May 17, 2004

Ms. Nancy Crane
Nutrition Programs and Labeling Staff
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

RE: Docket No. 2004Q-0102

Dear Ms. Crane:

I am responding to a request to submit comments about a petition for a qualified health claim for supplemental calcium and kidney/urinary stones by 5/17/04. I am an associate professor and the University of Texas Southwestern Medical Center at Dallas. My clinical and research focus over the last decade is the prevention of kidney stones, a disease that afflicts up to 12% of men and which recurs in 50% of them. Over the last three decades, we have seen over 2500 kidney stone formers in our center for this purpose. Based on my clinical experience and my thorough review of the available pertinent clinical studies, I am concerned that treatment of active kidney stone formers with calcium may exacerbate stone disease rather than ameliorate the risk. I will try summarize the key data below with the potential positives and negatives of calcium supplementation in regards to stone formation.

For intuitive reasons, dietary calcium restriction was strongly advocated for many years. The vast majority of kidney stones contain calcium.[1] Among the identified physiologic risk factors for stone recurrence, high urinary calcium is the most important. Curhan recently showed that urinary calcium directly correlates with the risk stone formation better than other stone risk factors.[2] High urinary calcium also diminishes the protection of protein inhibitors against stone formation.[3] Moreover, treatment with either thiazide diuretics or indapamide, agents with lower urinary calcium, reduced stone recurrence in several placebo-controlled trials.[4] Finally, dietary calcium raises urinary calcium, and this is accentuated in patients with high urinary calcium.[5] For these reasons, dietary calcium restriction was expected to reduce kidney stone risk despite the absence of any prospective trials.

Urinary calcium is affected by many other factors other than dietary calcium. Sodium, animal protein and glucose may raise urinary calcium, whereas phosphate and alkali intake may lower it.[6-9] In fact, the combination of high sodium intake and high animal protein intake will raise urinary calcium more than high calcium intake. The reason is that only a net of 100 to 300 mg of calcium is

absorbed from the intestine/day. In contrast, 10,000 mg of calcium is filtered and 9,700 to 9,900 mg is reabsorbed by the kidney. Since sodium and animal protein inhibit calcium reabsorption by the kidney, it is not surprising that they affect urinary calcium substantially.

Recently several studies have counterintuitively suggested that higher calcium intake prevents kidney stones. In 1993, Curhan published convincing data that higher calcium intake protects against first stone formation (-32%) in men.[10] In 1997, a similar protection against the first stone formation was demonstrated in women.[11]Despite careful adjustment for expected confounders, these large observational studies could not adjust for intake of two dietary factors with probably impact on stone disease- alkali and oxalate. After the 2nd study was published, I saw three patients in 1 month whose stone disease became much more aggressive after their urologist treated them with supplemental calcium.

The most convincing study was published by Borghi et al in the New England Journal in 2002.[12] In a 5-year prospective clinical trial, the authors compared normal calcium intake to low calcium intake, and demonstrated that the higher calcium diet prevented kidney stones much more effectively. However, even this study did not prove that higher calcium diet is more effective than low calcium diet at reducing stone recurrence. Unfortunately, there were other differences between diets. Only the high calcium group was additionally subjected to a diet restricted in sodium and animal protein and enriched in potassium (a source of alkali) and fiber (which binds dietary calcium). Thus, this otherwise well-done study did not directly compare the effect of dietary calcium alone.

The data relating supplemental calcium to stone risk is even less abundant. There is no prospective clinical trial. One epidemiologic trial found that supplemental calcium increased the risk of kidney stones by 20%.[11] Unlike calcium supplements, dairy, the key source of dietary calcium, may have factors that prevent the rise in urinary calcium including citrate and phosphate.

In summary, the data that dietary calcium prevents kidney stones is still controversial. That concerning calcium supplements is even less convincing. There is no trial that has directly compared higher calcium intake to lower calcium intake. On the other hand, it is possible that the higher calcium intake may cause more harm than good. Until this matter is more settled, it would be unwise to allow labeling suggesting that calcium supplements reduce stone risk.

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10 Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med 1993;328:833-838.

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12. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stoens in idiopathic hypercalciuria. N Engl J Med 2002;346:77-83.