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2004 Q-0180

Office of the Director

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U.S. Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 2004Q-0180
QHC: Lutein and Eye Disease

Dear Sir or Madame:

I submit this letter to comment on the proposed qualified health claim (Docket 2004Q-1080) that "*consumption of 12 mg of Xangold lutein esters per day may reduce the risk of age-related macular degeneration (AMD) and cataract formation.*" Lutein (often present with zeaxanthin) is present in a wide variety of plant foods especially dark-green leafy vegetables such as kale, spinach, turnip greens, and collards [1]. Lutein is also highly concentrated in egg yolks [2]. Research involving cell cultures, animal models, and human studies has been directed to the potential role of lutein in protecting against several chronic diseases, particularly AMD and cataract. Lutein is uniquely concentrated in the macular region of the retina [3-5] with zeaxanthin being the dominant component in the central macula and lutein distributed throughout the retina [4-6]. Lutein and zeaxanthin are the only carotenoids reported to be present in eye lens [7]. Possible biologic mechanisms of the protective role of lutein in the eye have been reviewed by Krinsky *et al.* [8] and include their ability to: [a] filter harmful short-wave blue light, [b] function as antioxidants, and [c] stabilize membrane integrity.

Increased consumption of foods rich in lutein [9,10] or ingestion of lutein supplements [11-13] have been reported to increase macular pigment density in healthy adults. In patients with inherited retinal degeneration, lutein supplementation augmented the macular pigment in many but not all patients, though central vision was unchanged after the supplementation [14]. The preservation of visual sensitivity in older people has been associated with macular pigment density [15]. Positive associations have been reported between dietary intakes of lutein vs. macular pigment density [32] and between serum concentrations of lutein vs. macular pigment density [16-18].

AMD is the most common cause of visual impairment and irreversible blindness among elderly Americans and a number of investigations have examined the relationship between lutein and AMD. In a case-control study, Bone *et al* [19] found that lutein concentrations in the fovea were lower in AMD donors than controls. Data from the Eye

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Disease Case-Control Study [20,21] are consistent with the hypotheses that a reduced risk of neovascular AMD is inversely associated with lutein intake and status. Snellen *et al.* [22] found that the prevalence rate of AMD in subjects with low lutein intake was more than twice that in subjects with high intake. In contrast, some results the Beaver Dam Eye Study in Wisconsin [23-25] and the Blue Mountains Eye Study in Australia [26] fail to show any significant association of lutein and the development of AMD.

In an examination of the relationship between lutein and cataract in the Nurses Health Study, Chasan-Taber *et al.* [27] found women with the highest intakes of lutein plus zeaxanthin had a significant reduction in relative risk of cataract severe enough to require extraction as compared to those with poorest intakes. A similar relationship was noted in men from the Health Professionals Follow-up Study by Brown *et al.* [28]. In contrast, associations of lutein and age-related cataract in the Beaver Dam Study were inconsistent with an inverse association between dietary lutein and cataract, but not between serum lutein and cataract [29,30]. However, in England, Gale *et al.* [31] found that the risk of posterior subcapsular cataract was lowest in those with higher concentrations of plasma lutein. Interestingly, in a small trial of people with cataract, lutein supplementation has been shown to improve visual acuity and glare sensitivity [32].

Thus, a compelling body of scientific evidence supports encouraging Americans to consume more lutein to reduce their risk of AMD and cataract formation. However, restricting a qualified health claim to only one form of lutein esters would prohibit similar statements on common lutein-rich foods and other forms of lutein in dietary supplements, including the bioactive free, non-esterified form of the molecule. In conclusion, I feel a qualified health claim that lutein (in any bioavailable form) may reduce the risk of AMD and cataract formation is substantiated by the totality of available scientific evidence and may assist Americans in better helping themselves promote their health.

Sincerely,



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References

1. USDA National Nutrient Database for Standard Reference, Release 16, Reports by Single Nutrients. USDA Nutrient Data Laboratory, Agricultural Research Service. <http://www.nal.usda.gov/fnic/foodcomp/Data/SR16>, accessed November 21, 2003.

2. Handelman GJ, Nightingale ZD, Lichtenstein AH, Schaefer EJ, Blumberg JB: Lutein and zeaxanthin concentrations in plasma after dietary supplementation with egg yolk. *Am J Clin Nutr* 70:247-251, 1999.
3. Bone RA, Landrum JT, Tarsis SL: Preliminary identification of the human macular pigment. *Vis Res* 25: 1531-1535, 1985.
4. Bone RA, Landrum JT, Fernandez L, Tarsis SL: Analysis of the macular pigment by HPLC: retinal distribution and age study. *Invest Ophthalmol Vis Sci* 29:843-849, 1988.
5. Handelman GJ, Dratz EA, Reay CC, van Kuijk FJGM: Carotenoids in the human macula and whole retina. *Invest Ophthalmol Vis Sci* 29:850-855, 1988.
6. Bone RA, Landrum JT, Friedes LM, Gomez CM, Kilburn MD, Menendez E, Vidal I, Wang W: Distribution of lutein and zeaxanthin stereoisomers in the human retina. *Exp Eye Res* 64:211-218, 1997.
8. Krinsky NI, Landrum JT, Bone RA: Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. *Annu Rev Nutr* 23:171-201, 2003.
7. Yeum KJ, Taylor A, Tang G, Russell RM: Measurement of carotenoids, retinoids, and tocopherols in human lenses. *Invest Ophthalmol Vis Sci* 36:2756-2761, 1995.
9. Hammond Jr BR, Johnson EJ, Russell RM, Krinsky NI, Yeum KJ, Edwards RB, Snodderly DM: Dietary modification of human macular pigment density. *Invest Ophthalmol Vis Sci* 38:1795-1801, 1997.
10. Johnson EJ, Hammond BR, Yeum KJ, Qin J, Wang XD, Castaneda C, Snodderly DM, Russell RM: Relation among serum and tissue concentrations of lutein and zeaxanthin and macular pigment density. *Am J Clin Nutr* 71:1555-1562, 2000.
11. Landrum JT, Bone RA, Joa H, Kilburn MD, Moore LL, Sprague KE: A one year study of the macular pigment: the effect of 140 days of lutein supplement. *Exp Eye Res* 65:57-62, 1997.
12. Berendschot TTJM, Goldbohm RA, Klopping WAA, van de Kraats J, van Norel J, van Norren D: Influence of lutein supplementation on macular pigment, assessed with two objective techniques. *Invest Ophthalmol Vis Sci* 41:3322-3326, 2000.
13. Bone RA, Landrum JT, Guerra LH, Ruiz CA: Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. *J Nutr* 133:992-998, 2003.
14. Aleman TS, Duncan JL, Bieber ML, de Castro E, Marks DA, Gardner LM, Steinberg JD, Cideciyan AV, Maguire MG, Jacobson SG: Macular pigment and lutein supplementation in retinitis pigmentosa and Usher syndrome. *Invest Ophthalmol Vis Sci* 42:1873-1881, 2001.
15. Hammond BR, Wooten BR, Snodderly DM: Preservation of visual sensitivity of older subjects: association with macular pigment density. *Invest Ophthalmol Vis Sci* 39:397-406, 1998.
16. Curran-Celentano J, Hammond Jr BR, Ciulla TA, Cooper DA, Pratt LM, Danis RB: Relation between dietary intake, serum concentrations, and retinal concentrations of lutein and zeaxanthin in adults in a Midwest population. *Am J Clin Nutr* 74:796-802, 2001.

17. Bone RA, Landrum JT, Dixon Z, Chen Y, Llerena CM: Lutein and zeaxanthin in the eyes, serum and diet of human subjects. *Exp Eye Res* 71:239-245, 2000.
18. Broekmans WMR, Berendschot TTJM, Klopping-Ketelaars IAA, de Vries AJ, Goldbohm RA, Tijburg LBM, Kardinaal AFM, van Poppel G: Macular pigment density in relation to serum and adipose tissue concentrations of lutein and serum concentrations of zeaxanthin. *Am J Clin Nutr* 76:595-603, 2002.
19. Bone RA, Landrum JT, Mayne ST, Gomez CM, Tibor SE, Twaroska EE: Macular pigment in donor eyes with and without AMD: a case control study. *Invest Ophthalmol Vis Sci* 42:235-240, 2001.
20. Eye Disease Case-Control Study Group: Antioxidant status and neovascular age-related macular degeneration. *Arch Ophthalmol* 111:104-109, 1993.
21. Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, Farber MD, Gragoudas ES, Haller J, Miller DT, Yannuzzi LA, Willett W; for the Eye Disease Case-Control Study Group: Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *J Am Med Assoc* 272:1413-1420, 1994.
22. Snellen ELM, Verbeek ALM, Van den Hoogen GWP, Cruysberg JRM, Hoyng CB: Neovascular age-related macular degeneration and its relationship to antioxidant intake. *Acta Ophthalmol Scand* 80:368-371, 2002.
23. Mares-Perlman JA, Brady WE, Klein R, Klein BEK, Bowen P, Stacewicz-Sapuntzakis M, Palta M: Serum antioxidants and age-related macular degeneration in a population based case control study. *Arch Ophthalmol* 113:1518-1523, 1995.
24. Mares-Perlman JA, Klein R, Klein BEK, Greger JL, Brady WE, Palta M, Ritter LL: Association of zinc and antioxidant nutrients with age-related maculopathy. *Arch Ophthalmol* 114:991-997, 1996.
25. VandenLangenberg GM, Mares-Perlman JA, Klein R, Klein BEK, Brady WE, Palta W: Associations between antioxidant and zinc intake and the 5 year incidence of early age-related maculopathy in the Beaver Dam Eye Study. *Am J Epidemiol* 148:204-214, 1998.
26. Flood V, Smith W, Wang JJ, Manzi F, Webb K, Mitchell P: Dietary antioxidant intake and incidence of early age-related maculopathy. *Ophthalmology* 109:2272-2278, 2002.
27. Chasan-Taber L, Willett WC, Seddon JM, Stampfer MJ, Rosner B, Colditz GA, Speizer FE, Hankinson SE: A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women. *Am J Clin Nutr* 70:509-516, 1999.
28. Brown L, Rimm EB, Seddon JM, Giovannucci EL, Chasan-Taber L, Spiegelman D, Willett WC, Hankinson SE: A prospective study of carotenoid intake and risk of cataract extraction in US men. *Am J Clin Nutr* 70:517-524, 1999.
29. Mares-Perlman JA, Brady WE, Klein BEK, Klein R, Haus GJ, Palta M, Ritter LL, Shoff SM: Diet and nuclear lens opacities. *Am J epidemiol* 141:322-334, 1995.
58. Lyle BJ, Mares-Perlman JA, Klein BEK, Klein R, Greger JL: Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. *Am J Epidemiol* 149:801-809, 1999.

30. Lyle BJ, Mares-Perlman JA, Klein BEK, Klein R, Palta M, Bowen PE, Greger JL: Serum carotenoids and tocopherols and incidence of age-related nuclear cataract. *Am J Clin Nutr* 69:272-277, 1999.
31. Gale CR, Hall NF, Phillips DIW, Martyn CN: Plasma antioxidant vitamins and carotenoids and age-related cataract. *Ophthalmology* 108:1992-1998, 2001.
32. Olmedilla B, Granado F, Blanco I, Vaquero M: Lutein but not α -tocopherol supplementation improves visual function in patients with age-related cataracts: a 2-y double-blind, placebo-controlled pilot study. *Nutrition* 19:21-24, 2003.