

**SPECIAL EDITION:**  
**OMNIACTIVE INSIGHTS NEWSLETTER**  
**THE MACULAR CAROTENOIDS: AN OVERVIEW**

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# THE MACULAR CAROTENOIDS: AN OVERVIEW

Lutein and the two zeaxanthin isomers, namely RR-zeaxanthin (3R,3'R-zeaxanthin) and meso-zeaxanthin (3R,3'R'S-meso-zeaxanthin) are the only three carotenoids found in the eye, specifically in the macula. RR-zeaxanthin and meso-zeaxanthin are both considered zeaxanthin. Their concentration in the macula is highly specific: lutein is the dominant carotenoid in the peripheral macula, RR-zeaxanthin in the mid-peripheral macula and meso-zeaxanthin at the center of the macula (Exp Eye Res 1997; 64:211-218). (Table 1)

*“Lutein and the zeaxanthin isomers (RR-zeaxanthin and meso-zeaxanthin), collectively referred to as macular pigment, individually and in combination play a critical role in ocular health. Because of the presence and placement of each of these carotenoids in the eye tissue, we should not underplay the importance of any one of these three macular pigments.”*

– Jeffrey Anshel, OD, FAAO, President Ocular Nutrition Society

Each carotenoid plays a distinctive role from their highly selective positions in the eye (J Nutr. 2003; 133(4): 992-8. Food and Chem Toxicol. 2013, 59; 455-463. HKJ Ophthalmol, 2000, Vol. 4 No.1). Lutein and RR-zeaxanthin are well known, and the science behind these two xanthophylls has grown at a steady rate.

Meso-zeaxanthin historically had been incorrectly coupled with RR-zeaxanthin as an impurity or its isomer, and the measurement of meso-zeaxanthin in serum and foods had largely been ignored until awareness of its specific role in the eye emerged.

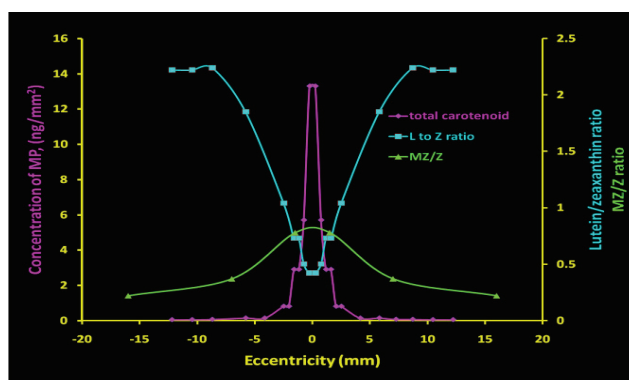


Chart: J Nutr. 2003; 133(4): 992-8

- Each carotenoid plays a distinctive role from their highly selective positions in the eye
- Meso-zeaxanthin is located at the very center of the macula, the focal point of visual function
- Its central location and stronger antioxidant potential make meso-zeaxanthin critical in protecting the most at risk tissue with the highest metabolic rate and light exposure

Each of the macular carotenoids is a potent antioxidant with specific targets (FDA 21 CFR Part 101 Docket No. 91N-0101, p.6). Meso-zeaxanthin is the most potent of the three, followed by RR-zeaxanthin, which is twice as potent as lutein in quenching ROS (Biochem Biophys Acta 2005; 1740: 116-121). The protective role of lutein focuses on the cellular membrane. Meso-zeaxanthin is located at the very center of the macula, the focal point of visual function. Its central location and stronger antioxidant potential make meso-zeaxanthin critical in protecting the most at risk tissue with the highest metabolic rate and light exposure, and it also provides the best protection for the lipid membrane (Methods Enzymol 1999;299:457-467. Rev Ophthal 2011, <http://www.revophth.com/content/d/features/i/1448c/27340/>). A mixture of the three macular carotenoids at a ratio of 1:1:1 has been shown to quench singlet oxygen more effectively than any of the three individually (Arch Biochem Biophys. 2010 Dec 1; 504 (1): 56-60). (Table 2)

Meso-zeaxanthin and RR-zeaxanthin are perpendicular to the cell membranes to better protect the lipid membrane from oxidation and absorb similar wavelengths of high energy light (Arch Biochem Biophys 1999; 371: 301-307). Lutein is both parallel and perpendicular to and oriented near the surface of the cell membrane, making it a better filter of blue light. However, because lutein and the zeaxanthin isomers absorb different wavelengths of light, together, the three absorb a broader spectrum of high

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energy light. Structural differences, orientation to cell membranes, macular location and differing absorption spectra help the three macular carotenoids work together to provide superior filtration of blue light as compared to each individually (Photochem Photobiol 2003; 78: 138-145. Arch Biochem Biophys 2010; 504(1): 56-60. J Food Composition Anal 2011; 24: 830-836). (Table 3)

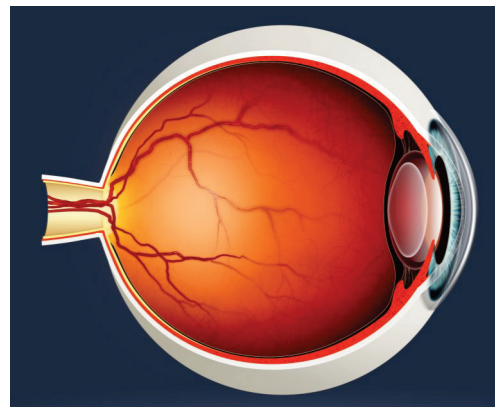
In addition, the three macular carotenoids work together for optimal eye health and visual function. Each individually and in combination with each other has been shown to increase macular pigment optical density. But typical central peak of macular pigment can be realized in subjects with atypical macular pigment spatial profiles at baseline only when supplemented with all three macular carotenoids, but not with a supplement lacking meso-zeaxanthin (Exp Eye Res 2012; 101: 9-15).

All three macular carotenoids have been studied in humans. However, although difficult to measure and typically not tested, commercial lutein and RR-zeaxanthin from virtually any source can sometimes show trace amounts of meso-zeaxanthin ranging from 0.02-0.07% if chiral analysis is performed (Eye 2013, 1-7. Internal OmniActive Chiral Analysis Report). As such, whether as dietary intake or part of lutein and/or zeaxanthin isomer(s) supplementation, meso-zeaxanthin has already been part of studies investigating the nutritional impact on visual performance and AMD risk reduction. There are over 70 lutein studies at doses of 6-40mg, over 10 RR-zeaxanthin studies at doses of 1-20mg and several meso-zeaxanthin studies at doses of 8-14.9mg. (Table 4)

Science continues to develop around the role of meso-zeaxanthin in eye health, and it is already established as a critical macular carotenoid with a specific function in ocular health. Today the significance of meso-zeaxanthin in the retina is well-established (Br J Nutr. 2008 Dec; 100(6):1307-14; Eye 2013, 1-7). Meso-zeaxanthin has also been shown to be present in human serum pre-supplementation, and supplementation of meso-zeaxanthin has resulted in both increased serum levels and macular pigment optical density (Curr Eye Res. 2010 Apr; 35(4):335-51). Meso-zeaxanthin has proven bioavailability in humans (Br J Nutr. 2008 Dec; 100(6):1307-14).



*“Many studies of meso-zeaxanthin have demonstrated that consumption of relatively high doses (e.g., 15 mg daily) over long periods of time (120 days or longer) have produced no adverse effects whatsoever. These studies have, however, demonstrated beneficial effects for ocular health.”*  
—James M. Stringham, PhD, Research Professor  
Univ. of Georgia



- *The three macular carotenoids work together to provide superior filtration of blue light as compared to each individually*
- *Commercial lutein and RR-zeaxanthin from virtually any source can sometimes show trace amounts of meso-zeaxanthin ranging from 0.02-0.07% if chiral analysis is performed*
- *Meso-zeaxanthin has also been shown to be present in human serum pre-supplementation, and meso-zeaxanthin supplementation has resulted in both increased serum levels and macular pigment optical density*
- *Meso-zeaxanthin has proven bioavailability in humans*



- *Meso-zeaxanthin is considered safe for use in food and dietary supplements*
- *Meso-zeaxanthin meets the regulatory criteria per the FDA-acknowledged GRAS notification filed by OmniActive Health Technologies for Lutemax® 2020 Lutein and Enhanced Levels of Zeaxanthin Isomers containing meso-zeaxanthin*
- *The body gets meso-zeaxanthin from both the diet and the conversion of naturally occurring lutein in the eye to meso-zeaxanthin*

There have been no reports of adverse events in the research. Meso-zeaxanthin is considered safe for use in food and dietary supplements and it meets the regulatory criteria per the FDA-acknowledged GRAS notification filed by OmniActive Health Technologies for Lutemax® 2020 Lutein with Enhanced Levels of Zeaxanthin Isomers containing meso-zeaxanthin (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-foods-gen/documents/document/ucm275974.pdf>). In addition, Lutemax® 2020 Lutein with Enhanced Levels of Zeaxanthin Isomers containing meso-zeaxanthin was proven safe in a GLP toxicological study (Food Chem Toxicol. 2011 Nov; 49(11):2841-8).

Meso-zeaxanthin in the body is not only from conversion of lutein in the eye, as has been reported by some researchers (Nutr Clin Care. 2002 Mar-Apr; 5(2):56-65. Nutr Metab (Lond) 2007; 4(12): 12). Trace amounts of meso-zeaxanthin are present in the diet in various parts of the world. Meso-zeaxanthin is found in 21 species of fish, shrimp and sea turtles, as well as eggs in California and Mexico (Comp Biochem Physiol B 1986; 83:121-124). Meso-zeaxanthin has been a component of a xanthophyll supplement added to chicken feed in Mexico over the last 10 years. Egg consumption in Mexico is approximately one egg/person per day and the potential contribution of this food source of meso-zeaxanthin to Mexican dietary intakes (J Food Composition Anal 2012; 27:139-144; Nutr Res Rev. 2007 Dec; 20(2):163-79).

*“Although food sources of meso-zeaxanthin are rare (fish skin, shrimp carapace, and turtle fat), they do exist, and have been consumed by humans for millennia. In sum, although meso-zeaxanthin might appear to be a novel, perhaps artificial nutrient, the overwhelming scientific evidence on the matter suggests that it is most certainly not; rather, it has existed for a long time, and is actively used by the body to promote health.”*

*–James M. Stringham, PhD, Research Professor, Univ, of Georgia*

Because of the lack of awareness of meso-zeaxanthin and the previous difficulty in measuring this particular carotenoid, it had typically not been tested. We therefore believe that its presence in the diet and serum has been underreported and it is most likely available in more foods than we know.

*“The body gets meso-zeaxanthin from both the diet and the conversion of naturally occurring lutein in the eye to meso-zeaxanthin. Meso-zeaxanthin is deposited in important tissues such as the retina, where it aids in maintaining eye health. In other words, meso-zeaxanthin is recognized by the human body as a substance so beneficial as to be deposited in neural tissues crucial to human performance and survival.”*

*–James M. Stringham, PhD, Research Professor, Univ, of Georgia*



- *It is now clear that meso-zeaxanthin is safe and plays a critical role alongside lutein and RR-zeaxanthin in eye health*
- *To enable our customers to meet the diverse needs of their formulators, markets and regulatory authorities, OmniActive Health Technologies offers the most innovative and complete range of macular carotenoids*

Lutein was the first commercially available macular carotenoid. As the science progressed, we discovered the need for higher levels of RR-zeaxanthin. It is now clear that meso-zeaxanthin is safe and plays a critical role alongside lutein and RR-zeaxanthin in eye health. Given the specialized locations and functions of each macular carotenoid, we cannot stand on the hypothesis alone that lutein will convert sufficiently to meso-zeaxanthin in the eye. The best way to support and protect eye health is to consume all three macular carotenoids, either from diet or from supplementation.

Since meso-zeaxanthin is difficult to achieve from the diet for many, supplementation is the most failsafe approach to meet the needs of today’s population, individuals who are living and staying active longer. With the proven safety of each of the three macular carotenoids, and the unique and collaborative roles they play in eye health, consumers can’t afford not to have all three in their diet to provide optimal support and protection for their eyes.

The eye contains three carotenoids – lutein and zeaxanthin isomers (meso-zeaxanthin and RR-zeaxanthin) – each with a specific location and distinctive roles, both individually and in combination with each other.

**OMNIACTIVE OFFERS THE COMPLETE RANGE OF MACULAR CAROTENOIDS**

To enable our customers to meet the diverse needs of their formulators, markets and regulatory authorities, OmniActive Health Technologies offers the most innovative and complete range of macular carotenoids. Through our internationally recognized and award-winning product ranges Lutemax® Lutein ingredients and OmniXan® RR-Zeaxanthin from Natural Paprika, OmniActive provides the following:

- Lutemax® Free Lutein
- Lutemax® Lutein Esters
- OmniXan® RR-Zeaxanthin From Natural Paprika
- Lutemax® 2020 Lutein with Enhanced Levels of Zeaxanthin Isomers
- Lutemax® 2020-RR Lutein and Enhanced Levels of RR-Zeaxanthin

PRODUCT RANGE	LUTEIN	RR-ZEAXANTHIN	MESO-ZEAXANTHIN
Lutemax® Free Lutein	✓	✓	
Lutemax® Lutein Esters	✓	✓	
OmniXan® RR-Zeaxanthin from Natural Paprika		✓	
Lutemax® 2020 Lutein with Enhanced Levels of Zeaxanthin Isomers	✓	✓	✓
Lutemax® 2020-RR Lutein with Enhanced Levels of RR-Zeaxanthin	✓	✓	

**TABLES**

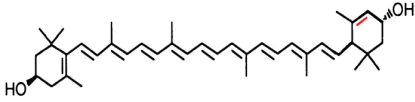
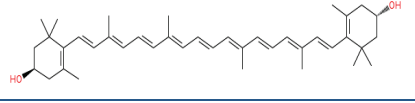
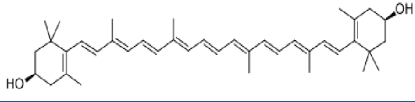
Carotenoid	Ave. Plasma Concentration (μmol/L)	Retinal Concentration			Structure
		Content (pmoles)	Total (pmoles)	%	
Lutein	0.25	Central: 17 Medial: 20 Outer: 22	59	58%	
Meso-zeaxanthin	Trace	Central: 10 Medial: 3 Outer: 2	15	15%	
RR-zeaxanthin	0.06	Central: 12 Medial: 9 Outer: 7	28	27%	

Table 1: Concentration and placement of macular carotenoids (Food and Chem Toxicol. 2013, 59; 455-463. HKJ Ophthalmol, 2000, Vol. 4 No.1)

Carotenoid	Lutein	Meso-zeaxanthin	RR-zeaxanthin
Structure	10 double bonds	11 double bonds	11 double bonds
Antioxidant Activity	Potent antioxidant	With Z-binding protein, more potent antioxidant than zeaxanthin	2x more efficacious than lutein at quenching ROS
Antioxidant Protection (focus)	Cellular membrane	Lipid membrane, central macula	Cellular membrane
Location	Periphery	Center	Mid periphery

Table 2: Antioxidant activity of macular carotenoids (Biochem Biophys Acta 2005; 1740: 116-121)

Carotenoid	Lutein	Meso-zeaxanthin	RR-zeaxanthin
Structure	10 double bonds	11 double bonds	11 double bonds
Structure	10 double bonds, 3 chiral centers	11 double bonds, 2 chiral centers	11 double bonds, 2 chiral centers
Blue Light Filtration	445 nm	451 nm	451 nm
Orientation to Cell Membrane Phospholipid Bilayer	Parallel, near the surface	Perpendicular	Perpendicular

Table 3: Blue light filtration of macular carotenoids (Photochem Photobiol 2003; 78: 138-145. Arch Biochem Biophys 2010; 504(1): 56-60. J Food Composition Anal 2011; 24: 830-836)

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	Lutein	Meso-zeaxanthin	RR-zeaxanthin
Number of human clinicals	>70 studies (solely lutein or compared to RR- and/or meso-zeaxanthin or combined with RR-zeaxanthin)	>3 (meso-zeaxanthin compared to lutein and zeaxanthin)  >70 as component of lutein and zeaxanthin	> 10 (RR-zeaxanthin in combination with other antioxidants or in combination with lutein)  >70 as a component of lutein
Dose (mg)	6-40	8-14.9	8 (zeaxanthin alone) 1-20 (in combination with or compared to lutein)
Study outcomes	<ul style="list-style-type: none"> <li>• MPOD</li> <li>• Plasma/serum lutein and zeaxanthin</li> <li>• Buccal mucosal cells lutein and zeaxanthin</li> <li>• Visual acuity Foveal and glare sensitivity</li> <li>• Visual field area</li> <li>• Luminous and chromatic sensitivity</li> <li>• Visual fatigue</li> <li>• Photostress recovery</li> <li>• Regression of AMD symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• MPOD</li> <li>• Plasma/serum meso-zeaxanthin</li> <li>• Regression of AMD symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• MPOD</li> <li>• Plasma/serum zeaxanthin</li> <li>• Buccal mucosal cells zeaxanthin</li> <li>• Visual acuity</li> <li>• Foveal and glare sensitivity</li> <li>• Visual field area</li> <li>• Luminous and chromatic sensitivity</li> <li>• Visual fatigue</li> <li>• Photostress recovery</li> <li>• Regression of AMD symptoms</li> </ul>
Bioavailability	Proven	Proven	Proven
Safety	Established	Established	Established

Table 4: Research review of macular carotenoids (Curr Eye Res. 2010 Apr; 35(4):335-51. Br J Nutr. 2008 Dec; 100(6):1307-14)

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This product is not intended to diagnose, treat, cure, or prevent any disease.

## CONTRIBUTIONS BY:



### **JEFFREY ANSHEL, OD, FAAO**

*Dr. Anshel is a 1975 graduate from the Illinois College of Optometry. He has written numerous articles and five books regarding nutritional influences on vision and computer vision concerns. Dr. Anshel is the principal of Corporate Vision Consulting, where he addresses the issues surrounding visual demands while working with computers. He also offers onsite consultations and seminars to corporations related to visual stress and productivity in the workplace. He lectures nationally to eye care providers on nutrition topics. Dr. Anshel is a Fellow of the American Academy of Optometry and President of the Ocular Nutrition Society. He maintains a private practice in Carlsbad, CA.*



### **JAMES M. STRINGHAM, PH.D.**

*Dr. Stringham is currently a Research Professor at the Nutritional Neuroscience Laboratories, University of Georgia, where he studies the potential benefits of lutein for infant neural and ocular development. Additionally because children do not generally consume an adequate quantity of vegetables, he is interested in studying how this population would respond, in the eye and systemically, to lutein supplements. Dr. Stringham has held appointments at the Schepens Eye Research Institute (Harvard Medical School), the Medical College of Georgia, and the Air Force Research Laboratory and is considered one of the leading research experts in lutein.*

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**VisionVitalize™ :** OmniActive provides VisionVitalize™ in several novel delivery forms to enable differentiated products in the eye health category. These NEW innovative formulas contribute to the maintenance of normal vision and provide vision benefits you can talk about.



**OmniActive Health Technologies:** OmniActive Health Technologies offers a range of quality ingredients, which are innovative and scientifically validated for dietary supplementation, nutritional fortification, functional food/beverage, coloring, flavor enhancement and personal care applications. We address complex challenges for customers in the dietary supplement, food and beverage space using technology-driven, sustainable solution with application support within a global regulatory framework. Whether you're looking for a new ingredient to add to a finished product, or technology to enhance an existing ingredient, you'll find unmatched innovation at OmniActive.

*Our core products are carotenoids, plant extracts and specialty functional ingredients. We leverage our international R&D strengths to deploy an array of state of the art manufacturing technologies in extraction, purification, isolation and delivery of nutritional actives. Our manufacturing operations are located at multiple sites in India and are cGMP and HACCP system compliant.*