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December 2, 2003

VIA UPS OVERNIGHT MAIL
Dr. Kathy Ellwood
Assistant Director for Nutrition Science
ONPLDS
Food and Drug Administration
Room 4A026; HFS-800
5100 Paint Branch Parkway
College Park MD 20740

Re: Health Claim Petition Glucosamine and Chondroitin Sulfate by Weider Nutrition International, Inc.

Dear Dr. Ellwood:

As per Dr. Lester Crawford's suggestion in the meeting on Monday, November 24, 2003 please find enclosed for filing in the docket for the above petition an original and one copy of the written comments of Dr. Michael Orth including his curriculum vitae and copies of the articles cited in his comments.

Sincerely,

Jonathan W. Emord
Andrea G. Ferrenz

Enclosures

cc: Mike Landa, Office of the Chief Counsel, FDA

2004P-0059

SUP 4

I have read Dr. Glade's report on the current state of literature regarding both glucosamine and chondroitin sulfate research. The report is quite exhaustive and fairly represents the peer-reviewed published material in the field. A large number of studies, both in animals and humans, support the ability of glucosamine and chondroitin sulfate to prevent and/or delay onset of degenerative joint disease and its symptoms. Those studies are cited and discussed extensively in Dr. Glade's report. I would like to add comment to particular points raised in Dr. Glade's report.

Study Results Consistently Show Glucosamine and Chondroitin Sulfate's Beneficial Effects in Preventing Cartilage Deterioration and Osteoarthritis; Those Results Are Directly Applicable to Glucosamine and Chondroitin Sulfate's Effects in Pre- or Non-Osteoarthritic Populations

Glucosamine and chondroitin sulfate have inhibitory effects on normal cartilage deterioration associated with aging; cartilage damage associated with a traumatic event; and cartilage damage associated with recurring joint stress, all of which are, individually, not osteoarthritis but are factors that may lead to osteoarthritis.[1-8] The inhibition of those factors reduces the overall risk of osteoarthritis and joint disease in otherwise healthy populations.

A "healthy" population is an aging population with cartilage that is slowly deteriorating. Like most, if not all, tissues in the body, articular cartilage deteriorates during the aging process. Articular cartilage becomes more acellular, less responsive to growth factors, and more susceptible to damaging molecules as it ages.[9,10] Furthermore, many potentially adverse changes seen in aging cartilage, such as decreased OP-1 (a bone morphogenic protein) concentrations[11], increased nitrotyrosine molecules[9], and decreased antioxidant capacity[a], are common to osteoarthritic cartilage. Human clinical trials and animal studies on glucosamine and chondroitin sulfate in osteoarthritic cartilage have shown beneficial effects on those same adverse changes that occur in aging cartilage. For example, chondroitin sulfate decreased membrane damage to human leukocytes by reactive oxygen species and increased synovial fluids levels of hyaluronate in gonoarthrosic patients.[12] A three-year study with patients taking glucosamine sulfate showed that glucosamine sulfate decreased joint space narrowing.[13] The CDC last year estimated that as many as 70 million people suffer from chronic joint pain (no reasons specified), suggesting it is relatively common in adults.[14] Glucosamine and chondroitin sulfate decrease joint pain in a number of studies.[2,3,13,15-17] Thus, glucosamine and chondroitin sulfate benefit an aging population without symptomatic OA by reducing OA risk. In support of this, recent in vitro research suggests that glucosamine and chondroitin sulfate could be especially advantageous for older individuals regardless of a known risk for OA.[18]

The strategy to prevent cartilage deterioration through supplementation is independent of the occurrence of a traumatic event. As an analogy, women are more susceptible than men to experiencing the deleterious effects of osteoporosis. One of the major reasons for that difference is the acute decrease in estrogen during menopause that induces an increased rate of bone loss. However, after a few years post-menopause the rate of bone loss in men and women is similar.

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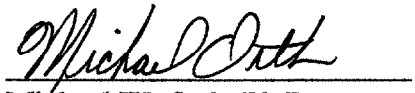
[a] Richard Loeser, "Aging and Osteoarthritis: The Potential Role of Oxidative Stress". Oral presentation given at The 32nd Annual Midwest Connective Tissue Workshop, Nov. 14-15, 2003 in Chicago, IL.

Increased calcium and vitamin D intake as well as high impact exercise are beneficial for both groups although one group has a more pressing need to implement the "osteoprotective" strategies. Those osteoprotective strategies to prevent bone loss are independent of the loss of estrogen. Similarly, those with a traumatic joint injury who are at risk for developing OA will benefit from the "chondroprotective" properties of glucosamine and chondroitin sulfate not because they reverse the effects of the injury but because they can maintain (and in some cases maybe improve) the health of cartilage in its current state. The cartilage protective strategy is independent of the trauma.

In animal and in vitro studies glucosamine and chondroitin sulfate have inhibited or reduced the adverse effects of stress on cartilage. Recently Lippiello has suggested that glucosamine and chondroitin sulfate should be considered "biological response modifiers," agents which boost natural protective responses of tissues under adverse environmental conditions.[18] In its October 3, 2003 report FDA states the "claims (concerning glucosamine and chondroitin sulfate) are clearly aimed at correcting abnormal physiological and biochemical functions..." To the contrary, taken as a whole the scientific evidence reveals that glucosamine and chondroitin sulfate inhibit or reduce the adverse effects of joint stress that – without the intervention –will lead some to experience diagnosable osteoarthritis. Thus, use of glucosamine and chondroitin sulfate in healthy populations reduces the risk of osteoarthritis, osteoarthritis-related symptoms, and joint diseases.



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References[b]

1. Van Blitterswijk WJ, Van De Nes JC, Wuisman PI. Glucosamine and chondroitin sulfate supplementation to treat symptomatic disc degeneration: Biochemical rationale and case report. *BMC Complement Altern Med* 2003;3:2.

2. Braham R, Dawson B, Goodman C. The effect of glucosamine supplementation on people experiencing regular knee pain. *Br J Sports Med* 2003;37:45-49. **[173]**

3. Leffler CT, Philippi AF, Leffler SG, et al. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study. *Mil Med* 1999;164:85-91. **[221]**

4. Schenk RC, Clare DJ, Gilley JS, et al. Role of Glucosamine/Chondoitin Sulfate Formula in Treatment of an Osteochondral Impaction Injury in a Collegiate Basketball Player. *Orthop Tech Rev* 2000;2:12-15.

[b] A complete copy of all of the references cited herein are attached either as exhibits to the Glade Report in the petition or attached to this report. The corresponding petition reference numbers are indicated in bold, in brackets at the end of each above citation.

5. Omata T, Segawa Y, Itokazu Y, et al. Effects of chondroitin sulfate-C on bradykinin-induced proteoglycan depletion in rats. *Arzneim Forsch* 1999;49:577-581. [**164**]
6. Omata T, Itokazu Y, Inoue N, et al. Effects of chondroitin sulfate-C on articular cartilage destruction in murine collagen-induced arthritis. *Arzneim Forsch* 2000;50:148-153. [**163**]
7. Lippiello L, Woodward J, Karpman R, et al. In vivo chondroprotection and metabolic synergy of glucosamine and chondroitin sulfate. *Clin Orthop* 2000;381:229-240. [**219**]
8. Beren J, Hill SL, Diener-West M, et al. Effect of pre-loading oral glucosamine HCl/chondroitin sulfate/manganese ascorbate combination on experimental arthritis in rats. *Exp Biol Med* 2001;226:144-151.
9. Loeser RF, Carlson CS, Del Carlo M, et al. Detection of nitrotyrosine in aging and osteoarthritic cartilage: Correlation of oxidative damage with the presence of interleukin-1beta and with chondrocyte resistance to insulin-like growth factor 1. *Arthritis Rheum* 2002;46:2349-2357.
10. Guerne PA, Blanco F, Kaelin A, et al. Growth factor responsiveness of human articular chondrocytes in aging and development. *Arthritis Rheum* 1995;38:960-968.
11. Chubinskaya S, Kumar B, Merrihew C, et al. Age-related changes in cartilage endogenous osteogenic protein-1 (OP-1). *Biochim Biophys Acta* 2002;1588:126-134.
12. Ronca F, Palmieri L, Panicucci P, et al. Anti-inflammatory activity of chondroitin sulfate. *Osteoarthritis Cart* 1998;6 Suppl A:14-21. [**131**]
13. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;357:251-256. [**181**]
14. CDC. Prevalence of self-reported arthritis or chronic joint symptoms among adults-United States, 2001. *Morbidity and Mortality Weekly Report*, 2002;948-950.
15. Pipitone VR. Chondroprotection with chondroitin sulfate. *Drugs Exp Clin Res* 1991;17:3-7.
16. Pujalte JM, Llavore EP, Ylescupidez FR. Double-blind clinical evaluation of oral glucosamine sulphate in the basic treatment of osteoarthrosis. *Curr Med Res Opin* 1980;7:110-114. [**179**]
17. Morreale P, Manopulo R, Galati M, et al. Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. *J Rheumatol* 1996;23:1385-1391. [**208**]
18. Lippiello L. Glucosamine and chondroitin sulfate: biological response modifiers of chondrocytes under simulated conditions of joint stress. *Osteoarthritis Cartilage* 2003;11:335-342.