

**Comments on the Qualified Health Claim Petition for Lutein and
Eye Diseases (Docket Number 2004Q-0180)**

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1.0 Introduction

A qualified health claim (QHC) petition was submitted by COGNIS Corporation to the Food and Drug Administration (FDA) for lutein esters and eye diseases, namely age-related macular degeneration and cataracts (Docket Number 2004Q-0180). Kemin Foods, L.C. (Kemin Foods) requests that FDA consider the following comments on the submitted petition, as there are further data to add to the scientific evidence in support of an association between lutein and age-related macular degeneration, clarifications that are needed in the petition with regard to lutein *versus* lutein esters, and other points to take into account, resulting in a proposed revision to the QHC. The following sections of this document provide discussion on the points listed above, with cross-references to the original petition.

2.0 Additional Scientific Evidence for a Role for Lutein in Age-Related Macular Degeneration and Macular Pigment Density

2.1 Clarification of the Identity of the Substance

It needs to be made clear in the petition that scientific evidence indicates free lutein, not lutein esters, is the substance that has a role in reducing age-related macular degeneration (AMD) and increasing macular pigment density. Lutein, and not lutein esters, is readily absorbed and utilized by the human body following ingestion (see Section 4.1.1 of this Comment). Free lutein, not lutein esters, has been shown in observational, case-control, and interventional studies to have beneficial effects in decreasing the incidence of AMD (1-7). Macular pigment optical

density has been correlated with dietary intake of lutein and zeaxanthin and the presence of these substances in the diet (8-10). While some studies have been conducted with lutein esters (*e.g.*, Landrum *et al.*, 1997, as presented in Section 4, Part C of the petition), it is important to recognize that lutein esters are cleaved to result in free lutein, which is absorbed by the gut to produce beneficial effects (*i.e.*, lutein esters are not directly absorbed). Therefore, the title of Section 4 on page 28 of the document as written by the petitioner, (“Role of Lutein Esters in Improving Macular Pigment Density and Reducing the Incidence of Age-Related Macular Degeneration”) is misleading and should be changed to remove the word ‘esters’. Other instances of text requiring clarification are described in Section 4.3 of this Comment.

2.2 Additional Scientific Evidence for the Health Claim

The scientific evidence provided in support of the original QHC petition can be strengthened and should be updated with the following:

1. The study by Richer *et al.* (2004) referenced in Section B.4.C (page 40) as an abstract (Richer *et al.* 2002) (11) has now been published in the peer-reviewed Journal of Optometry (5), providing greater detail with regard to the study methods and findings. This important study, the Lutein Antioxidant Supplementation Trial (LAST), was conducted using free lutein, not lutein esters. The objective of the LAST trial was to assess the effect of lutein (alone and in combination with a number of antioxidants) on the macular pigment and on the main ophthalmic parameters that evaluate central vision integrity in atrophic AMD. This prospective, placebo-controlled, randomized, double-blind clinical trial continued for 12 months. It consisted of 90 predominantly male U.S. military veterans with objective signs and symptoms of atrophic AMD. They were selected by an ophthalmologist and randomly assigned to one of three groups. Subjects

in group 1 were supplemented with 10 mg free lutein alone. Subjects in group 2 were supplemented with a combination of 10 mg free lutein and a supplement containing several additional vitamins, minerals, and antioxidants, while patients in group 3 received a placebo capsule. Ophthalmic tests were performed at baseline and repeated every 4 months until the end of the study. Macular pigment ocular density significantly increased 36 to 43% in subjects assigned to groups 1 or 2 compared to placebo. Significant improvements in visual function were also detected in subjects supplemented with lutein alone or in combination with other vitamins, minerals, and antioxidants. The data from this prospective study provide good evidence of a positive association between lutein and the improvement of macular pigment density and visual function in patients with symptoms of atrophic AMD. Currently in Section B.4.C (page 40), the LAST study (see point 3, below) is presented only as a brief discussion in the text. For reasons of completeness (see point 2, above), and taking into account the importance of this study conducted with free lutein, the published report of results from the LAST study (5) should be included in Table 4.

2. The study by Falsini *et al.* conducted in 2003 (12) should rightfully be included among the intervention studies described in Section B.4.C of the petition (it currently is described in Section B.4.A on page 33). In this non-randomized, comparative, placebo, clinical trial both normal subjects and AMD patients were given either lutein supplement (15 mg) (17 patients and 4 normal subjects) or no treatment (13 patients and 4 normal subjects) over the 180-day test period. Retinal function was recorded using focal electroretinograms. The data showed improvements in the macula in both normal and

patient groups, providing additional evidence that lutein might have an effect on macular function early in the development of AMD, as well as in normal aging.

3. For reasons of (1) substance identification (lutein esters being a source of lutein that is absorbed by the gut and is present in the circulation) and (2) completeness, the list of intervention trials should include studies of both lutein and lutein esters, with the identity of the test substance clear and distinguishable in the table on page 42 of the petition (Section B.4.C). As it currently is presented, Table 4 excludes the studies that were conducted using supplementation with free lutein. A more comprehensive table, which includes intervention studies conducted with free lutein, is included as Appendix A to this Comment. An early intervention study conducted by Richer (1999) (13), the LAST study (5), and the study by Falsini *et al.* (12) have been included in this revised table.
4. There is an additional important intervention study currently in progress. It is described by Bartlett and Eperjesi, 2003 (14) as a randomized controlled trial to assess the effect of lutein (6 mg/day) with and without additional vitamins and antioxidants *versus* placebo on visual function over an 18-month period of supplementation. The study will target the inclusion of at least 63 normal subjects and at least 96 AMD patients.
5. Lutein supplementation has also been shown to improve macular pigment density in two studies conducted in patients with choroideremia, retinitis pigmentosa, and Usher syndrome (Duncan *et al.*, 2002; Aleman *et al.*, 2001) (15,16), and ameliorate visual function in retinitis pigmentosa in another study (Dagnelie *et al.*, 2000) (17). While these data are from studies in patients with eye diseases and, thus, are relevant to a subset of

the U.S. population, they provide additional evidence that lutein supplementation clearly can have beneficial effects in the eye.

3.0 Comments on the Adequacy of the Claim for Lutein and Cataracts

3.1 Clarification of the Identity of the Substance

As in discussions of the association between lutein and AMD (see Section 2.1, above), it should be clear in the petition that free lutein, not lutein esters, is the substance that has an association with cataracts, as lutein is absorbed and utilized by the human body following ingestion (see Section 4.1.1 of this Comment document). Therefore, the title of Section 5 on page 43 of the document as written by the petitioner, (“Role of Lutein Esters in Reducing the Incidence of Cataract Formation and Extractions”) is misleading and should be changed to remove the word ‘esters’.

3.2 Comments on the Scientific Evidence

The petitioner presented a number of studies as evidence of an association between intake of lutein esters and decreased cataract formation. It is important to note that, of the studies presented in Section B.5 (starting on page 43), two interventional studies from one group of researchers showed a positive benefit of lutein in cataracts (Olmedilla *et al.*, 2001, 2003) (18,19). The prospective studies by Chasan-Taber *et al.* (1999) and Brown *et al.* (1999) (20,21) and the observational studies by Lyle *et al.*, 1999a and b; Gale *et al.*, 2001, and Jacques *et al.*, 2001 (22-25) provide clear supporting evidence connecting increased lutein intake and decreased cataract formation. While the discussion on page 11 (paragraph 2) states that there is an association between cataract risk and lutein and zeaxanthin consumed from xanthophyll-rich foods, such as green leafy vegetables and broccoli, an analysis of the available data indicate more intervention

trials should be done in this area to demonstrate conclusive lutein benefits in cataract formation. In summary, Kemin Foods believes that, unlike the strong evidence of an association between lutein and AMD, currently a link with cataracts has been shown but not conclusively.

4.0 Evidence that the Health Claim Should be for Free Lutein

Kemin Foods considers the claim as originally proposed by the petitioner to be misleading and limiting, in that the substance in the claim should be free, unesterified lutein, not lutein esters, based on the arguments presented in the following sections.

4.1 Absorption of Lutein Following Ingestion of Lutein-Containing Foods, Lutein Esters, and Dietary Supplements

4.1.1 Absorption and Tissue Distribution of Lutein

A distinction should be made between lutein and lutein esters, in that free, unesterified lutein is the substance that is absorbed from the gut following ingestion. Humans cannot synthesize lutein and must consume it in the diet, either as lutein or lutein esters (for sources of lutein, see following Section 4.1.2). As correctly stated by the petitioner, ingested lutein esters are hydrolyzed to lutein in the gut prior to absorption (the theoretical conversion rate by mass is 2:1; however, the *in vivo* conversion rate has not yet been documented). Once cleaved, free lutein is absorbed for use by the human body (18,26-29). Thus, the lutein released from lutein esters is no different from any other dietary or supplemental source of free lutein (*i.e.*, lutein esters are sources of free lutein).

As stated by the petitioner (see the Introduction, page 6; Section A.1; Section B.3.C.5), free, unesterified lutein, unlike lutein esters, is the active compound in the human body that is

deposited in the serum, eye, and other tissues of the body and may be responsible for reduction of risk of AMD (1,3,4,6-10,30-44). Lutein and its isomer, zeaxanthin, accumulate in, and are components of, the macula pigment (1,2,4,8-10,30-37,41,43). The supporting evidence presented in the original QHC petition is of the roles of lutein and zeaxanthin, not lutein esters, as the components of the macula pigment. Hence, it is Kemin Foods' position that the claim is valid for lutein as the active substance and should universally encompass all sources of lutein, and not be limited to just one source, lutein esters.

The relative bioavailability of lutein esters to lutein is still a point of controversy. It should be noted that the results of the study by Bowen *et al.* (2002) (26), discussed in Section B.3.C.5 of the petition, are insufficient to establish equivalence between lutein esters and lutein (both from dietary supplements). An important confounding effect attributed to differences in the formulations tested (free-lutein suspended in safflower oil *vs.* lutein ester powder) would greatly affect the bioavailability of these compounds.

4.1.2 Sources of Lutein, Including Lutein Esters

Lutein cannot be synthesized in the body, as mentioned by the petitioner (see Section A.2, paragraph 1), so humans must ingest xanthophylls (lutein and zeaxanthin and their esterified forms) in the diet. Although xanthophyll esters may be present in the diet, their prevalence in the typical American diet is very low (calculated from USDA Statistics reports (1999), USDA-NCC Carotenoid Database for U.S. Foods, and (45)). In yellow-orange fruits, lutein esters are found in small amounts (USDA-NCC Carotenoid Database for U.S. Foods, and (45)). Conversely, unesterified free lutein is commonly found in the typical American diet, in green-leafy vegetables, broccoli, corn, and eggs (calculated from USDA Statistics reports (1999), USDA-NCC Carotenoid Database for U.S. Foods, and (45)). It is also important to note that almost

80% of lutein consumed in the diet is in the free form. Dietary supplements may contain both lutein esters and free lutein purified from marigold flowers (FDA GRN No. 0140).

Based on the foregoing discussion and taking into account that lutein, and not lutein esters, are readily absorbed following digestion (see Section 4.1.1, above) it is clear that lutein esters, such as Xangold®, are one of a number of sources of lutein; this distinction should be made in the petition and reflected accurately in the proposed health claim. Other misleading statements include:

- Section A.3, page 15, paragraph 1: the phrase “...Xangold® lutein esters are composed of the xanthophylls lutein and zeaxanthin...” is misleading because it implies that the lutein esters product contains these carotenoids in the free form. The statement that lutein and zeaxanthin “is the subject of this petition” further contributes to Kemin Foods’ argument that the health claim should be for lutein, and not limited to lutein esters.
- Section B.2, page 20: “...lutein esters are a form of lutein...” should be corrected to more accurately reflect, “lutein esters are a source of lutein”.

4.2 Lutein and Age-Related Macular Degeneration

As discussed previously (see Section 2.1), lutein and zeaxanthin accumulate in and are the only components of macula pigment (see Section 4.1.1). While a rationale for preferentially using lutein esters in a health claim for lutein (esters) and eye diseases is presented in the Introduction section of the petition (see page 6), the available supporting evidence only documents the use of lutein esters as one of many sources of lutein from dietary supplements or supplemented foods (18,26-29). The majority of the scientific literature supports the role of lutein as the active molecule, not lutein esters (1,2,9,30-42), And, while there are epidemiological studies

demonstrating the relationship between increased lutein intake and the reduction of AMD (3,4,6,7,20,21), there are no such studies for lutein esters. Taking into account that Kemin Foods does not believe at this moment in time that there are sufficient data to support a role for lutein in cataract prevention (see Section 3.0) and that lutein may be obtained from a number of sources, including lutein esters, the following examples of statements should be amended to more accurately reflect the existing data:

- Section A.2, page 14, paragraph 2: the first sentence should have references to lutein esters removed, yielding the statement that “The scientific evidence suggests that the protective effects of lutein and zeaxanthin on the macula of the eye are derived from dietary lutein and zeaxanthin through a series of biological mechanisms in the eye.”
- Section B.6, page 49: based on lutein being the absorbed substance following the ingestion of a variety of lutein sources, and that the existing scientific literature supports the benefits of the molecule lutein in reducing the risk of AMD and delaying the progression of this eye condition (1,3-7,9,30-42), The statement that “...lutein esters are a dietary source of lutein and zeaxanthin...” should be broadened to include green leafy vegetables, broccoli, corn, eggs, free lutein-supplemented foods and free lutein dietary supplements as sources of lutein.

4.2.1 Lutein and Eligibility for a Health Claim

4.2.1.1 Association with a Disease

As an association must exist between a substance and a disease state in order for a substance to be eligible for a health claim, Kemin Foods believes that Section A.1 should be amended to reflect more accurately that lutein, not lutein esters, meets the requirements of a qualified health

claim. Based on 21CFR 101.14(b)(1), the substance in a health claim must be associated with a disease state. This has been shown for lutein and AMD, but not for lutein esters and AMD *per se*. Dietary intake of lutein, from any source, including vegetables, supplements, and lutein esters, has been associated with a reduction in risk of age-related macular degeneration (3,4,6,7). As such, the title of the section could be changed to: “21 CFR §101.14(b)(1) Dietary intake of lutein is associated with reduction in risk of age-related macular degeneration affecting the general U.S. population”, taking into account the relative paucity of evidence for an effect of lutein on cataract formation.

4.2.1.2 Nutritive Value

With regard to the nutritive value of the substance in the claim (see Section A.2 of the petition), it would be more accurate to state that lutein is the substance that contributes nutritive value to meet the requirements for a qualified health claim. Limiting the health claim to lutein esters would effectively ignore fruits, vegetables, and other sources of supplemental lutein, the active substance that is absorbed by the body (1,9,18,26-42) (See Sections 3.1.1 and 3.1.2). In this regard, statements such as in paragraph 1 of page 14 (“...Xangold® lutein esters as a source of lutein meeting the Agency’s intended meaning of nutritive value...”) should be amended to read, “...Clearly support lutein as meeting the Agency’s intended meaning of nutritive value....”

4.3 Other Distinctions Between Lutein and Lutein Esters

4.3.1 Chemical, Physical, and Biological Properties

Clarification of the title for Section B.3 (page 20) is required, in that the title as written by the petitioner implies that lutein esters are equivalent to lutein and zeaxanthin. The chemical/physical/biological properties of lutein esters are different from lutein. Appendix C

shows the molecular structural differences between these compounds. Free lutein contains hydroxyl groups on each of its ionone rings, which are responsible for the orientation of lutein within cell membranes. These hydroxyl groups no longer exist in lutein esters. Instead fatty acids are esterified to lutein to form lutein esters. These esters must be cleaved in the gut to release the active molecule (free lutein; theoretical conversion ratio 2:1 lutein esters: lutein; however, the *in vivo* conversion rate has not yet been documented), which is then absorbed and transported to various tissues of the body. As such, there are two possible corrections that could be made:

1. A description of the chemical, physical, and biological differences between lutein esters and lutein should be added to the petition, as the information on pages 21 to 27 of the petition (*i.e.*, Section B.3) describe the chemical, physical and biological properties of free lutein, not lutein esters.

Or

2. The title of the section should be altered to accurately reflect the data described (*e.g.*, “Chemical/Physical/Biological Properties of Lutein and Zeaxanthin, the Hydrolysis Products of Esterified Lutein and Zeaxanthin”).

4.3.2 *Safety*

Kemin Foods filed a GRAS notification for free lutein with the FDA (GRN No. 0140) (November 21, 2003). A “No Objection” letter from FDA was received June 14, 2004. Also in June 2004, JECFA approved submissions by Kemin Foods and DSM Nutritional Products for an ADI for lutein and zeaxanthin of 2 mg/kg bw. In addition, a published, peer-reviewed safety assessment of free lutein derived from marigold flowers provides evidence to support the safety

of lutein, including data from animal toxicology and mutagenicity studies (46). In this notification, the intake of lutein from plant sources was estimated to be 2 to 4 mg/person/day on average, based on U.S. data (47).

The combined mean intake of lutein and zeaxanthin for individuals that met their recommended daily intake of vegetables was 7.3 mg/person/day at the 90th percentile, based on the same data set used by the IOM (46). Lutein intake from consumption of proposed food-uses for lutein was estimated to be 7.3 mg/person/day (0.14 mg/kg body weight/day), with a potential maximum intake of lutein of 13.4 mg/person/day at the 90th percentile. Lutein intakes from proposed food-uses for free lutein are provided as Appendix B to these comments. The estimated lutein intake from conventional foods and lutein-supplemented foods was 20.7 mg/person/day (7.3 + 13.4 mg/person/day) at the 90th percentile level, and the proposed intake of lutein as an ingredient in medical foods intended as the sole item of the diet was 20 mg/day.

In summary, calculated estimates of lutein intake in the safety discussion (see Section A.3, page 16, paragraph 2), should be amended to reflect lutein from all sources (*i.e.*, conventional/natural foods, supplemented foods, and dietary supplements), as lutein is the active substance that is absorbed following ingestion, as well as the most commonly-occurring form of lutein.

It is important to note that, with regard to safety in Section A.3 (page 15, paragraph 2), the petitioner mentions the existence of seven clinical studies reporting the safe consumption of 18 to 60 mg/day lutein equivalents, indicating that the studies were conducted using free lutein as well as lutein esters (expressed as lutein equivalents). To Kemin Foods' knowledge, there is no universally accepted conversion factor of lutein esters to lutein. As mentioned previously, the theoretical conversion ratio is 2:1 but the *in vivo* conversion rate has not yet been documented.

However, scientific evidence exists to support the universality of a health claim for lutein, the biologically active substance, from any and all sources.

Note that in Section A.3 (page 15), the petitioner suggests that edible flowers are a source of lutein diesters; however, yellow flowers are not present in the typical American diet.

5.0 Comment on the Quantity of the Substance as Part of the Health Claim

A comparison of the daily U.S. intake of approximately 2 mg per day lutein *versus* studies reporting benefits of lutein in AMD at higher levels of lutein intake, such as 6 mg of lutein/day as in the study by Seddon *et al.* 1994 (6), indicate that additional lutein intake from vegetables or dietary supplements could reduce the risk of AMD. Studies such as the ones cited in the petition have shown a correlation between lutein and zeaxanthin level in the diet and in the plasma. With respect to lutein esters, however, the daily intake amount of lutein esters needed to provide a biologically meaningful quantity of lutein and zeaxanthin in the diet has not clearly been demonstrated. Kemin Foods does not believe that a quantity should be included in the health claim. It should be noted that eliminating the dosage, which applies only to lutein esters, also would allow for a wider range of lutein sources (including vegetables, fruits, eggs) to use the qualified health claim, and to promote the health benefits of lutein to the public.

6.0 Comment on the Inclusion of a Brand Name in the Claim

Based on the belief that lutein from a variety of sources, including the diet and free lutein and lutein esters supplements, is the substance to be addressed in the health claim, Kemin Foods does not agree that a trademark or registered named product should be included in the claim (*i.e.*, “Xangold®” lutein esters). As cleavage of lutein esters provides a source of free lutein, and as

the lutein that is released after digestion of the Xangold® product is not different from other dietary or supplemental sources of free lutein, a specific claim for benefits of Xangold® esters would not be appropriate and may be misleading or limiting in the scope of the potential benefits from increasing lutein exposure from all sources.

7.0 Summary and Proposed Revised Claim

In this Comment, Kemin Foods has presented a number of comments regarding COGNIS Corporation's QHC petition for lutein esters and eye diseases, specifically AMD and cataracts.

To summarize, Kemin Foods has presented the following points for the Agency's consideration:

- Lutein, and not lutein esters, is the active, physiologically relevant substance that is absorbed by the gut following ingestion.
- Lutein esters are clearly a source of lutein; however, they are only one of a number of other sources of lutein, including vegetables, fruits, eggs, supplemented foods, and dietary supplements. Free lutein is the most prevalent source in natural foods.
- Lutein, and not lutein esters, is the compound that is utilized in the macula as pigment, along with its isomer, zeaxanthin. Thus, lutein is the substance which provides nutritive value.
- In addition to the studies presented in the QHC, there are 10 other studies that have demonstrated a positive effect of increased lutein intake on the development of AMD.

Taking into account the additional studies on lutein and AMD provided in this Comment,

there clearly is a large body of evidence demonstrating a beneficial association between

increased lutein intake and AMD, but very few studies in this area of research that have been conducted with lutein esters. Thus, lutein is clearly eligible as the substance having an association with a disease for which the general U.S. population is at risk.

- The data indicating an association between lutein/lutein esters and cataract formation are in Kemin Foods' opinion compelling but preliminary to support a qualified health claim at this moment in time for an effect of lutein on cataracts.
- The health claim is considered to be limiting and misleading if restricted to Xangold® lutein esters, as currently proposed in the petition. Instead, the health claim should be broadened to more accurately present lutein (from a number of sources) as the substance that may potentially have benefits with regard to AMD.
- As free lutein is released by Xangold® esters following cleavage in the gut, and this lutein is no different than any other dietary or supplemental source of free lutein, a specific claim for benefits of Xangold® lutein esters is misleading to the general public. The same benefits may be obtained from eating supplemental lutein and a variety of vegetables, fruits, and other natural foods.

7.1 Proposed Revised Claim

In Section D, page 57, the petitioner proposes the following claim:

“Consumption of 12 mg Xangold® lutein esters per day may reduce the risk of age-related macular degeneration and cataract formation. FDA has determined that the evidence is supportive, but not conclusive, for this claim. (This food/dietary supplement provides ___ mg lutein esters per serving).”

After consideration of all of the points listed above, Kemin Foods proposes the following revised qualified health claim:

“Consumption of lutein may reduce the risk of age-related macular degeneration. FDA has determined that the evidence is supportive, but not conclusive, for this claim.”

Revising the health claim so that it correctly identifies the substance that provides benefit is not a contradiction of the goals of the original petitioner or of FDA. Specifically, in a discussion of the benefits of incorporation of “Xangold® lutein esters *as a source of lutein*” [emphasis, Kemin Foods’], into conventional foods that are widely consumed (see Section A.1, page 12, paragraph 2), the petition states that by “fully informing the consumer of the benefits of health claim labeling of these foods they will be able to select preferred foods which incorporate this added nutritive value”. Under this section, the petitioner suggests that the only way consumers can benefit from lutein is by consuming supplemented foods and vitamins containing lutein esters, specifically Xangold® lutein esters. By expanding the health claim to include lutein, consumers can choose to increase their intake of lutein from a balanced diet rich in vegetables, as well as commercially available supplemented conventional food products, and/or dietary supplements containing lutein or lutein esters as a source of lutein. A claim including only lutein esters will exclude most of the dietary sources of lutein (USDA-NCC Carotenoids Database for U.S. Foods).

It is considered that the public will benefit from a qualified health claim for lutein as the active substance. By changing the qualified health claim to lutein, a very positive message can be sent to the American population about the benefits of healthful eating, good nutrition, and eye health.

Although the petitioner states in Section B.6.B of the petition (see page 53) that no changes in dietary eating habits in the U.S. population are expected with the proposed health claim, a likely statement for a claim only including lutein esters, it should be pointed out that a claim broadened to include the lutein molecule itself may have a different outcome. Consumers concerned about the risk of AMD may be able to find the qualified health claim on a range of different foods and beverages in their supermarket. Therefore, a claim that includes lutein may provide additional incentives for the U.S. population to eat a variety of foods, possibly resulting in an increasing dietary intake of vegetables, as recommended by the U.S. government, and other lutein sources, such as free lutein and lutein esters, dietary supplements, and supplemented foods.

8.0 References

- 1. Landrum, J. T., Bone, R. A. & Kilburn, M. D. (1997) The macular pigment: a possible role in protection from age-related macular degeneration. *Adv Pharmacol* 38: 537-556.**
- 2. Krinsky, N. I., Landrum, J. T. & Bone, R. A. (2003) Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. *Annu Rev Nutr* 23: 171-201.**
- 3. (1993) Antioxidant status and neovascular age-related macular degeneration. Eye Disease Case-Control Study Group. *Arch Ophthalmol* 111: 104-109.**
- 4. Bone, R. A., Landrum, J. T., Mayne, S. T., Gomez, C. M., Tibor, S. E. & Twaroska, E. E. (2001) Macular pigment in donor eyes with and without AMD: a case-control study. *Invest Ophthalmol Vis Sci* 42: 235-240.**
- 5. Richer, S., Stiles, W., Statkute, L., Pulido, J., Frankowski, J., Rudy, D., Pei, K., Tsipursky, M. & Nyland, J. (2004) Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry* 75: 216-230.**
- 6. Seddon, J. M., Ajani, U. A., Sperduto, R. D., Hiller, R., Blair, N., Burton, T. C., Farber, M. D., Gragoudas, E. S., Haller, J., Miller, D. T. & et al. (1994) Dietary**

carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. *Jama* 272: 1413-1420.

7. Snellen, E. L., Verbeek, A. L., Van Den Hoogen, G. W., Cruysberg, J. R. & Hoyng, C. B. (2002) Neovascular age-related macular degeneration and its relationship to antioxidant intake. *Acta Ophthalmol Scand* 80: 368-371.

8. Curran-Celentano, J., Hammond, B. R., Jr., Ciulla, T. A., Cooper, D. A., Pratt, L. M. & Danis, R. B. (2001) 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.

9. Bone, R. A., Landrum, J. T., Dixon, Z., Chen, Y. & Llerena, C. M. (2000) Lutein and zeaxanthin in the eyes, serum and diet of human subjects. *Exp Eye Res* 71: 239-245.

10. Bernstein, P. S., Burrows, J. & Askew, E. W. (2002) Serum and Macular Response to Antioxidant Supplementation Versus a Carotenoid-Rich Dietary Intervention in Elderly (Conference Abstract). 157 (Final Program).

11. Richer, S. P., Stiles, W., Statkute, L., Pei, K. Y., Frankowski, J., Nyland, J., Pulido, J. & Rudy, D. (2002) The Lutein Antioxidant Supplementation Trial (Conference Abstract).

12. Falsini, B., Piccardi, M., Iarossi, G., Fadda, A., Merendino, E. & Valentini, P. (2003) Influence of short-term antioxidant supplementation on macular function in age-related maculopathy. A pilot study including electrophysiologic assessment. *Ophthalmology* 110: 51-60.

13. Richer, S. (1999) ARMD--pilot (case series) environmental intervention data. *J Am Optom Assoc* 70: 24-36.

14. Bartlett, H. & Eperjesi, F. (2003) Age-related macular degeneration and nutritional supplementation: a review of randomised controlled trials. *Ophthalmic Physiol Opt* 23: 383-399.

15. Duncan, J. L., Aleman, T. S., Gardner, L. M., De Castro, E., Marks, D. A., Emmons, J. M., Bieber, M. L., Steinberg, J. D., Bennett, J., Stone, E. M., MacDonald, I. M., Cideciyan, A. V., Maguire, M. G. & Jacobson, S. G. (2002) Macular pigment and lutein supplementation in choroideremia. *Exp Eye Res* 74: 371-381.

16. Aleman, T. S., Duncan, J. L., Bieber, M. L., de Castro, E., Marks, D. A., Gardner, L. M., Steinberg, J. D., Cideciyan, A. V., Maguire, M. G. & Jacobson, S. G.

(2001) Macular pigment and lutein supplementation in retinitis pigmentosa and usher syndrome. *Invest Ophthalmol Vis Sci* 42: 1873-1881.

17. Dagnelie, G., Zorge, I. S. & McDonald, T. M. (2000) Lutein improves visual function in some patients with retinal degeneration: a pilot study via the Internet. *Optometry* 71: 147-164.

18. Olmedilla, B., Granado, F., Blanco, I. & Vaquero, M. (2003) Lutein, but not alpha-tocopherol, supplementation improves visual function in patients with age-related cataracts: a 2-y double-blind, placebo-controlled pilot study. *Nutrition* 19: 21-24.

19. Olmedilla, B., Granado, F., Blanco, I., Vaquero, M. & Cajigal, C. (2001) Lutein in patients with cataracts and age-related macular degeneration: a long-term supplementation study. *J Sci Food Agric* 81: 904-909.

20. Chasan-Taber, L., Willett, W. C., Seddon, J. M., Stampfer, M. J., Rosner, B., Colditz, G. A., Speizer, F. E. & Hankinson, S. E. (1999) A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women. *Am J Clin Nutr* 70: 509-516.

21. Brown, L., Rimm, E. B., Seddon, J. M., Giovannucci, E. L., Chasan-Taber, L., Spiegelman, D., Willett, W. C. & Hankinson, S. E. (1999) A prospective study of carotenoid intake and risk of cataract extraction in US men. *Am J Clin Nutr* 70: 517-524.

22. Lyle, B. J., Mares-Perlman, J. A., Klein, B. E., Klein, R. & Greger, J. L. (1999) Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. *Am J Epidemiol* 149: 801-809.

23. Lyle, B. J., Mares-Perlman, J. A., Klein, B. E., Klein, R., Palta, M., Bowen, P. E. & Greger, J. L. (1999) Serum carotenoids and tocopherols and incidence of age-related nuclear cataract. *Am J Clin Nutr* 69: 272-277.

24. Gale, C. R., Hall, N. F., Phillips, D. I. & Martyn, C. N. (2001) Plasma antioxidant vitamins and carotenoids and age-related cataract. *Ophthalmology* 108: 1992-1998.

25. Jacques, P. F., Chylack, L. T., Jr., Hankinson, S. E., Khu, P. M., Rogers, G., Friend, J., Tung, W., Wolfe, J. K., Padhye, N., Willett, W. C. & Taylor, A. (2001) Long-term nutrient intake and early age-related nuclear lens opacities. *Arch Ophthalmol* 119: 1009-1019.

26. Bowen, P. E., Herbst-Espinosa, S. M., Hussain, E. A. & Stacewicz-Sapuntzakis, M. (2002) Esterification does not impair lutein bioavailability in humans. *J Nutr* 132: 3668-3673.
27. Bone, R. A., Landrum, J. T., Guerra, L. H. & Ruiz, C. A. (2003) Lutein and Zeaxanthin Dietary Supplements Raise Macular Pigment Density and Serum Concentrations of these Carotenoids in Humans. *J Nutr* 133: 992-998.
28. Landrum, J. T., Bone, R. A., Joa, H., Kilburn, M. D., Moore, L. L. & Sprague, K. E. (1997) A one year study of the macular pigment: the effect of 140 days of a lutein supplement. *Exp Eye Res* 65: 57-62.
29. Roodenburg, A. J., Leenen, R., van het Hof, K. H., Weststrate, J. A. & Tijburg, L. B. (2000) Amount of fat in the diet affects bioavailability of lutein esters but not of alpha-carotene, beta-carotene, and vitamin E in humans. *Am J Clin Nutr* 71: 1187-1193.
30. Bernstein, P. S., Khachik, F., Carvalho, L. S., Muir, G. J., Zhao, D. Y. & Katz, N. B. (2001) Identification and Quantitation of Carotenoids and their Metabolites in the Tissues of the Human Eye. *Exp Eye Res* 72: 215-223.
31. Bone, R. A., Landrum, J. T., Friedes, L. M., Gomez, C. M., Kilburn, M. D., Menendez, E., Vidal, I. & Wang, W. (1997) Distribution of lutein and zeaxanthin stereoisomers in the human retina. *Exp Eye Res* 64: 211-218.
32. Bone, R. A., Landrum, J. T., Hime, G. W., Cains, A. & Zamor, J. (1993) Stereochemistry of the human macular carotenoids. *Invest Ophthalmol Vis Sci* 34: 2033-2040.
33. Bone, R. A. & Landrum, J. T. (1992) Distribution of macular pigment components, zeaxanthin and lutein, in human retina. *Methods Enzymol* 213: 360-366.
34. Bone, R. A., Landrum, J. T., Fernandez, L. & Tarsis, S. L. (1988) Analysis of the macular pigment by HPLC: retinal distribution and age study. *Invest Ophthalmol Vis Sci* 29: 843-849.
35. Bone, R. A., Landrum, J. T. & Tarsis, S. L. (1985) Preliminary identification of the human macular pigment. *Vision Res* 25: 1531-1535.
36. Khachik, F., de Moura, F. F., Zhao, D. Y., Aebischer, C. P. & Bernstein, P. S. (2002) Transformations of selected carotenoids in plasma, liver, and ocular tissues of humans and in nonprimate animal models. *Invest Ophthalmol Vis Sci* 43: 3383-3392.

37. Khachik, F., Bernstein, P. S. & Garland, D. L. (1997) Identification of lutein and zeaxanthin oxidation products in human and monkey retinas. *Invest Ophthalmol Vis Sci* 38: 1802-1811.
38. Khachik, F., Spangler, C. J., Smith, J. C., Jr., Canfield, L. M., Steck, A. & Pfander, H. (1997) Identification, quantification, and relative concentrations of carotenoids and their metabolites in human milk and serum. *Anal Chem* 69: 1873-1881.
39. Khachik, F., Beecher, G. R. & Smith, J. C. (1995) Lutein, lycopene, and their oxidative metabolites in chemoprevention of cancer. *J Cell Biochem Suppl* 22: 236-246.
40. Khachik, F., Beecher, G. R., Goli, M. B., Lusby, W. R. & Smith, J. C., Jr. (1992) Separation and identification of carotenoids and their oxidation products in the extracts of human plasma. *Anal Chem* 64: 2111-2122.
41. Landrum, J. T. & Bone, R. A. (2001) Lutein, zeaxanthin, and the macular pigment. *Arch Biochem Biophys* 385: 28-40.
42. Micozzi, M. S., Brown, E. D., Edwards, B. K., Bieri, J. G., Taylor, P. R., Khachik, F., Beecher, G. R. & Smith, J. C., Jr. (1992) Plasma carotenoid response to chronic intake of selected foods and beta-carotene supplements in men. *Am J Clin Nutr* 55: 1120-1125.
43. Broekmans, W. M., Berendschot, T. T., Klopping-Ketelaars, I. A., de Vries, A. J., Goldbohm, R. A., Tijburg, L. B., Kardinaal, A. F. & van Poppel, G. (2002) 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.
44. Khachik, F., Englert, G., Daitch, C. E., Beecher, G. R., Tonucci, L. H. & Lusby, W. R. (1992) Isolation and structural elucidation of the geometrical isomers of lutein and zeaxanthin in extracts from human plasma. *J Chromatogr* 582: 153-166.
45. Holden, J. M., Eldridge, A. L., Beecher, G. R., Buzzard, M., Bhagwat, S., Davis, C. S., Douglass, L. W., Gebhardt, S., Haytowitz, D. & Schakel, S. (1999) Carotenoid Content of U.S. Foods: An Update of the Database. *Journal of Food Composition and Analysis* 12: 169-196.
46. Kruger, C. L., Murphy, M., DeFreitas, Z., Pfannkuch, F. & Heimbach, J. (2002) An innovative approach to the determination of safety for a dietary ingredient derived from a new source: case study using a crystalline lutein product. *Food Chem Toxicol* 40: 1535-1549.

47. IOM (2001) Vitamin A. In: Dietary reference intakes for : vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc (National Academy of Sciences, P. o. M., Food and Nutrition Board, Institute of Medicine (IOM), ed.), pp. 82-161. National Academy Press, Washington, DC.

APPENDIX A

Appendix A

Table A-1 Intervention Trials for AMD with Dietary Modification and/or Lutein and/or Lutein Ester Supplements						
Study Reference	Test Substance	Treatment Program	No. of Subjects	Duration of Follow-up	Age of Subjects	Outcome
Hammond <i>et al.</i> , 1997	Dietary modification	60 g/d spinach (10.8 mg L, 0.3 mg Z, 5 mg β-carotene) 150 g/d corn (0.3 mg Z, 0.4 mg L)	13	15 weeks	30-65 y	Increased macula pigment density in most subjects within 4 weeks
Johnson <i>et al.</i> , 2000	Dietary modification	60 g/d spinach (19.0 umol L/d) 150 g/d corn (0.5 umol Z/d)	7	15 weeks with an additional 2-month assessment after end of dietary modification	33-83 y	Increased serum and buccal L concentrations, significant sex differences noted with negative correlations between adipose L concentration and macular pigment for women and positive relation for men
Landrum <i>et al.</i> , 1997	Lutein esters	30 mg L/day (from lutein ester)	2	140 days		3-4 weeks after supplementation macular pigment increased in density; 30-40% reduction in blue light reaching vulnerable retinal tissue
Richer, 1999	Dietary modification or lutein	Diet group: 5 ounces spinach, 4-7 times/week	14	Up to 12 weeks	70±9 y	Improvements in visual function (<i>i.e.</i> , age-related macular degeneration tests)
Berendschot <i>et al.</i> , 2000	Lutein esters	10 mg L/day (from lutein ester)	8	12 weeks	18-50 y (mean of 40.6 y)	Supplementation with lutein increased the density of the macular pigment
Schweitzer <i>et al.</i> , 2002	Lutein	6 mg L/day		40 days		Supplementation with lutein increased macular pigment density within 30 days
Bone <i>et al.</i> , 2003	Lutein or lutein esters or zeaxanthin	Lutein: 2.4 mg L/d Lutein esters: 5 or 20 mg LE/d Zeaxanthin:	L group: 21 LE group: 2 (5 mg/d) and 8 (20 mg/d)	L group: 6 months LE group: 120 d Z group: 60 d (1 subject), 120 d	>18	Lutein, lutein esters, and zeaxanthin supplementation increased serum concentration of lutein and zeaxanthin and macular pigment density

Appendix A

Table A-1 Intervention Trials for AMD with Dietary Modification and/or Lutein and/or Lutein Ester Supplements						
Study Reference	Test Substance	Treatment Program	No. of Subjects	Duration of Follow-up	Age of Subjects	Outcome
			Z group: 2	(1 subject)		
Cardinault <i>et al.</i> , 2003	Lutein	9 mg/day	12 younger subjects; 17 older subjects	5 weeks	Mean of 26.9 y Mean of 67.3	Increase in plasma lutein concentration, but no increase in macular pigment density
Falsini <i>et al.</i> , 2003	Lutein	15 mg/day plus Vitamin E and nicotinamide	30 AMD patients; 8 normal subjects	180 days	65±5y	Improvements in the macula in both normal and patient groups as measured by focal electroretinograms
Richer <i>et al.</i> , 2004	Lutein	Group 1: 10 mg/d Group 2: 10 mg/d plus additional vitamins, minerals, antioxidants Group 3: placebo	90	12 months	Mean Group 1=74.4y Group 2=73.5 Group 3=76.1	Increase in macular pigment density and improvement in visual function in Groups 1 and 2 vs. Group 3

Abbreviations: d, day; L, lutein; LE, lutein esters; Z, zeaxanthin

APPENDIX B

Appendix B

Table B-1 Proposed Food-Uses for Free Lutein and Corresponding Use-Levels for Lutein in the U.S.¹			
Food Category	Proposed Food-Use for Free Lutein	Use-Levels for Lutein (mg/RACC²)	Use-Levels for Lutein (%)³
Baked Goods and Baking Mixes	Cereal and Energy Bars	2.0	5.0 x 10 ⁻³
	Crackers and Crispbreads	2.0	6.7 x 10 ⁻³
Beverages and Beverage Bases	Bottled Water	0.5	2.1 x 10 ⁻⁴
	Carbonated Beverages	2.0	8.3 x 10 ⁻⁴
	Meal Replacements	2.0	8.3 x 10 ⁻⁴
	Tea, Ready-to-Drink	0.6	2.6 x 10 ⁻⁴
Breakfast Cereals	Instant and Regular Hot Cereals	2.0	8.3 x 10 ⁻⁴
	Ready-to-Eat Cereals	2.0	3.6 x 10 ⁻³ - 1.3 x 10 ⁻²
Chewing Gum	Chewing Gum	1.0	3.3 x 10 ⁻²
Dairy Product Analogs	Imitation Milks	2.0	8.3 x 10 ⁻⁴
	Soy Milks	1.5	6.3 x 10 ⁻⁴
Egg Products	Liquid, Frozen, or Dried Egg Substitutes	2.0	4.0 x 10 ⁻³
Fats and Oils	Margarine-like Spreads	1.5	1.0 x 10 ⁻²
	Salad Dressings	1.5	5.0 x 10 ⁻³ - 1.0 x 10 ⁻²
Frozen Dairy Desserts and Mixes	Frozen Yogurt	1.0	8.3 x 10 ⁻⁴
Gravies and Sauces	Tomato-Based Sauces	0.3	2.6 x 10 ⁻⁴
Hard Candy	Hard Candy	1.0	6.7 x 10 ⁻³
Infant and Toddler Foods*	Junior, Strained, and Toddler Type Baby Foods	1.0	5.9 x 10 ⁻⁴ - 1.4 x 10 ⁻²
Milk Products	Dry Milk	3.0	1.3 x 10 ⁻³
	Fermented Milk Beverages	0.6	2.6 x 10 ⁻⁴
	Flavored Milk and Milk Drinks	3.0	1.3 x 10 ⁻³
	Milk-Based Meal Replacements	3.0	1.3 x 10 ⁻³
	Yogurt	3.0	1.3 x 10 ⁻³
Processed Fruits and Fruit Juices	Energy, Sport, and Isotonic Drinks	2.0	8.3 x 10 ⁻⁴
	Fruit-Flavored Drinks	2.0	8.3 x 10 ⁻⁴
	Fruit Juice	2.0	8.3 x 10 ⁻⁴
	Nectars	2.0	8.3 x 10 ⁻⁴
	Vegetable Juice	2.0	8.3 x 10 ⁻⁴
Soft Candy	Chewy and Nougat Candy	1.0	2.5 x 10 ⁻³
	Fruit Snacks	1.0	2.5 x 10 ⁻³
Soups and Soup Mixes	Canned Soups	0.6	2.6 x 10 ⁻⁴

¹ Adapted from FDA GRAS Notice No. GRN 000140, submitted by Kemin Foods.

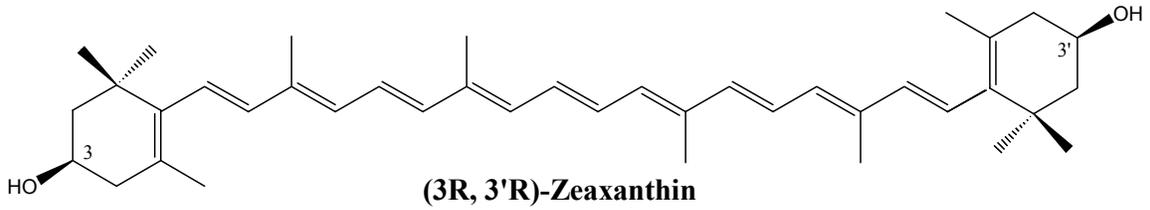
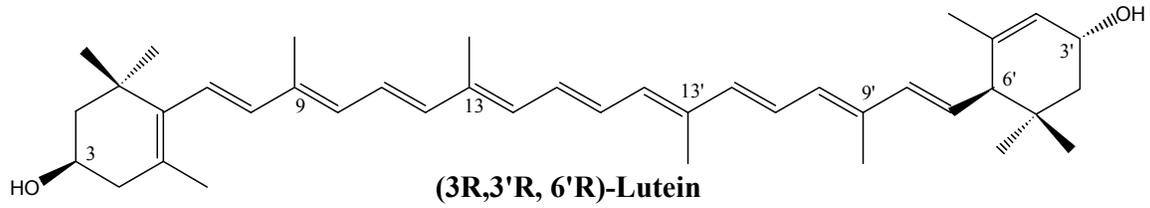
² RACC – Reference amounts customarily consumed per eating occasion (21 CFR §101.12).

³ When a range of use-levels (%) is reported for a proposed food-use, particular foods within that food-use may differ with respect to their RACC.

*Does not include infant formula.

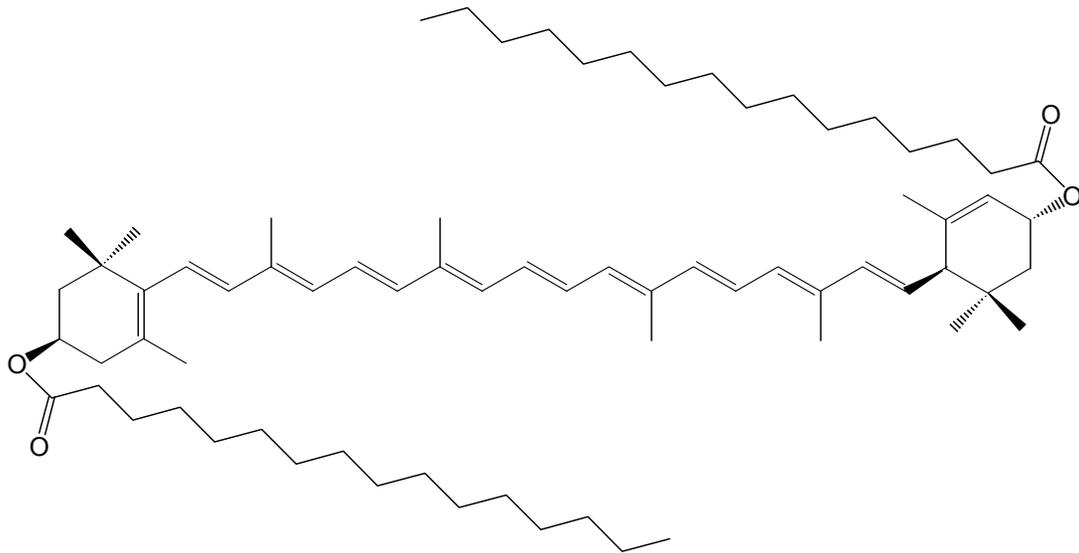
Appendix C

Chemical Structure and Molecular Weight of Lutein and Zeaxanthin Compared to Lutein dipalmitate ester



Lutein molecular wt.= 568.88 g/mol

Zeaxanthin molecular wt.=568.88 g/mol



lutein dipalmitate ester (lutein esters)

Lutein dipalmitate ester molecular wt.=1045.71 g/mol