo. There were also significant differences at the mid-distal radius. There were no significant differences between the placebo group and the calcium carbonate supplemented group throughout the study. The application of this study is limited because the inpatient-based population it studied does not reflect the normal, healthy U.S. population.]Study score = 1-]

Haines *et.al.* (1995) conducted a one-year randomized, controlled intervention trial to study the effect of HT with or without calcium supplementation on BMD among 102 perimenopausal (mean duration of menopause <1 year) women. The subjects were assigned to receive HT (conjugated estrogens, 0.625 mg/d) and randomized into a supplementation group that received 1,000 mg elemental calcium (Calcium Sandoz; the form of calcium in this supplement was not specified) or a non-supplemented group. A double-placebo control group was not used. There were no differences between the groups at baseline in age, duration of menopause, height, weight or BMD at the lumbar spine of three femoral sites. Mean calcium intake at baseline was also similar but was considerably below recommended amounts (319 mg/d in the non-supplemented group vs. 364 mg/d in the supplementation group). BMD of the femoral neck was greater in the supplemented group at the end of the study ($p=0.23$), but there were no differences due to supplementation at the other sites examined. The authors concluded that women with a

low dietary calcium intake may benefit from the use of supplemental calcium while taking HT. [Study score = 1+]

The effect of vitamin D supplementation on biochemical parameters and BMD of 348 postmenopausal women (mean age 70 years) was studied by Ooms *et.al.* (1995) using a two-year randomized, placebo-controlled, double-blind protocol. The experimental group received 400 IU of vitamin D₃ per day while the control group was given a placebo. Current calcium intake was estimated by a questionnaire restricted to dairy products, which was noted to underestimate intake by 200-300 mg/d. There were no significant differences at baseline between the two groups in age, years since menopause, body weight BMI, BMD at two femoral sites and distal radius, or serum 25(OH)D. Mean calcium intake from dairy was also similar between the two groups (876 and 859 mg/d for the vitamin D and control groups, respectively). Vitamin D supplementation significantly increased serum 25(OH)D (from 27 nmol/L at baseline to 62 nmol/L) after one year (p=001). This parameter did not change in the placebo group. There was a parallel decrease in serum PTH during the same period (p=0.005). Vitamin D supplementation resulted in significantly improved bone retention at the left femoral neck (p=0.01) and the right femoral neck (p=0.001), but not at the right or left femoral trochanter or the distal radius. The authors concluded that vitamin D supplementation with 400 IU per day slightly decreased serum PTH and improved BMD at the femoral neck. [Study score = 1Ø]

Prince *et al.* (1995) studied the effect exercise and calcium supplementation from tablets or skim milk powder for two years on BMD in 168 postmenopausal (mean age ~63 years) women. The participants were randomized to receive a calcium supplement (1,000 mg/d in the form of calcium lactate-gluconate) with or without exercise (4-hours weight bearing exercise per week), a calcium supplement from skim milk powder (containing ~1,000 mg calcium) or a placebo. There were no differences at baseline between the four groups in any variable measured except that BMD at the femoral neck was greater ($p < 0.05$) in the milk powder group compared to the placebo group and the calcium and exercise group. Dietary calcium intake ranged from 778 mg/d in the milk powder group to 919 mg/d in the calcium and exercise group ($p > 0.05$). Discretionary calcium intake remained constant throughout the study except for a "significant but small" decrease in the milk powder group at 12 months (from 778 to 536 mg/d). Supplementation with either form of calcium resulted in significantly reduced loss of BMD at the trochanter, intertrochanter and ultradistal ankle site ($p < 0.05$) regardless of exercise compared to the placebo group. Calcium supplementation plus exercise resulted in diminished loss of BMD at the femoral neck ($p < 0.05$) compared to calcium supplementation alone. Spine BMD was maintained in all groups. The authors concluded that the data support the concept that a lifestyle regimen of increased dietary intake of calcium to ~1.8 g/d plus an exercise regimen of a 10% increase in the average exercise undertaken will significantly reduce bone loss at the clinically important hip site. [Study score = 10]

A continuation of the study by Reid *et al.* (1993) (discussed above in this section) was conducted to see if the significant effects of calcium supplementation at two years would

be sustained during an additional two year period (Reid *et.al.*, 1995). Eighty-six women out of 122 who completed the original study agreed to extend their participation for two years. Seventy-eight women (38 in the experimental group and 40 controls) completed the study. There were no significant differences between the two groups at baseline for age, years since menopause, weight, height, BMD at any site, physical activity or smoking incidence. Calcium intake from the diet was also similar (760 and 710 mg/d for the supplemented and control groups, respectively). There were sustained reductions in the rate of TBBMD loss throughout the 4-year study period ($p=0.002$) with bone loss significantly less in the calcium-treated subjects during years 2-4 ($p=0.02$). Bone losses at the lumbar spine and proximal femur were also significantly less in the supplemented group during the entire study ($p=0.03$) but the benefit occurred primarily during the first year. The authors concluded that calcium supplementation produces a sustained reduction in the rate of loss of total body BMD in healthy postmenopausal women.

[Study score = 1+]

Cepollaro *et.al.* (1996) conducted a randomized, placebo-controlled 13-month study among 45 early postmenopausal women (mean age = 52 years) who received one liter per day of calcium bicarbonate-containing mineral water (408 mg/L) or a low-calcium (80 mg calcium bicarbonate/L) placebo. There were no differences at baseline between the two groups in age, weight, height, BMI, years since menopause or BMD at the nondominant distal radius. Calcium intake was 1,510 mg/d in the experimental group and 949 mg/d in the control group ($p<0.001$). Energy intake was also higher in the experimental (2,020 kcal/d) compared to the control (1,893 kcal/d) group ($p<0.05$).

BMD of the distal radius was significantly higher in the experimental group at the end of the study ($p < 0.05$) and decreased significantly ($p < 0.001$) only in the placebo group. The authors concluded that this study provides evidence to support the use of a high calcium mineral water as an effective prophylaxis against postmenopausal bone loss. [Study score = 10]

Fujita *et al.* (1996) studied the effect of calcium supplementation with either 900 mg/d calcium carbonate or 900 mg/d oyster shell-seaweed calcium (AAA Ca, Fujix, Tokyo) for 24 months on BMD to 58 chronically hospitalized elderly (mean age = 80 years) patients living in Japan. This study will not be discussed in detail because the subjects do not reflect the healthy, U.S. elderly population. Nevertheless, the study found that supplementation with AAA Ca significantly improved BMD of the lumbar spine, but no effect was seen with calcium carbonate. The study has several serious limitations including a questionable randomization process and failure to report dietary and other baseline data. [Study score = 1-]

The effect of supplementing the diet of 2,578 healthy, elderly (mean age = 80 years) Dutch men and women with 400 IU of vitamin D₃ daily was reported by Lips *et al.* (1996). The study used a randomized, placebo-controlled, double-blind design with a period of supplementation of 3- 3.5 years with additional follow-up after supplementation to four years. There were no significant differences between the experimental and control groups in gender, age, ability to walk, exposure to sunshine or mean calcium intake (859 mg/d for the placebo group and 876 mg/d for the vitamin D group). Serum

25(OH)D increased significantly ($p=0.001$) among a 270-member subset of the participants after one year (from a mean of 27 nmol/L to 62 nmol/L). There was no change in this parameter in the placebo group. There was no significant difference in hip or other fracture incidence during the experiment between the two groups. The authors speculated that the relatively healthy status of their population affected the results. The study did not measure BMD or serum PTH so it is not possible to determine whether vitamin D supplementation affected bone mass or osteoporosis. [Study score = 1+]

Mizunuma *et.al.* (1996) studied the effect of low-dose calcium supplementation (600-800 mg/d of calcium lactate) with or without HT for ≥ 2 years on BMD among 19 postmenopausal women with depressed serum calcium concentrations. There were no significant differences between the calcium supplemented and the combination group at baseline for anthropometric or BMD data. Dietary intake data were not collected. The combination group had significantly greater BMD of the lumbar spine than the group with HT alone ($p<0.01$). Although this study provides evidence that calcium supplementation augments the effect of HT in postmenopausal women, it has limited applicability to the proposed claim because dietary data were not collected and the subjects do not reflect the healthy, U.S. population. [Study score = 1-]

Recker *et.al.* (1996) studied the effect of calcium supplementation (1,200 mg/d as calcium carbonate) for 4.3 years on BMD of 197 elderly (mean age = 73.5) women with and without a history of prevalent fractures whose habitual calcium intake was $<1,000$ mg/d. The study used a randomized, placebo-controlled, double-blind design. There

were no significant differences at baseline between the treatment and placebo groups. As expected, the women with history or prevalent fractures had significantly ($p < 0.002$) lower BMC than their non-fracture-prone counterparts. Mean calcium intake at baseline ranged from 386 mg/d in the nonprevalent/calcium group to 451 mg/d in the prevalent/calcium group ($p > 0.05$). Calcium supplementation prevented loss of forearm BMC in the prevalent fracture group, and change in this parameter was significantly different from the placebo group at the end of the study ($p < 0.001$). There was no difference between the treatment and placebo groups among subjects in the nonprevalent fracture group. Calcium supplementation did not reduce the risk of fractures in the nonprevalent group, but among prevalent fracture subjects, those in the calcium-supplemented group were 2.8 times less likely to experience a fracture than the controls ($p = 0.023$). The authors concluded that in elderly postmenopausal women with spine fractures and self-selected calcium intakes of < 1 g/d, a calcium supplement of 1.2 g/d reduces the incidence of spine fractures and halts measurable bone loss. [Study score = 1+]

Positive effects of daily supplementation with a combination of vitamin D (700 IU) and calcium (500 mg) on bone loss and fracture incidence among 389 elderly (mean age ~71 years) subjects were reported by Dawson-Hughes *et al.* (1997). This study used a three-year, randomized, placebo-controlled, double-blind design and included 213 women and 176 men ≥ 65 years of age. There were no differences in age, height, weight, smoking incidence, physical activity or BMD for the femoral neck, spine or total body at baseline. Calcium and vitamin D intakes were also similar between the two groups.

Supplementation with calcium and vitamin D had a significant positive effect on the change in BMD over three years at the femoral neck ($p=0.02$), spine ($p=0.04$), and total body ($p<0.001$) in all subjects. These changes were also significant for male subjects. The women in the supplemented group had significantly less total body bone mass (TBBM) loss ($p<0.001$) than those in the placebo group, but not in the spine or femoral neck. These differences tended to be more pronounced during the first year of the study, but significant differences in total change in body BMD occurred during years 2-3 of the study in both men ($p<0.001$) and women ($p=0.02$). There was also a reduced risk of a first non-vertebral fracture in the supplemented group (RR = 0.40; 95% CI, 0.2, 0.8). The supplemented group experienced a significant increase in serum 25(OH)D ($p<0.005$) and a parallel decrease in serum PTH ($p<0.005$) compared to the control group. The authors concluded that calcium and vitamin D supplementation leads to a moderate reduction in bone loss and may substantially reduce the risk of nonvertebral fractures among men and women 65 years of age or older who live in the community. [Study score = 1+]

Devine *et al.* (1997) reported follow-up data to a two-year calcium supplementation study (Prince *et al.*, 1995) discussed earlier in this section. All subjects at the conclusion of that two-year study were advised to take a daily calcium supplement (1,000 mg calcium lactate gluconate). Eighty-four subjects (mean age ~66 years) were available for examination after two years. These subjects included a "compliant" group ($n=14$) who had continued to take calcium supplements during entire four-year period, a control group ($n=21$) who had not taken supplements during this time and a "non-compliant" group ($n=49$) who had discontinued supplement use at the conclusion of the original

study. The control group was significantly heavier than the placebo group (72.9 kg vs. 62.3 kg; $p < 0.05$). Baseline calcium intake in the supplemented group (1,988 mg/d) was significantly greater ($p < 0.05$) than in the control (952 mg/d) or the non-compliant (981 mg/d) groups. There were no differences in BMD between the three groups at any site at the beginning of the original study. The compliant group had significantly less bone loss than the controls at the intertrochanteric ($p < 0.05$), trochanteric ($p < 0.05$), femoral neck ($p < 0.01$), total hip ($p < 0.01$), mid-tibia ($p < 0.05$), ultradistal tibia ($p < 0.05$) and the ankle ($p < 0.05$) after four years. In addition, subjects in the non-compliant group lost more bone at the mid-tibia ($p < 0.05$), ultradistal tibia ($p < 0.05$) and the ankle ($p < 0.01$) than subjects who continued to take calcium for the entire four-year period. There were no significant differences between the two groups for spine BMD. The authors concluded that calcium supplementation to a total of approximately two grams per day in women more than ten years post-menopause can arrest bone loss at the hip and ankle. [Study score = 10]

Graafmans *et al.* (1997) examined the effect the vitamin D receptor (VDR) genotype on BMD in vitamin D supplemented and non-supplemented subjects during a two-year study. Participants were 81 women (mean age = 78 years) and were randomly assigned to an experimental group (400 IU vitamin D/d) or a placebo group. The VDR genotype with respect to the *BsmI* restriction fragment length polymorphism was determined. Absence of the restriction site is indicated by "B" and presence by "b". There were no differences at baseline between the experimental and placebo groups, or between the three VDR genotypes for any of the parameters measured in the study. Dietary calcium

intake was 959, 894 and 956 mg/d for the BB, Bb and bb genotypes, respectively. The loss in BMD at the femoral neck was significantly reduced in the vitamin D group compared to the placebo group for the BB ($p=0.04$) and Bb ($p<0.01$) genotypes, but not for the bb VDR genotype ($p=0.61$). Vitamin D supplementation resulted in a significant increase in serum 25(OH)D in all groups ($p<0.01$) but serum PTH did not change for any genotype. The authors concluded that assessment of the VDR genotype might help explain the variance of BMD in response to vitamin D supplementation. [Study score = 10]

Komulainen *et al.* (1997) conducted a randomized, placebo-controlled, double blind study to determine the effect of vitamin D supplementation (300 IU/d) with or without HT for 2.5 years on BMD among 464 early postmenopausal (mean age ~52 years) women living in Finland. Vitamin D supplementation was not provided in the summer months (June – August) and the placebo group received 93 mg/d of calcium as calcium lactate. There were no significant differences in any of the parameters measured at the beginning of the study. Mean dietary calcium intake ranged from 802 mg/d in the HT group to 862 mg/d in the HT + vitamin D group. HT, either with or without vitamin D, was effective in preventing bone loss during the study and there were no significant differences between these two groups at the lumbar spine or femoral neck. Subjects in the vitamin D only and the placebo groups experienced similar ($p>0.05$) declines in BMD at both sites. The authors concluded that HT is an effective therapy for the prevention of osteoporosis, and that low-dose vitamin D supplementation has little effect on BMD in postmenopausal women. These results are not surprising given the relatively small dose

of vitamin D used. The paper did not provide data on serum 25(OH)D or PTH to ascertain the vitamin D status of the subjects. [Study score = 1+]

Bæksgaard *et.al.* (1998) studied the effect of supplementation with a combination of calcium and vitamin D and a combination of calcium and a vitamin D-containing multivitamin in a randomized, placebo-controlled, double-blind trial. The subjects were 240 healthy women (mean age = 62.5 years) studied for two years. There were no significant differences in baseline characteristics. Calcium intake was reasonably high at baseline (889, 1,003 and 863 mg/d in the calcium + vitamin D, calcium + multivitamin and the placebo groups, respectively). Analogous values for vitamin D were 4.0, 3.9 and 3.5 µg/d, respectively). There were no differences between the two active treatment groups for any parameter measured so the results from those two groups were combined for data analysis. Supplementation resulted in a significant increase in BMD of the spine at 12 months ($p < 0.01$) and two years ($p < 0.05$) compared to the placebo groups. There were no significant changes in the femoral neck or distal forearm. Serum PTH was significantly lower in the treatment groups at one year ($P < 0.001$) and at the end of the study ($p < 0.01$) compared to the control. The authors concluded that a positive effect of supplementation with calcium and vitamin D was seen in a group of elderly subjects even though they had fairly good initial calcium and vitamin D status. [Study score = 1+]

Ricci *et.al.* (1998) investigated the effect of calcium supplementation (1,000 mg/d as CCM) on biochemical parameters and BMD among 31 obese (mean BMI = 33) postmenopausal women (mean age = 58.3) consuming a moderate energy-restricted diet

for six months. Calcium intake at baseline was 706 mg/d in the treatment group and 602 mg/d in the placebo group. There were no significant differences between the two groups at baseline for any parameter measured. Calcium intake in the supplemented, weight loss group was 1,646 mg/d compared to 515 mg/d in the non-supplemented weight loss group. Serum PTH was significantly lower in the experimental group ($p < 0.05$) and loss of BMD tended to be lower in this group but did not reach statistical significance ($p < 0.08$). The authors concluded that calcium supplementation normalizes the increased calcium-PTH axis and elevated bone turnover rate observed during moderate energy restriction in postmenopausal women. The low number of subjects who completed this experiment and relatively short duration may have made it difficult to see an effect of calcium supplementation. [Study score = 1Ø]

The effect of calcium supplementation (1,600 mg elemental calcium as the citrate salt) on BMD was measured in a 4-year randomized, placebo-controlled, double-blind study among 177 postmenopausal women (mean age 66 years) by Riggs *et al.* (1998). Calcium intake at baseline was 711 mg/d in the calcium-supplemented group and 717 mg/d in the placebo group. There were no significant differences between the two groups in any variable measured. There was significantly less bone loss at the spine ($p < 0.001$), proximal femur ($p = 0.002$) and total body ($p = 0.003$) for the treatment vs. control group at one year. These changes persisted in the proximal femur ($p = 0.016$) and total body ($p = 0.019$), but not the spine ($p = 0.127$) after four years of supplementation. There were no differences in fracture incidence between the two groups, but the study was not powered to detect such an effect in this lower risk population. The authors concluded

that calcium supplementation to elderly women partially decreases bone loss. [Study score = 1+]

Storm *et.al.* (1998) studied the effect of calcium intake from diet (primarily from milk) or a supplement (calcium carbonate) on BMD and markers of bone turnover during a two year period among 53 elderly (mean age ~71 years) women living in northern Maine. The study used a randomized, placebo-controlled, single-blind design and collected data during both the summer and winter months. There were no significant differences between the two treatment groups or the placebo group at baseline in any of the characteristics examined. Baseline calcium intake was 699 mg/d in the placebo group, 603 mg/d in the calcium group and 644 mg/d in the dietary group. Calcium supplementation was provided as two 500-mg doses of calcium carbonate per day, and the dietary group was given four eight-ounce glasses of milk per day. Mean intake of calcium during the study did not change for the placebo group (699 mg/d) but increased significantly ($p < 0.01$) for the dietary (1,052 mg/d) and the supplementation group (1,678 mg/d). At the end of the study subjects in the calcium carbonate group had significantly greater BMD at the spine ($p < 0.01$) and greater trochanter ($p < 0.02$) than the dietary or placebo groups. Femoral bone loss in the placebo group occurred exclusively during the two winters of the study. The authors concluded that calcium supplementation of 1,000 mg/d was adequate prophylaxis against wintertime femoral bone loss in elderly postmenopausal women. [Study score = 1+]

A study by Tuppurainen *et.al.* (1998) found that HT therapy combined with vitamin D supplementation (300 IU/d) was more effective in increasing BMD in osteoporotic women than vitamin D alone. However, this study will not be discussed in detail because it does not reflect a segment of the healthy human population. [Study score = 1Ø]

Krieg *et.al.* (1999) studied the effect of combined daily calcium (1,000 mg elemental calcium as calcium carbonate) and vitamin D (880 IU) supplementation on bone mass among 124 very old (mean age 84.5 years) institutionalized women during a 2-year randomized, controlled study. The treatment group (n = 50) was provided with the supplemental nutrients as two daily doses and the control group was unattended (i.e. a placebo was not used). Bone mass was measured using quantitative ultrasound (QUS) measurements. There was no information provided on baseline calcium or vitamin D intakes however mean serum 25(OH)D was low (11.9 µg/L) and serum PTH was in the normal range (44 ng/L). The treatment group experienced a significant increase in serum 25(OH)D at one (p<0.01) and two (p<0.01) years compared to the controls. Parallel decreases in serum PTH were also observed at both one and two years (p<0.01).

Broadband ultrasound attenuation (BUA), a measure of QUS was significantly higher in the supplemented group compared to the controls (p<0.01), but a second QUS measure, speed of sound (SOS) was not. This paper supports the contention that supplemental vitamin D and calcium results in improved bone mass, and suggests that QUS is a valid method for estimating this parameter in human subjects. [Study score = 1+]

A short-term study (12 weeks treatment) using 31 healthy elderly women (mean age 70 years) compared the effects of estrogen treatment (0.5 mg/d micronized 17 β -estradiol) with and without a combination of 1,500 mg calcium (from calcium carbonate) and 800 IU vitamin D per day on markers of bone formation and resorption (Prestwood, *et al.*, 1999). The study used a randomized, placebo-controlled, open-label design. The study did not measure BMD or other indicators of bone health, but found that markers of bone resorption (e.g. urinary cross-linked C-telopeptides) decreased incrementally when calcium/vitamin D supplementation was added to estrogen therapy. Markers of bone formation decreased with calcium/vitamin D treatment, but not with subsequent estrogen treatment. The authors concluded that low dose estrogen plus calcium/vitamin D therapy is likely to be more effective in older women than either treatment alone. Although this short-term study did not measure the effect of treatment on osteoporosis directly, it suggests that supplementation with calcium and vitamin D has a positive influence on bone dynamics in elderly women that is consistent with reduced risk of osteoporosis.

[Study score = 1+]

Dawson-Hughes *et al.* (2000) reported a two-year follow-up study of 295 healthy, elderly subjects who had participated in a three-year calcium and vitamin D supplementation trial (Dawson-Hughes *et al.*, 1997) (see discussion above in this section). The original study found that supplementation improved skeletal parameters, and the purpose of the follow-up study was to determine if these changes persisted after supplementation was discontinued. Baseline calcium intake was lower in the women who had previously been treated with vitamin D and calcium compared to the former placebo group (686 and 821

mg/d, respectively; $p=0.029$), however this difference became smaller during the follow-up study and became statistically insignificant. No other parameters investigated (including dietary vitamin D) were different between the former treatment and control groups at the beginning of the follow-up period. There were also no significant differences between these groups with respect to medications known to affect BMD (e.g. HT) or use of supplemental calcium or vitamin D. TBBMD in the male subjects, but not in females, was still significantly higher ($p<0.05$) at the end of the two-year follow-up period in the former treatment group compared to the controls, but there were no differences at any other bone site for men or women. The authors concluded that discontinued use of calcium and vitamin D supplementation has limited cumulative effect on bone loss in elderly men and women. This study suggests adequate vitamin D and calcium intake must be maintained on an ongoing basis to ensure optimal bone health.

[Study score 1+]

The effect of vitamin D supplementation (800 IU cholecalciferol/d) for two years on bone mass among 79 postmenopausal monozygotic female twin pairs (mean age = 58.7 years) was reported by Hunter *et.al.* (2000). The subjects were randomized to the treatment group or a placebo control group using a double-blind protocol. There were no differences between the groups at baseline in any of the characteristics measured. Mean calcium intake was estimated by FFQ and found to be close to recommended amounts in both groups (1,084 mg/d in the supplemented group and 1,026 mg/d for controls). Baseline vitamin D intakes (~ 135 IU/d) and serum 25(OH)D (~ 28 $\mu\text{g/L}$) were the same for both groups. Serum 25(OH)D increased by 57% and was significantly different (p

value not provided) from the placebo group, which increased by 15% after 24 months. There were no changes in serum PTH throughout the study. There were no significant differences between the treatment and control groups for BMD at any site measured. The calcium replete status of these relatively young, healthy postmenopausal women, or the fact that vitamin D supplementation was given without calcium may have contributed to the negative results of this study. [Study score = 1+]

Iwamoto *et.al.* (2000) studied the effect of supplementation with 0.75 μ g/d of an activated form of vitamin D₃ (1 α -hydroxyvitamin D₃) with or without vitamin K (45 mg/d as menatetrenone) on BMD of 92 osteoporotic women who were more than 5 years postmenopausal. The study found that supplementation with this vitamin D analogue had positive effects on BMD compared to a diet calcium supplementation alone with or without vitamin K. However, this study will not be summarized in detail because the subjects used were osteoporotic women and the results cannot be generalized to the normal, healthy population. [Study score = 1Ø]

The effect of supplementation with calcium (750 mg/d as CCM) or 25-(OH)D₃ (5 μ g/d) for four years on bone loss among 316 women and 122 men age (mean age ~75 years) was studied by Peacock *et.al.* (2000) using a randomized, placebo-controlled, double-blind protocol. The subjects were randomized to one of 16 strata by age, gender, serum 25(OH)D, and dietary calcium intake (<480 mg/d and \geq 480 mg/d). Subjects were then assigned to receive supplementation with calcium, 25-(OH)D₃ or a placebo. The male subjects were significantly taller, heavier, older, and had greater calcium intake,

TBBMD, BMD at three sites and several other skeletal and biochemical parameters than the women ($p < 0.01$). There were no significant differences among the experimental or control groups for any of these parameters. There were no significant differences between men and women in response to supplementation so the data were combined for subsequent analyses. Calcium supplementation resulted in significantly higher BMD after four years at the total hip ($p < 0.008$) and lumbar spine ($p < 0.02$) compared to the placebo group. Similar results for TBBMD approached significance ($p < 0.08$). The effects of 25-(OH) D_3 supplementation were intermediate compared to the other two groups, but were not statistically significant from the placebo group. In subjects with calcium intakes less than the median intake (716 mg/d), there was a positive relationship between serum 25(OH)D and change in total hip BMD (< 0.06) and a negative relationship with the change in serum PTH ($p < 0.001$). In subjects with calcium intakes above this amount, these relationships were absent and significantly different for BMD ($p < 0.007$) and PTH ($p < 0.001$) compared to subjects with lower calcium intakes. The authors concluded that a calcium supplement that increases calcium intake close to the Adequate Intake (AI) of 1,200 mg/d prevents bone loss at the hip and at other skeletal sites and has beneficial effects on bone structure at the upper femur. The effect of vitamin D supplementation is less marked and is most beneficial in subjects who are vitamin D and calcium insufficient. [Study score = 1+]

Sosa *et.al.* (2000) reported that supplementation with 0.622 mg (10,640 IU) per week of 25-hydroxycholecalciferol and 1,000 mg calcium/d for one year resulted in significantly increased BMD in the femoral neck among 58 postmenopausal (mean age ~78 years)

women with osteoporosis compared to calcium supplementation alone. This study will not be discussed in detail because the results cannot be generalized to the healthy U.S. population. [Study score = 1+]

The short-term effect (7-10 days) of consuming three servings per day of yogurt or a "jelled fruit flavored snack" on a marker for bone resorption (N-telopeptide (TNx)) among 29 postmenopausal white women (mean age 61 years) was reported by Heaney *et.al.* (2002). The subjects had habitually low calcium intakes (<600 mg/d) and were not taking estrogen or supplemental calcium. The subjects were randomized to one of the treatment groups for 7-11 days and crossed-over to the other group after a two-week washout period. Three servings of jelled snack or yogurt were consumed during the intervention periods and no further dietary restrictions were imposed. Urinary TNx was significantly reduced in the yogurt regimen ($p < 0.03$) compared to the jelled snack. This finding indicates a rapid, diet-induced reduction in bone resorption in response to yogurt. Calcium intake during the yogurt period was 1,259 mg/d compared to the jelled snack period (356 mg/d). The yogurt also contributed protein, riboflavin, vitamin B₁₂ potassium, magnesium and zinc compared to the fruit snack. This study shows that yogurt containing 900 mg of calcium as well as other nutrients characteristic of dairy products can have rapid effects on bone resorption. While this study does not provide direct evidence on the effect of dairy/calcium intake on BMD or other markers of osteoporosis, it is consistent with the premise that calcium intake has a positive effect on the skeleton and is consistent with the proposed claim. [Study score = 1Ø]

Jensen *et al.* (2002) studied the effect providing a dietary supplement with a combination of calcium (1,450 mg/d; form not provided) and vitamin D (400 IU), a multi-vitamin/mineral mix containing the same amount of calcium and vitamin D or dietary instructions aimed at increasing calcium intake through foods. The subjects were 99 healthy postmenopausal women (mean age 66 years) randomized to one of the three treatments noted above and followed for three years. A placebo group was not employed because withholding calcium supplementation from the subjects for the length of the study raised ethical concerns. There were no significant differences between the groups with respect to age, time since menopause, BMI, smoking, physical activity score, BMD at three sites, TBBMD or several biochemical parameters. Baseline intake of protein, vitamin D and zinc were also similar, but the calcium + vitamin D group had significantly lower calcium intake (672 mg/d; $p=0.03$) than the multinutrient (831 mg/d) or the dietary instruction (dietary control) group (871 mg/d). Calcium intake increased significantly after baseline in the dietary control group to 1,242 mg/d ($p<0.001$) and remained significantly greater than baseline throughout the study. Dietary calcium intake did not change in the supplementation groups after baseline, but total calcium (including that provided by the supplements) increased to approximately 2,150 mg/d in the calcium + vitamin D group and to approximately 2,300 mg/d in the multinutrient group. There were no significant changes in BMD at any site measured. Serum 25(OH)D increased significantly from baseline in the calcium + vitamin D group ($p<0.05$ after one year and $p<0.0001$ after three years), and in the multinutrient group ($p<0.001$ after one year and $p<0.0001$ after four years) but did not change in the dietary control group. Serum PTH decreased significantly in the two supplementation groups after one year ($p<0.05$), but

was no longer different than baseline for the remainder of the study. The authors concluded that the beneficial effect of nutrient interventions in bone health can be achieved through dietary or supplementation approaches. The lack of difference in BMD between the dietary control and supplementation groups was probably due to the high baseline intake of calcium, which may have been above a threshold for additional effects on bone. The small size of the study may also have been a factor. [Study score = 10]

Meyer *et.al.* (2002) conducted a randomized, placebo-controlled, double-blind trial to study the effect of supplementing 1,144 elderly (mean age 84.7 years) nursing home residents (~75% female) with vitamin D (10µg/d) on fracture incidence and biochemical parameters during a two year period. The treatment group was provided with a daily dose of cod liver oil and the placebo group was given the same oil with the vitamin D removed. There were no differences between the groups at baseline in any of the parameters measured. Calcium intake was estimated using a questionnaire designed to measure the intake of cheese and milk filled out for each subject by the nursing staff. Calcium intake was 446 mg/d in the supplementation group and 456 mg/d in the control group ($p>0.05$). The study did not measure BMD or other parameters of bone health. Fracture incidence did not differ between the two groups at any site during the study. The authors concluded that supplementation with vitamin D alone does not reduce the risk of fractures among frail elderly. The authors pointed out that previous studies using a combination of calcium and vitamin D were effective in this regard. It is also possible that the relatively low dose of vitamin D used in this study was inadequate to cause a positive effect. [Study score = 1+]

A randomized, placebo-controlled, double-blind study with 126 osteoporotic women (mean age ~53 years) found that supplementation with 1 µg/d of 1α-hydroxyvitamin D₃, with or without vitamin K (45 mg/d menaquinone) resulted in significant improvements in BMD compared to non-supplemented controls (Ushiroyama *et.al.*, 2002). However, this study will not be discussed in detail because it does not reflect the healthy, U.S. population. [Study score = 1Ø]

Chee *et.al.* (2003) studied the effect of supplementing the diet with 1,200 mg calcium/d (from skim milk powder) for two years on BMD among 173 postmenopausal (at least 5 years) women (mean age = 59 years) using a randomized, controlled protocol. The treatment group consumed the skim milk powder reconstituted with 400 ml water. The supplement contained 1,200 mg calcium, 10 µg vitamin D₃, 750 mg phosphorus, 70 mg magnesium, 17.8 g protein and 170 kcal. The control group continued to consume their habitual diet after randomization and did not receive a placebo. There were no significant differences between the two groups in any of the anthropometric or lifestyle variables measured. Dietary calcium as measured by FFQ was 523 and 500 mg/d in the treatment and control groups, respectively ($p > 0.05$). Compared to the milk group, the control group had significantly greater TBBMD ($p < 0.05$) and BMD at the femoral neck (0.79 g/cm^2 for the milk group vs. 0.84 g/cm^2 for controls; $p < 0.001$) and total hip (0.84 vs. 0.90 g/cm^2 ; $p < 0.001$). The experimental group increased BMD at the femoral neck compared to a net loss in the control group ($p < 0.01$) and lost significantly less bone at the lumbar spine ($p < 0.05$), total hip ($p < 0.01$) and total body ($p < 0.001$) compared to the controls. The authors concluded that consuming a high-calcium diet from skim milk was

beneficial in slowing down bone loss in postmenopausal Chinese women in Malaysia. This study provided calcium and vitamin D in the form of skim milk so that it is not possible to attribute the positive effects to these nutrients *per se*. Nevertheless, the study provides suggestive evidence in support of the proposed claim. [Study score = 1Ø]

The effect of supplementing the diet with calcium (500 mg/d as calcium carbonate) and vitamin D (400 IU/d) for one year on BMD among 192 elderly (mean age ~74 years), vitamin D deficient (serum 25(OH)D = 7.0 ng/ml) women was studied using a randomized, placebo-controlled, double-blind protocol (Grados *et.al.*, 2003). There were no differences in age or BMI between the two groups at baseline. Mean calcium intake was low in both groups (697 vs. 671 mg/d in the treatment and control groups, respectively) as was the intake of vitamin D (67 vs. 62 IU/d, respectively). The supplemented group lost significantly less bone for the whole body ($p=0.01$), lumbar spine ($p=0.0009$), femoral neck ($p=0.015$) and trochanter ($p=0.015$) compared to the placebo group at the end of the study. The authors concluded that elderly female outpatients living in France have a high prevalence of calcium and vitamin D deficiency, and that supplementation with these nutrients corrects the deficiency, slows bone remodeling and increases BMD. This study demonstrates that supplementing the diet of vitamin D-deficient individuals with a combination of vitamin D and calcium has a beneficial effect on bone health, but 46.1 percent of the subjects had osteoporosis and, therefore, did not reflect the healthy U.S. population. [Study score = 1+]

Cooper *et.al.* (2003) compared the effect of calcium supplementation (1,000 mg/d from calcium carbonate) with or without vitamin D₂ (10,000 IU/wk) for two years among 187

postmenopausal (mean age ~56 years) women. The study used a randomized, double-blind protocol, but a placebo group was not included. There were no significant differences in any of the characteristics measured in the study at baseline. Mean dietary calcium was 811 mg/d in the calcium group and 754 mg/d in the calcium + vitamin D group at baseline. Analogous data at 12 months were 825 and 836 mg/d, respectively. Both groups experienced significant increases in BMD at the trochanter and Ward's triangle ($p < 0.005$) and significant decreases at the proximal radius and ulna ($p < 0.005$) at the end of the study compared to baseline. There were no differences between the two groups. These data suggest that calcium and vitamin D supplementation may have had a beneficial effect at the hip, but the lack of a placebo control makes such a conclusion speculative. The lack of an effect of vitamin D supplementation in addition to calcium is likely due to the replete status of the subjects. Serum 25(OH)D concentrations in the calcium group and the calcium + vitamin D groups at baseline were 82.6 and 81.6 nmol/L, respectively. [Study score = 10]

Trivedi *et al.* (2003) conducted a randomized, placebo-controlled, double-blind study to examine the effect of providing 100,000 IU of vitamin D₃ orally every four months on fracture incidence among 2,037 men and 649 women (mean age = 75 years). The intervention period was five years. There were no significant differences between the treatment and placebo groups at baseline in any of the variables measured. Mean calcium intake was 742 mg/d. Supplementation resulted in a lower rate of age-adjusted first fracture at any site (RR=0.78; 95% CI, 0.61, 0.99) and at the hip, wrist, forearm or vertebra (RR=0.67; 95% CI, 0.48, 0.93). The effect tended to be more pronounced in

women than in men. The authors concluded that four monthly supplementation with 100,000 IU oral vitamin D may prevent fractures without adverse effects in men and women living in the general community. [Study score = 1+]

Harwood *et.al.* (2004) studied the effect of vitamin D and calcium supplementation among 150 elderly (mean age = 81 years) formerly independent hip fracture victims. The subjects were randomized to a no-treatment group (no placebo was used) or one of three intervention groups: a single injection of 300,000 IUs vitamin D₂, injected vitamin D₂ plus 1,000 mg/d oral calcium (from calcium carbonate) or the same dose of calcium combined with 800 IU of vitamin D₃ per day. This study does not reflect the healthy, U.S. population and will not be discussed in detail, but the vitamin D and calcium supplementation had significant positive effects on BMD during the one-year follow-up period. The authors concluded that vitamin D supplementation, either orally or with injected vitamin D, suppresses PTH, increases BMD and reduces falls. [Study score = 10]

3. Summary and conclusions

The observational studies discussed in this section are generally consistent with the premise that adequate dietary calcium and vitamin D status and are associated with reduced risk of osteoporosis in elderly male and female subjects.

Six prospective studies that looked exclusively at dietary calcium provided direct or suggestive evidence of a protective association between this nutrient and bone health in

older men or women (Davis *et.al.*, 1995; Devine *et.al.*, 1995; Fujiwara *et.al.*, 1997; Burger *et.al.*, 1998; Pines *et.al.*, 1999; Huuskonen *et.al.*, 2001). In addition, four prospective cohort studies that reported data on both vitamin D and calcium provided direct or suggestive evidence of an association between calcium and skeletal parameters in elderly men or postmenopausal women (Ensrud *et.al.*, 2000; del Puente *et.al.*, 2002; Feskanich *et.al.*, 2003; Macdonald *et.al.*, 2004).

However, several prospective studies failed to find such an association. Van Beresteijn *et.al.* (1990) did not find an association between dietary calcium and BMD in a small cohort of postmenopausal women, but more than 80% of the subjects were consuming ≥ 800 mg calcium per day. Looker *et.al.* (1993) reported protective RR's of 0.52 in males and 0.53 in females for hip fracture incidence based on calcium intake, but these associations were not statistically significant. This study used a single 24-hour diet recall to estimate calcium intake and does not reflect habitual consumption of this nutrient. Cummings *et.al.* (1995) did not find an association between calcium intake or HT and fracture risk in a cohort of 9,516 white women aged ≥ 65 years, but BMD was not measured. Hosking *et.al.* (1998) also failed to find a positive result, but subjects with low calcium intakes in this cohort were advised to take supplemental calcium, which may have biased the results. Cumming *et.al.* (1997) found a *positive* association between calcium intake and fracture incidence in a cohort of 9,704 postmenopausal women. The authors were unable to explain these results but concluded that they were most likely due to inadequately controlled confounding variables. Hannan *et.al.* (2000) were also surprised by not finding a correlation between calcium intake, physical activity or serum

25(OH)D and bone loss among 800 elderly members of the Framingham cohort and speculated that the follow-up period used for the study may have been inadequate.

The case-control studies conducted in elderly men or postmenopausal women were of marginal quality and provided mixed results. Cumming and Klineberg (1994) found low calcium intake to be a risk for hip fracture but the quality of the study was poor. Johnell *et.al.* (1995) also reported a protective association between calcium intake (and sunlight exposure) in a 14-center study conducted in Europe, and Stracke *et.al.* (1992) found similar evidence. Chan *et.al.* (1996) found that low calcium intake was associated with vertebral fractures among elderly Chinese women. Finally, Kanis *et.al.* (1999) reported a protective effect on fracture incidence of cheese consumption but not milk intake among a group of Europeans.

The remaining case-control studies did not find evidence of a protective association between calcium intake and fracture incidence, but the quality of these studies was poor. Lips *et.al.* (1987) used fewer controls than cases, Tavani *et.al.* (1995) used an inadequate dietary assessment instrument, and Ramalho *et.al.* (2001) also used a limited number of controls and cursory dietary data.

The cross-sectional studies with respect to calcium and bone mass among older subjects provided consistent evidence of a positive association. Studies that reported direct or suggestive evidence of such associations were Hu *et.al.* (1993), Murphy *et.al.* (1994), Soroko *et.al.* (1994), Stone *et.al.* (1996), Ulrich *et.al.* (1996), Kiel *et.al.* (1997),

Michaëlsson *et.al.* (1997), Suleiman *et.al.* (1997), Uusi-Rasi *et.al.* (1998), Aptel *et.al.* (1999), Nguyen *et.al.* (2000) and Ilich *et.al.* (2003).

Only two of the cross-sectional studies reviewed in this section failed to find an association between dietary calcium and bone health. However, Hoover *et.al.* (1996) used a cohort of women with high mean calcium intakes (1,392 mg/d) and the study by Turner *et.al.* (1998) had numerous methodological constraints (e.g. inadequate dietary data) and did not adjust for potentially confounding variables.

The randomized clinical trials that studied calcium supplementation without vitamin D, provide consistent and compelling evidence that supplementation with this mineral reduces the loss of bone mass and/or fracture incidence in elderly men and postmenopausal women.

Studies that found a protective effect of calcium supplementation (without vitamin D) on bone health were: Reid *et.al.* (1993), Elders *et.al.* (1994), Chevalley *et.al.* (1994), Strause *et.al.* (1994), Fujita *et.al.* (1995), Haines *et.al.* (1995), Prince *et.al.* (1995), Reid *et.al.* (1995), Cepollaro, *et.al.* (1996), Fujita *et.al.* (1996), Mizunuma *et.al.* (1996), Recker *et.al.* (1996), Devine *et.al.* (1997), Riggs *et.al.* (1998), Storm *et.al.* (1998) and Heaney *et.al.* (2002). Only the study of Ricci *et.al.* (1998) failed to report such an effect, but this study was conducted in obese women on weight reducing diets and used a very short (six months) duration.

The literature discussed above clearly shows that adequate dietary calcium reduces the risk of osteoporosis in elderly men and postmenopausal women. The following studies support the premise that vitamin D, especially when combined with adequate dietary calcium, also provides this health benefit.

The prospective observational studies that monitored dietary intake or nutritional status of vitamin D in older subjects provide reasonable evidence of a positive association with bone mass. Studies that reported positive results were: Rosen *et.al.* (1994), Ensrud *et.al.* (2000), del Puente *et.al.* (2002) and Feskanich *et.al.* (2003). Cumming *et.al.* (1997) and Macdonald *et.al.*, (2004) did not find protective associations between vitamin D intake and bone mass, but data on serum 25(OH)D were not provided. As noted earlier, the study by Hannan *et.al.* (2000) failed to detect an association between any nutritional factor (including vitamin D and calcium) in the Framingham cohort.

The case-control studies reviewed in this section consistently support an association between vitamin D intake or status and reduced fracture risk in elderly subjects. The majority of studies found a positive result with respect to either vitamin D status or exposure to sunlight (von Knorring *et.al.*, 1981; Olivieri *et.al.*, 1986; Lips *et.al.*, 1987; Lamberg-Allardt *et.al.*, 1989; Lau *et.al.*, 1989; Johnell *et.al.*, 1995; Kanis *et.al.*, 1999). In addition, Ranstam and Kanis (1995) did not see an association between use of vitamin D supplements and fracture incidence among all of the subjects in their study, but did observe such an association among participants with BMIs <20. Dietary intake of vitamin D was not measured in this study.

One case-control study (Rudman *et.al.*, 1989) found a *positive* association between vitamin D status (i.e. serum 25(OH)D) and fracture risk, but the study had many limitations. The authors speculated that the association was due to a lack of conversion of 25(OH)D to 1-25-(OH)₂D in their subjects.

Both cross-sectional studies reviewed in this section (Aguado *et.al.*, 2000; Bischoff-Ferrari *et.al.*, 2004a) reported positive associations between serum 25(OH)D and BMD.

The randomized intervention trials that studied both vitamin D and calcium supplementation (either individually or as a combined supplement) provided very consistent evidence that one or both of these nutrients has a positive effect on bone health. All of the studies that provided supplementation of these nutrients in combined form reported direct evidence of a positive effect on bone health (Chapuy *et.al.*, 1992, 1994; Aloia *et.al.*, 1994; Dawson-Hughes *et.al.*, 1997; Bæksgaard *et.al.*, 1998; Krieg *et.al.*, 1999; Prestwood *et.al.*, 1999; Dawson-Hughes *et.al.*, 2000; Sosa *et.al.*, 2000; Chee *et.al.*, 2003; Grados *et.al.*, 2003). Three studies provided vitamin D and calcium supplementation separately. Peacock *et.al.* (2000) found that vitamin D supplementation had an intermediate effect between calcium supplementation and a placebo. Harwood *et.al.* (2004) found that vitamin D supplementation resulted in improved BMD among fracture victims and that co-supplementation with calcium enhanced the effect, and Jensen *et.al.* (2002) found that increasing intake of calcium and vitamin D through supplementation or diet had positive effects on markers of bone remodeling and calciotropic hormones.

Dietary intervention studies with vitamin D alone are less consistent than studies that employed a combination supplement, but still provide compelling support for the proposed claim. Studies that reported direct or suggestive evidence that vitamin D supplementation have a positive effect on bone health are: Dawson-Hughes *et.al.* (1991), Chapuy *et.al.* (1992), Ooms *et.al.* (1995), Graafmans *et.al.* (1997), Tuppurainen *et.al.* (1998), Iwamoto *et.al.* (2000), Ushiroyama *et.al.* (2002) and Trivedi *et.al.* (2003).

Other intervention studies did not find a positive effect of vitamin D supplementation. Lips *et.al.* (1996) did not find an effect on fracture rates among healthy Dutch men and women, but the dose of 400 IU of vitamin D₃ may not have been sufficient to prompt a significant response in this relatively calcium replete population. Komulainen *et.al.* (1997) did not find an additional benefit to vitamin D supplementation in conjunction with HT, but, once again, the dose used (300 IU) may not have been sufficient. Hunter *et.al.* (2000) found no effect of vitamin D supplementation among 79 postmenopausal twin pairs. The subjects were consuming a diet high in calcium (>1,000 mg/d) and the authors speculated that the calcium replete status of the population may have mitigated against an effect of vitamin D. Meyer *et.al.* (2002) did not find an effect on fracture incidence with supplementation of 10 µg vitamin D per day from cod liver oil to nursing home residents. It is possible that the dose was inadequate to cause an effect. This study did not measure vitamin D status of the subjects. Finally, Cooper *et.al.* (2003) also did not find a positive effect of vitamin D supplementation, but the subjects in this study (187 postmenopausal women) were replete in vitamin D status at baseline.

In conclusion, as noted earlier, the studies reviewed in this section provide strong evidence in support of the proposed claim.

E. META-ANALYSES

The conclusion that adequate vitamin D and/or calcium intake can increase bone mineral density in young people, reduce bone loss in older people and/or reduce fracture incidence is also supported by several meta-analyses.

Welten *et al.* (1995) conducted a meta-analysis of 33 well-designed observational and intervention trials designed to study the impact of calcium intake on bone density in young and middle aged males and females. Pooled results from 29 observational studies showed a positive correlation coefficient ($p < 0.05$) for calcium intake and bone mass in premenopausal women 18 to 50 years of age. The intervention trials also showed a significant positive effect. The authors concluded, "...the studies published to date seem to offer overall evidence that calcium intake is positively associated with bone mass in premenopausal females. This association is fairly consistent across the different study designs and is strengthened by the fact that the results are based only on studies with a high methodological quality." There were not enough studies published using male subjects to make a definitive conclusion.

A meta-analysis of 16 observational studies on the association of calcium intake and fracture incidence in postmenopausal women was conducted by Cumming and Nevitt (1997). Pooled data gave an odds ratio of 0.96 (95% CI, 0.93, 0.99) per 300 mg/d

increase in calcium intake with respect to fracture incidence. The authors conclude, "This review supports the current clinical and public health policy of recommending increased calcium intake among older women for fracture prevention."

Nieves *et.al.* (1998) conducted a meta-analysis of clinical trials among postmenopausal women to determine whether calcium supplementation augments the effect of estrogen or calcitonin (a polypeptide hormone that decreases bone resorption and bone loss) on bone density. An analysis of 31 trials showed that combined use of calcium and estrogen resulted in significantly greater bone mass at the femoral neck ($p=0.04$) and forearm ($p=0.04$). The authors concluded, "...a high calcium intake potentates the positive effect of estrogen on bone mass at all skeletal sites and perhaps that of calcitonin on bone mass of the spine."

Weatherall (2000) conducted a meta-analysis of 28 intervention trials to determine whether older people with fractures of the proximal femur have lower vitamin D status than normal controls. The pooled reduction in serum 25(OH)D for the fracture group compared to controls was 0.66 of a standard deviation (95% CI, 0.74, 0.59). The authors concluded, "...there is very good evidence that older people with fracture of the proximal femur have reduced levels of vitamin D compared to controls. Older people with fracture of the proximal femur should be treated with vitamin D."

A meta-analysis designed to assess the effect of vitamin D treatment in preventing osteoporosis in postmenopausal women was conducted by Papadimitropoulos *et.al.*

(2002). The analysis included 25 randomized trials that used standard or hydroxylated vitamin D with or without calcium. Vitamin D reduced the incidence of vertebral fractures (RR=0.63; 95% CI, 0.45, 0.88) and showed a trend to a reduction of nonvertebral fractures (RR=0.77; 95% CI, 0.57, 1.04). The authors concluded, "Vitamin D decreases vertebral fractures and may decrease nonvertebral fractures. The available data are uninformative regarding the relative effects of standard and hydroxylated vitamin D."

Shea *et al.* (2002) conducted a meta-analysis of 15 randomized trials of calcium supplementation to postmenopausal women. The pooled difference in percentage change in BMD from baseline was 2.05% (95% CI, 0.24, 2.39) for the total body, 1.66% (95% CI, 0.70, 2.57) for the lumbar spine, 1.65% (95% CI, 0.70, 2.57) for the hip and 1.91% (95% CI, 0.33, 1.72) for the distal radius. There was not a significant effect of calcium supplementation on vertebral or nonvertebral fractures. The authors concluded, "We found calcium to be more effective than placebo in reducing rates of bone loss after two or more years of treatment."

A meta-analysis of 12 observational studies (four prospective cohort and eight cross-sectional) on the association between dietary calcium from foods and fractures in women was conducted by Xu *et al.* (2004). Pooled analysis of the ten studies that measured hip fracture found no significant associations with calcium intake (RR=1.01; 95% CI, 0.96, 1.07). The authors observed that the relatively high baseline calcium intakes seen in most of the studies may have overshadowed a modest effect of dietary calcium and suggested

that calcium from foods may have a protective effect if calcium intakes are below a certain threshold. This meta-analysis did not consider the association between calcium intake and BMD.

F. OVERALL CONCLUSIONS – SIGNIFICANT SCIENTIFIC AGREEMENT

FDA's guidance "Interim Evidence-based Ranking System of Scientific Data" specifies that meeting the SSA standard requires consistent support of the highest quality studies available. A list of the studies for each age segment that were given a "+" quality rating are presented in Tables 2 through 4. Table 2 identifies the studies that investigated calcium alone, Table 3 includes studies that investigated only vitamin D and Table 4 lists studies that examined both vitamin D and calcium. The percentage of such studies that provided direct support for the proposed claim is presented in Table 5.

The BIHW strongly believes that the totality of available science warrants expanding the existing health claim to include vitamin D, and to remove qualifying language regarding age, gender, race and physical activity. We believe that the streamlined claim, "Adequate vitamin D and calcium may reduce the risk of osteoporosis in later life," meets the standard for SSA, would more effectively communicate this important public health message to *all* American consumers, and would be more likely to be used by food manufacturers than the existing claim. Our rationale for this conclusion is presented below:

Table 2
Calcium studies assigned a high quality ("+") rating

| Age segment | Study design type | | | |
|------------------------------------|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Prepubescent children | Johnston (92) Bonjour (97) Dibba (00) Bonjour (01) | Barr (01) | - | Ruiz (95) VandenBergh (95) <i>Tsukahara (97)</i> Wang (97) Hoppe (00) Black (02) |
| Adolescent children | Johnston (92) Lloyd (93) Lloyd (96) Nowson (97) Bonjour (01) Rosen (01) Stear (03) | Wang (03) | | Ruiz (95) Moro (96) Wang (97) <i>Kardinaal (99)</i> <i>Maggiolini (99)</i> Elgán (02) |
| Adult men & premenopausal women | Shapses (01) | Recker (92) <i>Feskanich (97)</i> <i>Owusu (97)</i> <i>Holm (02)</i> Uusi-Rasi (02) | - | Mets (93) Ramsdale (94) Nivens (95) Davis (96) Salmon (96) Ulrich (96) Teegarden (98) Uusi-Rasi (98) <i>Rubin (99)</i> Filner (02) |
| Elderly men & postmenopausal women | Reid (93) Chevalley (94) Elders (94) <i>Strause (94)</i> Hanes (95) Reid (95) <i>Recker (96)</i> Riggs (98) Storm (98) | Cummings (95) Burger (98) Huuskonen (01) | - | Hu (93) <i>Murphy (94)</i> Soroko (94) Hoover (96) Ulrich (96) <i>Kiel (97)</i> Suleiman (97) Turner (98) Uusi-Rasi (98) Aptel (99) Nguyen (00) Ilich (03) |

Table 3
Vitamin D studies assigned a high quality (“+”) rating

| Age segment | Study design type | | | |
|------------------------------------|--|------------------------------|---|--|
| | 1 | 2 | 3 | 4 |
| Prepubescent children | - | - | - | Cheng (03)* |
| Adolescent children | - | Lehtonen-Veromaa (02) | | Outila (01) Chen (03) |
| Adult men & premenopausal women | Patel (01) | - | - | Mazes (85) Tsai (87) Bischoff-Ferrari (04a) |
| Elderly men & postmenopausal women | Dawson-Hughes (91) Lips (96) Komulainen (97) Hunter (00) Mayer (02) Trivedi (03) | - | - | Aguado (00) Bischoff-Ferrari (04a) |

*Studies in **bold** provide direct support of the proposed claim, studies in *italics* provide suggestive support and studies in plan type do not support the proposed claim

Table 4
Studies that examined both vitamin D and calcium assigned a high quality (“+”) rating

| Age segment | Study design type | | | |
|------------------------------------|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Prepubescent children | - | - | - | Ilich (98)* (Ca only) <i>Kardinaal (99)</i> (Ca only) Oliveri (00) |
| Adolescent children | - | - | - | <i>Kristinsson (98)</i> (Ca only) |
| Adult men & premenopausal women | Orwoll (90) | - | - | Lamberg-Allardt (01) (D in males only) |
| Elderly men & postmenopausal women | Chaputy (92) Aloia (94) Chaputy (94) Dawson-Hughes (97) Kreig (99) Prestwood (99) Dawson-Hughes (00) Peacock (00) Sosa (00) Grados (03) Bæksgaard (98) | Cumming (97) Ensrud (00) Hannan (00) | - | - |

*Studies in **bold** provide direct support of the proposed claim, studies in *italics* provide suggestive support and studies in plan type do not support the proposed claim

Table 5
Percent of High Quality Studies that Provide Direct Support for the Proposed Claim

| Age segment | Calcium studies | | | Vitamin D studies | | | "Combination" studies ^a | | |
|-----------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|------------------------------------|--------------------------------|--------------------------------|
| | Study design type ^b | Study design type ^b | Study design type ^b |
| Prepubescent children | 1 ^c | 100% (n=4) | 100% (n=1) | - | 67% (n=6) | - | - | - | 100% (n=1) |
| | 2 | - | - | - | - | - | - | - | - |
| Adolescent children | 1 ^c | 86% (n=7) | 100% (n=1) | - | 17% (n=6) | 100% (n=2) | - | - | 0% (n=1) |
| | 2 | - | - | - | - | - | - | - | - |
| Adult men & women | 1 ^c | 100% (n=1) | 40% (n=5) | - | 70% (n=10) | 0% (n=1) | - | 67% (n=3) | 0% (n=1) |
| | 2 | - | - | - | - | - | - | - | - |
| Elderly men & women | 1 ^c | 78% (n=9) | 67% (n=3) | - | 67% (n=12) | 33% (n=6) | - | 100% (n=2) | 100% (n=11) |
| | 2 | - | - | - | - | - | - | - | - |
| TOTAL | 1 ^c | 86% (n=21) | 60% (n=10) | - | 59% (n=34) | 29% (n=7) | 100% (n=2) | 88% (n=8) | 92% (n=12) |
| | 2 | - | - | - | - | - | - | - | - |
| | | | | | | | | | 20% Ca (n=5) 0% D |

^aCombination studies assessed the effect of both calcium and vitamin D as either: 1) A supplement containing both nutrients; 2) separate supplements of each nutrient; or 3) separate exposure assessments (for observational studies).
^bAccording to FDA's "Interim Evidence-based Ranking System for Scientific Data": 1=Randomized, controlled intervention studies; 2=Prospective cohort studies; 3=Case-control studies; 4=Cross-sectional studies.
^cFor design type studies 1, 2 and 3, only studies with a "high quality factor" according to FDA's ranking system were considered. Cross-sectional cohort studies (Design type 4) were not assigned a quality factor because the weight given to such studies in assessing potential health claims is very low. Therefore, all such studies were considered in order to provide the broadest possible assessment of this largest, but least relevant segment of the literature.

1. Adequate vitamin D is necessary for optimal bone health for all age segments of the population

As noted previously, the DRIs for vitamin D were increased substantially by the Food and Nutrition Board (1997) in recognition of the importance of this nutrient for optimal bone health. In addition, numerous studies cited earlier in this document show that intake of vitamin D is marginal or deficient in large segments of the U.S. population and elsewhere. The high quality studies presented in Table 5 present strong, consistent evidence that vitamin D supplementation, especially when combined with calcium, decreases loss of BMD and/or decreases fracture incidence in postmenopausal women and older men. *All* of the randomized trials that provided a supplement containing both nutrients yielded positive results. Intervention studies that did not show a benefit of vitamin D supplementation can be explained by a probable inadequate dose (Lips *et.al.*, 1996; Komulainen *et.al.*, 1997), high calcium intake (Hunter *et.al.*, 2000) or the fact that supplementation was discontinued (Dawson-Hughes *et.al.*, 1997).

The observational studies noted in Table 5 provided less consistent support for an association between vitamin D and/or calcium and bone health. However, the limitations of such studies are well known, and FDA has placed much less emphasis on epidemiologic data in considering the authorization of health claims. Specifically, epidemiologic studies cannot be used to establish a cause and effect relationship (or lack thereof) between vitamin D or calcium intake and BMD or any other parameter. The studies that reported a positive association provide evidence of such a relationship, but the negative studies do not preclude such a possibility. Factors which may explain failure to detect a true association include limited sample size, a narrow range of vitamin D or

calcium intake, increased intake of calcium/vitamin D among subjects at high risk of osteoporosis due to participation in the study, errors associated with estimating nutrient intake, inadequate length of follow-up period, the presence of unrecognized confounding variables in the population and inability to correct completely for known confounding variables (e.g. age, gender, race, body weight, menopause, physical activity, HT, cigarette smoking, exposure to sunlight, nutrient status, nutrient interactions, energy intake, alcohol intake, genetic factors). The limitations of making conclusions on epidemiologic data in the area of vitamin D/calcium and bone health have been specifically discussed by Reid (1998) and Heaney (2000).

High quality data are not available to demonstrate the direct effect of vitamin D supplementation on bone health in younger people, but there is consensus in the literature that this nutrient is essential for bone health regardless of age.

Heaney (2003) recently described the evolving understanding of vitamin D as an essential nutrient for bone health throughout life,

The modest vitamin D fortification of milk and a few other foods over the past several decades, coupled with the use of vitamin D supplements in children, has eliminated most cases of stage-3 vitamin D deficiency in North America. However, these same stratagems have not been sufficient to prevent the lesser degrees of deficiency...Indeed, the stratagems were not designed to do so. The vitamin D requirements are pegged to the prevention of stage-3 deficiency, and there still remains a presumption that if one does not have rickets or osteomalacia, then one has sufficient vitamin D. This position is no longer tenable, not just for the theoretical reasons just outlined, but because a rapidly growing body of evidence indicates malfunctioning and morbidity, which are correctable with vitamin D, in persons who do not have the index

[rickets] disease. For example, increasing serum 25-hydroxyvitamin D [25(OH)D] concentrations from ~50 nmol/L to ~80 nmol/L (both values within the usual reference range) improves calcium absorption efficiency by nearly two-thirds and reduces osteoporotic fracture risk by one-third. Thus, it is now incontrovertible that vitamin D deficiency that is less extreme than that required to produce rickets or osteomalacia nevertheless produces disease, although of a long-latency character.

Holick (2002) also noted the importance of vitamin D for bone health in young individuals,

Even if vitamin D deficiency is common among healthy young female adults, why should we care, given that their skeletons have matured and there is no evidence of significant osteoporosis in this age group? Are there other more insidious consequences of vitamin D deficiency for this age group? Vitamin D is essential to maximize skeletal health from birth until death. Vitamin D as 1,25(OH)₂D accomplishes this by increasing the efficiency of intestinal calcium and phosphorus transport. Vitamin D deficiency causes a mineralization defect that results in growth retardation and rickets in growing children...Vitamin D deficiency also causes secondary hyperparathyroidism, which can precipitate and exacerbate osteoporosis by increasing mobilization of mineral and matrix from the skeleton.

Furthermore, the essentiality of vitamin D for optimal calcium absorption and bone health was acknowledged by the Food and Nutrition Board (1997) in establishing DRIs for this nutrient.

In summary, the BIHW strongly believes that the essentiality of vitamin D as a determinant of bone health for all ages has been demonstrated by the totality of available evidence, and we recommend that vitamin D be included in the health claim for osteoporosis as proposed.

2. Adequate vitamin D and calcium reduce the risk of osteoporosis at all ages

The high quality studies presented in Table 5 provide very consistent evidence that adequate calcium intake increases peak bone mass among young children and adolescents and reduces bone loss and/or fracture rates in adults (including premenopausal women) and the elderly. The BIHW strongly believes that these data justify removing the reference to age from the current osteoporosis health claim.

Despite the limitations described above, a clear majority of the high quality observational studies supports this conclusion. Heaney (2000) noted the relative importance of observational studies in a recent review paper,

...the overwhelmingly positive data from the stronger, controlled trials renders these observational studies, in a certain sense, superfluous. Nevertheless, it is distinctly helpful to know that the effects achievable in the artificial context of a controlled trial, often using non-food sources of calcium, can be seen also in a more natural situation, in which the principal calcium source is food (and high calcium intakes almost always mainly from dairy sources).

The most compelling support for removing age as a component of the claim, however, is provided by the randomized, controlled trials. High quality evidence is apparent for all age ranges with 85% of the studies providing direct support of a positive effect on bone health. The few studies that did not provide direct support were suggestive of a positive effect (Strause *et.al.*, 1994), were conducted in unhealthy (i.e. fracture victims) subjects that do not reflect the healthy U.S. population (Recker *et.al.*, 1996) or found positive results in a different aged subset of the subjects studied (Johnston *et.al.*, 1992). In

addition, as noted above, *all* of the randomized trials that used a supplement containing both calcium and vitamin D (which is reflected in the wording of the proposed claim) yielded positive results.

The importance of adequate calcium intake for lifelong skeletal health was recently reviewed by Heaney (2002). In addition, Heaney and Weaver (2003) recently concluded,

A very large body of studies...demonstrates that augmented calcium intakes increase bone acquisition during growth, slow age-related bone loss, and reduce fragility fractures in the elderly population. Moreover, there is general agreement that a high peak bone mass is strong protection against low bone mass and its associated fragility in late life. During adolescent growth, almost 40% of adult bone mass is potentially accrued. A number of environmental factors influence achieving maximal peak bone mass within the genetic potential; these include diet, exercise, and other behaviors such as tobacco and alcohol use and eating disorders. Increasing calcium/dairy food intakes has enormous potential for increasing peak bone mass.

In conclusion, the BIHW believes the available data provide compelling evidence that adequate calcium and vitamin D intake are required throughout life for optimal skeletal health, and we strongly recommend that the language regarding age restriction (i.e. "young") be eliminated from the osteoporosis health claim as proposed.

3. Adequate vitamin D and calcium intake reduce the risk of osteoporosis among all races

The BIHW believes that the available data justify removing reference to the "white" and "Asian" races in the current health claim. The use of these terms implies that African Americans are not susceptible to osteoporosis and need not be as concerned about

consuming adequate calcium and vitamin D as are other ethnic groups. We believe this notion is false, and that newer data demonstrate the need for persons of all races to consume adequate amounts of these nutrients.

African Americans typically have higher bone density and experience lower fracture rates than other races. Results from the National Osteoporosis Risk Assessment study (Siris *et.al.*, 2001) show that the RR for new fractures among African American postmenopausal subjects was 0.54 (95% CI, 0.41, 0.72) compared with their white counterparts. Nevertheless, fracture rates among African Americans are 57.3 per 100,000 people, and by 80 years of age, there are substantial numbers of black women who have sufficiently low BMD to be considered osteoporotic by the WHO definition (Aloia *et.al.*, 1996). In addition, African Americans tend to have lower serum 25(OH)D concentrations and greater serum PTH values than non-blacks, and vitamin D supplementation raises serum 25(OH)D in this group. These observations led Aloia *et.al.* (1996) to conclude, "Low-risk strategies to enhance peak bone mass and to lower bone loss, such as calcium and vitamin D augmentation of the diet, should be examined for black women."

As noted earlier, the Food and Nutrition Board did not find sufficient evidence to set a separate DRI for calcium or vitamin D for the African American population (Bryant *et.al.*, 1999). This conclusion demonstrates that all ethnic groups should be treated equally with respect to dietary recommendations for these nutrients. Given the fact that all ethnic groups are susceptible to osteoporosis and that significant numbers of fractures

occur among African Americans, the BIHW believes there is no compelling evidence to exclude this ethnic group from the osteoporosis health claim. Furthermore, FDA proposed to remove the required language with respect to race in its 1995 proposal (60 FR 66206 at 66217). Therefore, we strongly recommend that the language “white and Asian” be eliminated as from the current claim as proposed.

4. Adequate vitamin D and calcium intake reduces the risk of osteoporosis for both genders

The BIHW believes that the available data justify removing reference to “women” in the current health claim. Although osteoporosis is more common in women, data from the National Osteoporosis Foundation (2002) show that there are currently 14,000,000 men in the U.S. with osteoporosis or low BMD and the incidence is projected to exceed 30,000,000 by 2020. Geier (2001) estimated that the cost of osteoporosis for men was approximately \$2.8 billion in 1995. These statistics clearly indicate that osteoporosis is not a public health issue confined to the female gender.

As noted earlier, the Food and Nutrition Board (1997) increased the recommended intakes of both calcium and vitamin D for males compared to the 1998 RDAs. This measure reflects the growing awareness and knowledge of the importance of these nutrients in affecting bone health among males.

The majority of randomized intervention studies using vitamin D and/or calcium have been performed in females, however *all* of the controlled trials that are available using male subjects reported positive results. These studies were conducted with prepubertal

children (Johnston *et.al.*, 1992; Lee *et.al.*, 1995; Dibba *et.al.*, 2000), adolescents (Renner *et.al.*, 1999) and elderly (Dawson-Hughes *et.al.*, 1997; Peacock *et.al.*, 2000; Trivedi *et.al.*, 2003). These data clearly show that calcium and/or vitamin D supplementation has a positive effect on bone health in male subjects. Furthermore, FDA proposed to eliminate the required language with respect to gender in its 1995 proposal (60 FR 66206 at 66216). Therefore, we strongly recommend that the word “women” be eliminated as from the current claim as proposed.

5. Adequate vitamin D and calcium intake reduces the risk of osteoporosis regardless of the level of physical activity

Physical activity has been convincingly shown to increase bone density in human subjects (Heaney and Weaver, 2003). However, virtually all of the high quality dietary intervention studies cited in this petition controlled for physical activity between the placebo and experimental groups. These studies demonstrated that calcium and/or vitamin D supplementation increases bone mass regardless of the level of physical activity. This information supports the position that information about the importance of physical activity on bone health should be permitted in the osteoporosis health claim, but should not be mandatory. Furthermore, FDA proposed to eliminate the required language with respect physical in its 1995 proposal (60 FR 66206 at 66216). Therefore, the BIHW strongly recommends that the term, “physical activity” be made an optional part of the new claim as proposed.

6. Summary and overall conclusions

In summary, the BIHW strongly believes the SSA standard has been met for the proposed claim. The available observational data support the premise that vitamin D and/or calcium intake is associated with bone health, and the randomized, controlled supplementation trials are extremely consistent in demonstrating a positive effect. Furthermore, these data apply without regard to age, ethnic group, gender or level of physical activity. We therefore strongly recommend that FDA move forward to authorize the proposed claim as quickly as possible.

IV. NATURE OF THE FOOD ELIGIBLE TO BEAR THE CLAIM

The BIHW proposes that foods that qualify as excellent sources of vitamin D and calcium (i.e. at least 20% DV per RACC for non-meal-type foods) and meet all of the general health claim requirements set forth in 21 CFR § 101.14 be eligible to bear the proposed claim. As noted previously, we also propose that foods that meet the current eligibility criteria for the calcium and osteoporosis health claim be permitted to use the simplified claim language described above.

A. Minimum content of vitamin D and calcium

The BIHW believes that the eligibility criteria for the proposed claim should be consistent with those of the current calcium and osteoporosis health claim. The general requirements for health claims dictate that when a substance that is the object of a claim is to be consumed at other than decreased dietary levels it must meet the definition of “excellent source” as defined in 21 CFR § 101.54(b) (see 21 CFR § 101.14(d)(2)(vii)).

Application of this criterion dictates that a minimum of 20% DV per RACC for both calcium and vitamin D be required for conventional, non-meal-type foods to be eligible to bear the claim.

Application of the “excellent source” criterion is also consistent with the scientific evidence reviewed in this document. According to 21 CFR § 101.14(d)(2)(vii), application of the “excellent source” criterion ensures that a serving of food that bears a health claim will provide “a sufficiently high proportion of the DV of that nutrient to justify the claim”. The DV for vitamin D is 400 IU. Eight of the 12 high quality intervention studies reviewed in this document that found a positive effect of vitamin D (or a combination of vitamin D and calcium) on bone health employed a vitamin D dose in this range. Four studies (Dawson-Hughes *et.al.*, 1991; Aloia *et.al.*, 1994; Kreig *et.al.*, 1999; Grados *et.al.*, 2003) provided 400 IU per day, three studies (Chaputy *et.al.*, 1992; Chaputy *et.al.*, 1994; Prestwood *et.al.*, 1999) provided 800 IU per day and intermediate levels were provided by Bæksgaard *et.al.* (1998) and Dawson-Hughes *et.al.* (2000).

Application of the “excellent source” criterion is also consistent with the regulations that control the addition of vitamin D to prepared foods. As noted previously, 21 CFR § 184.1950 allows the addition of vitamin D to breakfast cereals (350 IU/100 g), grain products and pastas (90 IU/100 g), milk (42 IU/100g) and milk products (89 IU/100 g). In addition, 21 CFR § 166.110 permits fortification of margarine (330 IU/100 g) and the newly promulgated 21 CFR § 172.380 permits the addition of vitamin D to calcium-fortified 100% fruit juice and fruit drinks (100 IU/serving) not intended for infants. Of

these foods, those that are excellent sources of calcium (i.e. milk, yogurt, certain fortified breakfast cereals and juices) are permitted to add enough vitamin D to qualify for the proposed claim. On the other hand, foods that would be ineligible to bear the claim because they are not excellent sources of calcium (e.g. margarine, enriched grain products and pastas) are generally not permitted to add sufficient quantities of vitamin D to qualify for the claim⁸.

In summary, the BIHW believes there is sound regulatory, scientific and practical rationale to warrant application of the "excellent source" criterion to the proposed claim.

B. Calcium and vitamin D levels beyond which there are no additional benefits

The BIHW proposes to adopt FDA's 1995 proposal (60 FR 66206 at 66219) to require foods that contain 1,500 mg calcium or more per RACC be required to state, "a total dietary intake greater than 200 percent of the recommended daily intake (2,000 milligrams (mg) of calcium) has no further known benefit to bone health," as set forth in 21 CFR § 101.72 (c)(2)(ii)(E). However, we do not believe such a requirement is necessary or appropriate for vitamin D.

Current data suggest that intakes of vitamin D beyond the current DV are beneficial to older Americans, and may be beneficial to many other individuals. The DV for vitamin D is based on the 1968 RDA of 400 IU/d for all age/gender segments of the population (Food and Nutrition Board, 1968). This benchmark was increased to 600 IU/d for men

⁸ Although fruit drinks are permitted to be fortified with up to 25% DV of vitamin D, currently available products would not qualify for the proposed claim because technical constraints prevent them from being fortified with more than 10% DV of calcium.

and women over the age of 70 with establishment of the current AI. The IOM cited strong evidence that, “elderly are at high risk for vitamin D deficiency” as a basis for this change (Food and Nutrition Board, 1997).

More recently, it has been demonstrated that supplementation with vitamin D at levels considerably higher than the AI result in favorable changes in serum 25(OH)D and PTH but does not affect serum calcium concentrations. Heaney *et al.* (2003) reported that serum 25(OH)D concentrations increased, and levels of PTH decreased, in a dose response fashion as healthy men (mean age = 38.7) living in Omaha were supplemented with 0, 25, 125 and 250 µg (10,000 IU) of vitamin D per day for five months. Serum calcium concentrations were unchanged during this experiment. In addition, Vieth *et al.* (2001) reported that serum 25(OH)D concentrations were higher in healthy men and women (mean age = 41 years) supplemented with 100 µg/d (4,000 IU) of vitamin D for three months compared to subjects given 25 µg/d. There was no difference in serum calcium between these two groups. These data demonstrate that consumers may benefit from consuming vitamin D in amounts substantially above the AI and that the claim should not be required to specify a level beyond which no further benefit would be expected.

C. Additional eligibility requirements

The BIHW further recommends that the remaining eligibility requirements of the current calcium and osteoporosis health claim set forth in 21 CFR § 101.72 (c)(2)(ii) also apply to the proposed claim. Specifically, the calcium content of the product shall be

assimilable, any existing standards for disintegration and dissolution of calcium salts stated in the United States Pharmacopoeia must be met (dietary supplements only) and the food or daily recommended supplement shall not contain more phosphorous than calcium on a weight per weight basis.

D. General health claim criteria

Finally, the BIHW proposes that all of the general requirements for health claims set forth in 21 CFR § 101.14 be applied to the proposed claim. Specifically, foods eligible to bear the claim must meet the disqualifier levels for total fat, saturated fat, cholesterol and sodium as well as the 10% DV minimum nutrient contribution requirement.

V. DIETARY CONSIDERATIONS

The BIHW believes that availability of the new claim has the potential to improve quality of the U.S. diet with very little risk. This conclusion is based on the fact that only nutrient dense foods (already recommended for frequent consumption by the Dietary Guidelines for Americans and the Food Guide Pyramid) would be eligible to bear the claim. In addition, availability of the claim is likely to prompt consumers to switch to vitamin D/calcium fortified forms of foods already being consumed rather than to increase consumption of such foods. Furthermore, existing regulations ensure that excessive intakes of vitamin D will not occur. Finally, we believe that authorization of the proposed claim will provide an incentive for food manufacturers to utilize the existing regulations to make a wider selection of vitamin D-fortified foods available to the American consumer.

A. ONLY NUTRIENT DENSE FOODS WILL QUALIFY FOR THE PROPOSED CLAIM

As discussed in the previous section, foods that qualify for the proposed claim must be excellent sources of both vitamin D and calcium, meet the disqualifier levels for fat, saturated fat, cholesterol and sodium as well as comply with the 10% DV nutrient contribution requirement. Application of these criteria will limit use of the proposed claim to nutrient dense foods including low fat (2% fat or less) fluid milks, vitamin D-fortified yogurts, calcium and vitamin D-fortified fruit juices and certain vitamin and mineral-fortified breakfast cereals (see Appendix D for a survey of currently available products eligible to bear the proposed claim).

The nutritional benefits of such foods are well recognized. CSFII data show that milk is the largest source of calcium, phosphorous, potassium, magnesium and riboflavin in the U.S. diet of adults (Subar *et.al.*, 1998) and of protein, calcium and magnesium for children (Subar *et.al.*, 1998a). In addition, consumption of flavored milks and pre-sweetened cereals has been shown to increase nutrient density of the diet of U.S. children (Frery *et.al.*, 2004). Data reported by Subar *et.al.* (1998, 1998a) also show that orange/grapefruit juice is the largest source of vitamin C for both children and adults, and that ready-to-eat breakfast cereals are the leading sources of folate, vitamin B₆ and iron for U.S. adults, and of vitamin A, folate and iron for children.

Fruits (including juices), vegetables and low-fat dairy products have been shown to lower blood pressure and to reduce the incidence of hypertension when fed as components of the DASH diet (Appel *et.al.*, 1997).

The high nutrient density and other health benefits of fruits, vegetables and low-fat dairy products have prompted numerous dietary recommendations and educational programs designed to increase their consumption. Examples include the National Cancer Institute/Produce for Better Health Foundation's Five-a-Day program⁹ and the National Dairy Council's Three-a-Day¹⁰ initiative. In addition, the Food Guide Pyramid (United States Department of Agriculture, 1996) recommends frequent consumption of low-fat dairy products and the Dietary Guidelines for Americans (U.S. Department of Agriculture/Health and Human Services, 2000) lists milk, yogurt, fruit juice with added calcium and breakfast cereal with added calcium as recommended sources of this nutrient.

Unfortunately, 1994-96 CSFII data (United States Department of Agriculture, 1999) show that the mean intake of dairy products among U.S. consumers at least two years of age is only 1.5 servings per day, and just 23 percent of this population consumes the recommended number of servings based on age and physiological status¹¹. Similarly, mean servings of fruit (including fruit juices) is 1.5 per day and only 23 percent of the population age 2 or more meet the recommended number of servings based on physiological status¹².

⁹ <http://www.5aday.gov/>

¹⁰ <http://www.nationaldairycouncil.org/health/digest/dcd74-1.asp>

¹¹ The recommendation for an individual is based on age and physiological status. Women who were pregnant or lactating and individuals 11 to 24 years of age were counted as meeting the recommendation if they consumed at least 3 servings of dairy products per day; all other individuals were counted as meeting the recommendation if they consumed at least 2 servings of dairy products per day.

¹² Recommended servings were derived from sample patterns in "The Food Guide Pyramid" (USDA 1992). Individuals consuming less than 2,200 calories met the recommendation if they ate at least 2 servings of fruit per day; individuals consuming 2,200 to 2,800 calories met the recommendation if they ate at least 3 servings of fruit per day; and individuals consuming 2,800 calories or more met the recommendation if they ate at least 4 servings of fruit per day.

In summary, the BIHW believes that authorization of the proposed claim would provide new opportunities to help educate the public about the benefits of consuming nutrient dense foods already broadly targeted for increased consumption.

B. DIETARY PATTERNS ARE UNLIKELY TO CHANGE SIGNIFICANTLY AS A RESULT OF THE CLAIM

The BIHW believes that consumers are more likely to respond to the proposed claim by switching to vitamin D-fortified products within the affected categories (e.g. low-fat dairy, calcium-fortified juices) than by increasing total consumption of foods within these categories. Such a response would result in increased intake of vitamin D (and possibly calcium) without notable changes in the overall dietary pattern. This conclusion is supported by consumer response to the availability of calcium-fortified orange juice. Specifically, the orange juice category has increased only 6.7% since 1996, but the consumption of calcium-fortified varieties has increased by 207% during the same period (see Table 6).

Table 6
Sales Calcium and Non-Calcium Fortified of Orange Juice in the U.S.

| Year | Calcium-fortified Orange Juice (Millions of gallons) | Non-fortified Orange Juice (Millions of gallons) | Total category (Millions of gallons) |
|------|--|--|---|
| 1996 | 67 | 691 | 758 |
| 1997 | 89 | 707 | 798 |
| 1998 | 121 | 676 | 797 |
| 1999 | 165 | 635 | 800 |
| 2000 | 206 | 607 | 813 |

Source: ACNielsen Supermarkets \$4MM+ With Supercenters

Sales of calcium-fortified juices currently represent approximately 40% of all juices sold by the Minute Maid Company. We believe availability of a health claim for vitamin D and calcium will stimulate the current trend toward consumption of fortified, rather than non-fortified juices, while maintaining total consumption at or near current levels.

It is likely that availability of the proposed claim will have a similar effect in other categories (i.e. yogurt) where the use (and availability) of non-vitamin D-fortified products prevails. FDA used similar reasoning to justify the exemption of sterol/stanol ester-containing salad dressings and spreads from the 50-gram criterion of the total fat disqualifier level (65 FR 54686, 54710, September 8, 2000).

It is hoped that the proposed claim will encourage consumers to increase consumption of vitamin D-fortified low-fat milk, but we believe the claim is unlikely to have a dramatic effect in this area. Per capita consumption of total beverage milks (expressed as gallons per year) is shown in Table 7. Although the consumption of the total category has decreased gradually during the past decade, the total change has been less than 10%. Milk consumption is based on many factors, and it seems unlikely that availability of the proposed claim will dramatically alter the stability of this category.

In summary, the BIHW believes the most important effect of proposed health claim will be to encourage Americans to choose vitamin D-fortified forms of the foods they are already consuming. There is little evidence to suggest that overall dietary patterns will be significantly affected.

Table 7
Per Capita Consumption of Beverage Milks in the United States

| Beverage milks: Whole; lower fat and fat-free; and total (Gallons per capita per year) | | | |
|---|-------|---------------------------|-------------------------|
| Year | Whole | Lower fat and fat-free 1/ | Total beverage milks 2/ |
| 1993 | 9.2 | 15.2 | 24.4 |
| 1994 | 9.0 | 15.3 | 24.3 |
| 1995 | 8.6 | 15.3 | 23.9 |
| 1996 | 8.5 | 15.3 | 23.8 |
| 1997 | 8.3 | 15.2 | 23.4 |
| 1998 | 8.1 | 14.9 | 23.0 |
| 1999 | 8.2 | 14.8 | 22.9 |
| 2000 | 8.0 | 14.4 | 22.5 |
| 2001 | 7.8 | 14.2 | 22.0 |

1/ Includes 2% reduced fat milk, low fat milk (1%, 0.5%, and buttermilk), and skim milk (fat-free).
2/ Calculated from unrounded data.

Source: USDA/Economic Research Service.

C. EXPOSURE TO EXCESSIVE AMOUNTS OF VITAMIN D IS VERY UNLIKELY¹³

The BIHW believes that several factors provide strong assurances that the proposed health claim will not result in “over-fortification” of the food supply with vitamin D or put the population at risk of excessive intakes of this nutrient. These factors include existing regulations that control the addition of vitamin D to foods, suboptimal amounts of vitamin D in the current diet and new evidence that suggests the current UL for this nutrient is very conservative.

¹³ The addition of vitamin D to the existing calcium and osteoporosis health claim does not affect previous conclusions by FDA regarding the appropriateness of calcium as an object of the claim. Therefore, discussions in this section will be limited to vitamin D.

1. Existing regulations control the addition of vitamin D to foods

As noted previously, the addition of vitamin D to foods for children and adults is controlled under 21 CFR §§ 166.110, 172.380 and 184.1950. A recent study by the ENVIRON International Corporation¹⁴ demonstrated that these regulations are doing an excellent job of ensuring that intakes of this nutrient are not excessive. This study included a thorough assessment of vitamin D intake among all age/gender segments of the U.S. population based on the 1994-96 and 1998 CSFII databases (See Appendix E). The results of this study are summarized in Table 8. The 90th percentile intakes of vitamin D were less than the UL of 2,000 IU/d for all non-infant age/gender segments of the population. These calculations included all dietary sources of vitamin D, assumed that all eligible juice products were fortified and that all individuals took 400 IU/d supplemental vitamin D per day. The report concluded,

Among the fruit juice and juice drink consuming populations of Americans ages 1 year and older and non-breastfeeding infants 7 through 12 months of age, the estimated intakes of vitamin D resulting from the proposed fortification scenario falls below the Tolerable Upper Intake Levels of vitamin D as established by the Institute of Medicine.

At the 90th percentile of vitamin D intake, non-breastfeeding infants ages 0 through 6 months who consume the vitamin D fortified beverages and a vitamin D-containing supplement in addition to formula have the potential for exceeding the UL for vitamin D by approximately 60 IU per day.

¹⁴ This study was conducted in conjunction with a petition to FDA from the Minute Maid Corporation requesting the authorization of vitamin D as a food additive for calcium-fortified juices and juice drinks

Table 8
Summary of Estimated Daily Per Person Vitamin D Consumption from All Current Food Sources and Proposed Uses in the U.S. by Population Group

| Population Group | Survey Population n | Users of fruit juices & juice drinks | | Vitamin D intake prior to fortification of fruit juices & juice drinks ^a | | Vitamin D intake including fortification of fruit juices & juice drinks ^a | | Vitamin D intake from a dietary supplement (IU) ^b | Tolerable Upper Intake Level ^c (IU) |
|--|------------------------|--------------------------------------|------------------------|---|--|--|--|--|--|
| | | n | % of survey population | Average intake per user per day (IU) | 90 th percentile intake per user per day (IU) | Average intake per user per day (IU) | 90 th percentile intake per user per day (IU) | | |
| 0 through 6 months (non-breastfeeding) | 157 | 49 | 33 | 386 | 583 | 443 | 663 | 400 | 1000 |
| 0 through 6 months (breastfeeding) | 71 | 16 | 25 | 84 | 165 | 103 | 189 | | |
| 7 through 12 months (non-breastfeeding) | 112 | 75 | 67 | 373 | 516 | 425 | 566 | 400 | 1000 |
| 7 through 12 months (breastfeeding) | 19 | 9 | 41 | 159 | 293 | 235 | 391 | | |
| 1 through 3 years (non-breastfeeding) | 1791 | 1443 | 81 | 229 | 389 | 336 | 518 | 400 | 2000 |
| 1 through 3 years (breastfeeding) | 43 | 32 | 69 | 148 | 268 | 215 | 327 | | |
| 4 through 8 years | 1650 | 1194 | 73 | 220 | 368 | 322 | 490 | 400 | 2000 |
| 9 through 13 years | 1112 | 717 | 64 | 229 | 395 | 336 | 536 | 400 | 2000 |
| 14 through 18 years | 882 | 476 | 55 | 220 | 452 | 365 | 657 | 400 | 2000 |
| 19 through 30 years | 1614 | 695 | 45 | 168 | 331 | 303 | 530 | 400 | 2000 |
| 31 through 50 years | 3298 | 1266 | 39 | 186 | 366 | 293 | 508 | 400 | 2000 |
| 51 through 70 years | 3145 | 1374 | 45 | 182 | 343 | 274 | 466 | 400 | 2000 |
| 71 through 90 years | 1297 | 640 | 50 | 199 | 355 | 279 | 468 | 400 | 2000 |
| Pregnancy/Lactation ≤ 18 years | 6 | 6 | 100 | 274 | 363 | 413 | 521 | 400 | 2000 |
| Pregnancy/Lactation 19 through 50 years | 106 | 60 | 51 | 247 | 395 | 396 | 691 | 400 | 2000 |
| Total population: 2 years and older | 14262 | 7355 | 49 | 197 | 368 | 306 | 519 | 400 | 2000 |

Data source: U.S. Department of Agriculture, Agricultural Research Service. Continuing Survey of Food Intakes by Individuals (CSFII) 1994-96 (USDA 1998). Estimates represent 2-day average intakes by users of fruit juices and/or juice drinks. All estimates were calculated with USDA survey weighting factors.

^a Estimates of means and 90th percentiles that are based on sample sizes fewer than 48 and 128, respectively, are potentially unreliable in a statistical sense due to insufficient sample size as recommended in statistical reporting standards (FASEB/LSRO 1995).

^b Mode of intake; results from NHANES III, Vitamin and/or Mineral Supplement use (US DHHS 1998).

^c The Tolerable Upper Intake Level (UL) is defined as the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects to members of the healthy general population. Unless specified otherwise, the UL represents total intake from food (excluding breast milk), water, and supplements (IOM 1997).

FDA relied heavily on this report to justify granting the Minute Maid food additive petition. The agency concluded that persons one year of age and older would not be exposed to amounts of vitamin D greater than the UL after fortification of eligible juice products. The agency also decided not to allow vitamin D fortification of juice products specifically formulated for infants because very young non-breast fed infants had a potential to slightly exceed the UL of 1,000 IU/d (68 FR 9000, 9002, February 27, 2003).

These data provide a high level of assurance that authorization of the proposed claim will not result in excessive consumption of vitamin D in the U.S. population. The juices that will be fortified with vitamin D and calcium and are eligible to bear the claim are not intended for consumption by infants and are not promoted as such. As noted above, juice products that *are* intended for infants will not be eligible to be fortified with vitamin D and would also be excluded from use of the claim by 21 CFR § 101.14(e)(4) of the general health claim requirements. We therefore believe that authorization of the proposed claim would not pose a risk to any segment of the population.

2. Current intakes of vitamin D in the U.S. are suboptimal

As noted previously, a large majority of the adult population fails to receive the recommended amounts of dietary vitamin D. It is difficult to envision how authorization of the proposed claim could contribute to excessive intakes of this nutrient given this situation.

3. The current UL for vitamin D is probably very conservative

The current UL for vitamin D was based on a single study in which 30 healthy subjects were fed doses of 10, 20, 30, 60 and 90 $\mu\text{g}/\text{d}$ for three months (Food and Nutrition Board, 1997). The subjects who were fed 60 μg (2,400 IU) experienced a slight but insignificant increase in serum calcium from 9.73 to 10.47 mg/dl while subjects given 90 $\mu\text{g}/\text{d}$ experienced a slightly greater rise (from 9.82 to 11.32), which the IOM considered hypercalcemic (>11 mg/dl). These data were used to establish a no-observed-adverse-effect level (NOAEL) of 60 $\mu\text{g}/\text{d}$ and a UL of 50 $\mu\text{g}/\text{d}$ (2,000 IU) for the non-infant population.

As noted previously, new data have become available since the IOM report that suggest much larger doses of vitamin D can be consumed without affecting serum calcium. Vieth *et.al.* (2001) reported that serum calcium was similar among 61 healthy men and women (mean age = 41 years) randomized to receive either 25 or 100 $\mu\text{g}/\text{d}$ of vitamin D for three months. These investigators concluded that 100 $\mu\text{g}/\text{d}$ (4,000 IU) is safe. In addition, Heaney *et.al.* (2003) showed that serum calcium was similar among 67 healthy male subjects (mean age = 38.7 years) supplemented with 0, 25, 125 and 250 μg vitamin D per day for five months. These data have prompted several researchers (Holick, 2002a; Heaney, 2000a; Hollis and Wagner, 2004) to suggest that both the UL and the AI for vitamin D be increased.

These data provide an additional layer of confidence that approval of the proposed claim poses virtually no risk to the American population from excessive intakes of vitamin D.

D. INCENTIVE TO INDUSTRY FOR MORE VITAMIN D FORTIFIED FOODS

The BIHW believes authorization of the proposed claim will provide an incentive for food manufacturers to develop and market more foods fortified with vitamin D. Of the foods that will be eligible to bear the proposed claim, only fluid milk is universally fortified. Fortified yogurts are becoming more widely available, but many such products are not yet fortified. In addition, vitamin D is typically added to ready-to-eat breakfast cereals at 10% DV, but most of these products are eligible to be fortified to 20-25% DV. We believe increased availability of vitamin D-fortified foods is important to help consumers obtain adequate amounts of this nutrient. The benefits of additional vitamin D fortification will accrue to all consumers regardless of their awareness of the new claim.

VI. MODEL HEALTH CLAIMS

Model statements for the proposed claim are as follows:

- *Adequate vitamin D and calcium may reduce the risk of osteoporosis in later life.*
- *Adequate vitamin D and calcium helps maintain good bone health and may reduce the risk of osteoporosis in later life.*
- *Regular exercise and a healthy diet with enough vitamin D and calcium may reduce the risk of osteoporosis in later life. In persons at high risk for the disease, including menopausal women and elderly men and women, these nutrients work by slowing the rate of bone loss.*

Similar model statements (but without the reference to vitamin D) are proposed for foods that qualify for the existing calcium and osteoporosis claim (21 CFR § 101.72 (c)(2)(ii)) but do not meet the proposed eligibility requirements for vitamin D.

The BIHW believes these model statements are consistent with the totality of scientific evidence presented in this document, and would help consumers make healthy dietary choices regardless of their age, gender or ethnic origin.

We further believe it is important to provide food manufacturers with the option to use the simplest and most concise claim possible. Such claims are attractive to industry because they are generally the most effective from a communications perspective and require a minimal amount of label space. FDA recognized this need in its 1995 proposed revision of the calcium and osteoporosis claim (60 FR 66206 at 66216),

As stated above, however, FDA acknowledges that the number of food products bearing health claims is not as great as the agency had anticipated. FDA is concerned that manufacturers have been disinclined to use lengthy health claims on food labels, and that too many words will detract from the central consumer message of the claim. As a result, FDA is concerned that health claims like the calcium/osteoporosis claim will continue to be infrequently used, and that the benefits of communicating information on diet-disease relationships through such claims will not be realized.

Because of these concerns, the agency has reevaluated the requirement in § 101.72(c)(2)(i)(A) that a calcium/osteoporosis health claim “*** list[] specific factors, including sex, race, and age that place persons at risk of developing osteoporosis and stat[e] that an adequate level of exercise *** [is] also needed.”

Nevertheless, the BIHW believes that optional information regarding physical activity, the impact of vitamin D and/or calcium on bone health during adolescence and additional information about osteoporosis be included in the claim on an optional basis. This information is described in detail in the proposed regulatory text provided later in this document.

VII. ANALYTICAL METHODS

Two standard methods for vitamin D from the Association of Official Analytical Chemists (AOAC) are applicable to monitor compliance of foods that bear the proposed claim (Association of Official Analytical Chemists, 1995). These methods include AOAC Official Method #981.17 for fortified milk and milkpowder, and AOAC Official Method #982.29 for mixed feeds, premixes and pet foods. The latter method is applicable to all food products containing vitamin D in the range of 2 to 200 IU/g.

The analytical methods currently used by the agency to monitor the calcium content of foods will continue to apply.

VIII. REQUEST FOR INTERIM FINAL RULE

FDA has the authority under Section 403(r)(7) of the Federal Food, Drug, and Cosmetic Act to issue an interim final rule a for health claim if such action is necessary for public health. The BIHW believes that the three criteria specified by the Act that enable FDA to take this approach have been satisfied:

A. Enable consumers to develop and maintain healthy dietary practices

The majority of American consumers fail to consume the AI for vitamin D and calcium, which are essential for the development and maintenance of a healthy skeletal system. Furthermore, more than 43 million men and women in the U.S. currently suffer from low bone mass or osteoporosis, and the incidence of these conditions is projected to increase dramatically during the next twenty years. In addition, authoritative bodies including the

FDA, IOM, NIH, National Osteoporosis Foundation and the American Academy of Pediatrics have recognized the importance of consuming adequate amounts of vitamin D and calcium for bone health. The proposed claim would provide an important new opportunity to educate consumers about the importance of consuming adequate amounts of these nutrients, and would provide an incentive for the food industry to develop and market more foods that are excellent sources of vitamin D.

B. Enable consumers to be informed promptly and effectively of important new knowledge regarding nutritional and health benefits of food

Food and dietary supplement manufactures have not been permitted to call attention to the role that vitamin D plays in reducing the risk of osteoporosis on labels or in labeling. A recent survey¹⁵ found that only 49% of 1,020 randomly selected adults living in the U.S. were aware of the role that vitamin D plays in this regard. Expedited availability of the proposed claim would allow the food industry to more effectively address this lack of knowledge.

C. Ensure that scientifically sound nutritional and health information is provided to consumers as soon as possible

A tentative final rule would shorten the length of time necessary to utilize product labels to disseminate information on the role of vitamin D in bone health by a minimum of one year. This information is urgently needed to bolster educational efforts designed to combat a disease that is estimated to cost Americans approximately \$17 billion per year in direct medical costs.

¹⁵ Conducted by Opinion Research Corporation March 21-24, 2002

In conclusion, the BIHW believes that all three conditions for an interim final rule have been met. FDA took this approach in authorizing use of the sterol/stanol esters health claim (65 FR 54686 at 54713) and we believe the public health rationale to do the same for the proposed claim is at least as compelling.

IX. ENVIRONMENTAL IMPACT ASSESSMENT

The BIHW chooses to avail itself of the categorical exclusion with respect to an environmental impact assessment provided by 21 CFR § 25.32(p). Accordingly, an environmental impact assessment is not required for this submission.

X. CONCLUSION

In conclusion, the BIHW strongly believes that the totality of available evidence demonstrates that adequate intake of vitamin D and calcium reduces the risk of osteoporosis in later life by enhancing bone mass regardless of age, gender, ethnicity or level of physical activity. This conclusion is based epidemiological evidence as well as numerous randomized, controlled studies that show supplementation with vitamin D and/or calcium increases bone mass, reduces fracture incidence and/or protects against osteoporosis in virtually all segments of the population. The importance of vitamin D and calcium for bone health was the basis for establishing AIs for these nutrients (Food and Nutrition Board, 1997) and has been formally recognized by numerous governmental, professional and public health organizations. An expanded health claim for osteoporosis that includes vitamin D and does not exclude men, African Americans or older individuals will assist in educating all consumers about the importance of these

nutrients, and we strongly recommend that the agency issue an interim final rule authorizing use of the proposed claim as quickly as possible.

XI. PROPOSED REGULATORY TEXT

The following proposed regulatory text uses FDA's 1995 proposed modification of 21 CFR § 101.72 (60 FR 66206 at 66225) as a template.

§ 101.72 Health claims: Calcium, vitamin D and osteoporosis

(a) *Relationship between calcium, vitamin D and osteoporosis.* An inadequate calcium or vitamin D intake can contribute to low peak bone mass and has been identified as one of many risk factors in the development of osteoporosis. Vitamin D is required for normal absorption of calcium, and to prevent the occurrence of high serum parathyroid hormone (PTH) concentration, which stimulates mobilization of calcium from the skeleton and can lower bone mass. Calcium, along with several other nutrients, is required for normal bone mineralization. Although vitamin D is also required for optimal bone mineralization, it is less effective unless calcium intakes are adequate. Peak bone mass is the total quantity of bone present at maturity, and experts believe that it has the greatest bearing on whether 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 and vitamin D 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 and vitamin D intake and optimal peak bone mass reduce the risk of osteoporosis is thought to be as follows. 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 and vitamin D 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, but a significant protective effect is also seen among men and younger women.

(b) *Significance of vitamin D and calcium and vitamin D.* Calcium and vitamin D intake is not the only recognized risk factor in the development of osteoporosis, a multifactorial bone disease. 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 affect the risk of osteoporosis.

(1) Heredity and being female are two key factors identifying those individuals at increased risk for the development of osteoporosis. Hereditary risk factors include race: Notably, Caucasians and Asians are characterized by low peak bone mass at maturity. Caucasian women, particularly those of northern European ancestry, experience the highest incidence of osteoporosis-related bone fracture. American women of African heritage are characterized by the highest peak bone mass and lowest incidence of osteoporotic fracture, despite the fact that they have low calcium intake. Nevertheless, approximately 35 percent of African American men and women were afflicted with

osteoporosis or low bone mineral density in 2002, and the incidence is expected to increase as the population ages.

(2) Although certain population subgroups including adolescent and young adult Caucasian and Asian women are at particular risk for osteoporosis, experts agree that maintenance of an adequate intake of calcium and vitamin D throughout life increases peak bone mass and/or reduces the risk of osteoporosis among male and female children, adolescents, adults and elderly persons regardless of ethnic origin.

(3) Maintenance of adequate vitamin D and calcium intakes throughout life is necessary to achieve optimal peak bone mass and to reduce the risk of osteoporosis in later life. However, vitamin D is most effective in this regard when calcium intakes are adequate. Increasing intake of calcium has been shown to have beneficial effects on bone health independent of dietary vitamin D.

(c) *Requirements.* (1) All requirements set forth in § 101.14 shall be met.

(2) *Specific requirements* –(i) *Nature of the claim.* A health claim associating calcium, or a combination of vitamin D and calcium, with a reduced risk of osteoporosis may be made on the label or labeling of a food described in paragraphs (c)(2)(ii) and (d)(1) of this section, provided that:

(A) The claim states that adequate intake of calcium, or vitamin D and calcium, as set forth in paragraphs (c)(2)(ii) and (d)(1) of this section, may be linked to reduced risk of osteoporosis in later life. The claim does not imply that adequate dietary calcium intake is the only recognized risk factor for the development of osteoporosis;

(B) The claim does not state or imply that the risk of osteoporosis is equally applicable to the general United States population. An optional statement that identifies

other populations at risk for developing osteoporosis including women in their bone forming years from approximately 11 to 35 years of age may be made in accordance with paragraph (d)(4) of this section;

(C) The claim does not attribute any degree to which maintaining adequate calcium intake, or a combination of adequate vitamin D and calcium intake if applicable, throughout life may reduce the risk of osteoporosis; and

(D) The claim states that total dietary intake of calcium greater than 2,000 milligrams (mg) per day (200 percent of the DV for calcium for adults and children 4 or more years of age or 154 percent of the daily value (DV) for pregnant or lactating women) provides no further benefit to bone health in reducing the risk of osteoporosis. This requirement does not apply to a food that provides 1,500 mg or less of calcium per day (150 percent or less of the DV for calcium for adults and children 4 or more years of age or 115 percent or less of the DV for pregnant or lactating women) when used as directed in labeling.

(ii) *Nature of the food.* (A) The food shall meet or exceed the requirements for a "high" level of calcium as defined in § 101.54(b);

(B) The calcium content of the product shall be assimilable;

(C) Dietary supplements shall meet the United States Pharmacopeia (U.S.P.) standards for disintegration and dissolution applicable to their component calcium salts, except that dietary supplements for which no U.S.P. standards exist shall exhibit appropriate assimilability under the conditions for use stated on the product label;

(D) A food or total daily recommended supplement intake shall not contain more phosphorus than calcium on a weight per weight basis.

(d) *Optional information.* (1) The claim may include the term “vitamin D” if the food meets or exceeds the requirements for a “high” level of vitamin D as defined in § 101.54(b);

(2) The claim may include information from paragraphs (a) or (b) of this section.

(3) The claim may list specific risk factors for osteoporosis, identifying them among the multifactorial risks for the disease. Such factors include a person’s sex, age, and race. The claim may state that an adequate amount of exercise may also reduce risk of the disease.

(4) The claim may further identify the population at particular risk for the development of osteoporosis as including white (or “Caucasian”) women and Asian women in their bone forming years (approximately 11 to 35 years of age). The claim may also identify menopausal (or the term “middle-aged”) women, persons with a family history of the disease, and elderly (or “older”) men and women as being at risk.

(5) The claim may state that adequate calcium intake, or adequate intake of vitamin D and calcium if applicable, 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 intake of calcium, or adequate intake of vitamin D and calcium if applicable, is linked to reduce risk of osteoporosis through the mechanism of slowing the rate of bone loss.

(6) The claim may include information on the number of people in the United States who have osteoporosis or low bone density. The sources of this information must be identified, and it must be current information from the National Center for Health Statistics, the National Institutes of Health, the National Osteoporosis Foundation, or "Dietary Guidelines for Americans."

(e) *Model health claim.* The following model health claims may be used in food labeling to describe the relationship between calcium or vitamin D and calcium and osteoporosis:

MODEL HEALTH CLAIM APPROPRIATE FOR MOST CONVENTIONAL FOODS:

Adequate vitamin D and calcium may reduce the risk of osteoporosis in later life.

Adequate vitamin D and calcium helps maintain good bone health and may reduce the risk of osteoporosis in later life.

Regular exercise and a healthy diet with enough vitamin D and calcium may reduce the risk of osteoporosis in later life. In persons at high risk for the disease, including menopausal women and elderly men and women, these nutrients work by slowing the rate of bone loss.

MODEL HEALTH CLAIM APPROPRIATE FOR FOOD EXCEPTIONALLY HIGH IN CALCIUM AND MOST CALCIUM SUPPLEMENTS:

Regular exercise and a healthy diet with enough calcium helps maintain good bone health and may reduce the risk of osteoporosis in later life. Adequate calcium intake is important, but daily intakes above about 2,000 mg are not likely to provide any additional benefit.

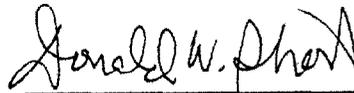
XII. CERTIFICATION

I hereby certify that to the best of my knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information known to me to be pertinent to the evaluation of the proposed health claim.

Respectfully submitted,

**THE BEVERAGE INSTITUTE FOR HEALTH &
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By



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