Macushield Original Plus – Clinical Overview

Contents

Scientific Background

The Macular Carotenoids

The MacuShield range is comprised of products containing the three core ingredients; lutein (10mg) *meso*-zeaxanthin (10mg) and zeaxanthin (2mg) ("the macular carotenoids") derived from a botanical extract obtained from the marigold flower (Tagetes Erecta). The macular carotenoids, lutein (L), *meso*-zeaxanthin (MZ), and zeaxanthin (Z) are a group of pigments that are concentrated in the macula at the back of the eye, where they are collectively known as the macular pigment (MP); sometimes referred to as "the yellow pigment" (*Li 2010, Bernstein 2016*). The fovea (the central most part of the macula) [see figure 1] is often referred to as "the yellow spot" due to its yellow pigmentation, the absorption spectra of the pigments from this region were recognized to be similar to those of xanthophylls and subsequently, they were chemically identified to be lutein, zeaxanthin, and *meso*-zeaxanthin (*Bernstein 2016, Bone 1988, Bone 1993*). The fovea is free of rod receptors and is composed of tightly packed foveal cone cells (*Bernstein 2016*).

The macular carotenoids are highly concentrated at the fovea and their concentration decreases with increasing distance from the fovea. In the very central retina, equal concentrations of lutein, zeaxanthin and *meso*-zeaxanthin are present while lutein is the dominant carotenoid in the peripheral macula, zeaxanthin is dominant in the mid-peripheral macula and *meso*-zeaxanthin is dominant at the epicentre of the macula (*Bone 1997*). Near the fovea there is twice as much *meso*-zeaxanthin as lutein (*Bernstein 2016*).

Bone and Landrum (*Bone 1985*) identified lutein and its structural isomer, zeaxanthin, as the specific xanthophylls in the retina, with the xanthophyll pigment in the Henle fibre layer discovered in primates in the 1980's (*Snodderly 1984*).

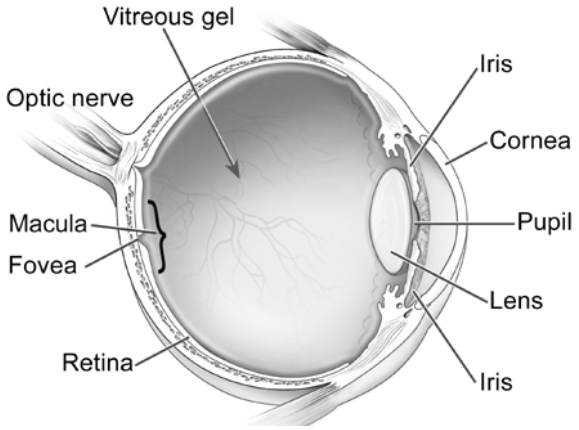

Figure 1 – National Eye Institute [https://nei.nih.gov/health/eyediagram – last accessed: 10 October 2017]

Macular Carotenoids in the diet

The MP is composed of the xanthophyll carotenoids of which there have been over 700 identified in nature (*Khachik 1991, Britton 2004, Bernstein 2016*) however, carotenoids cannot be synthesized "de novo" by humans and therefore must be obtained through the diet (*Jaswir 2011*). Historical research identified only ~6-8 carotenoids and their metabolites in human blood and tissue, of which lutein, zeaxanthin, cryptoxanthin, α-carotene, β-carotene and lycopene are the most common (*Khachik 1991*, *Parker 1989*) however, more recent research reports up to 15-30 found in the blood (*Bernstein 2016*).

Lutein and zeaxanthin have been an established nutritional component in the human diet for a long time and literature suggests a typical Western diet intake is 1.3-3mg per day, with approximately 7 times more lutein than zeaxanthin (*Connolly 2011, Abdel-Aal 2013, O'Neill 2001*) and a lower intake seen in other parts of the world (*Alvarado-Ramos 2018*). The lutein and zeaxanthin dietary intake of the general US population falls in the lowest quintile, where the dietary intake of lutein and zeaxanthin is typically less than 1mg per day.

Lutein and zeaxanthin are predominantly found in vegetables such as kale and spinach along with corn products, eggs and peppers (*Walsh 2015, Perry 2009, Abdel-Aal 2013*). *Meso*-zeaxanthin and the isomer (3S,3'S)-zeaxanthin was previously thought to be non-dietary due to the lack of identification in these particular foods. Studies do not detect *meso*-zeaxanthin in fruits or vegetables but, using retention time matching, absorption spectrum comparison, and sample spiking, the presence of *meso*-zeaxanthin has been verified in salmon skin, sardine skin, trout skin and trout flesh (*Nolan 2014*) and was identified as early as 1986 in 21 species of fish including shrimp (*Moaka 1986, Prado-Cabrero 2016*).

Clinical Studies

No clinical studies have been detailed for MacuShield Original Plus as it is classified as a food supplement in the UK any many other countries, although legal status does vary. The ingredients are well established in food supplement use.

Although there is no recommended daily amount (RDA), the generally accepted recommendation by the NHS in the UK is to eat "5 a day" fruit and/or vegetables (*Public Health England 2018*), this would give approx. 3-6mg/ day of carotenoids (*Otten 2006*). This is not always achievable, so MacuShield could suit those individuals who who may benefit from supplementation.

Safety data – Macular Carotenoids

Regulatory body assessments

Safety assessments of lutein, zeaxanthin and *meso*-zeaxanthin have been conducted by various regulatory bodies such as the US Food and Drug Administration (The FDA), The European Food Safety Authority (EFSA) and the Joint Food and Agriculture (FAO)/ World Health Organisation (WHO) Expert Committee on Food Additives (JECFA), all with positive conclusions:

- The FDA has received a number of "Generally Recognised As Safe (GRAS)" notices on lutein, zeaxanthin and meso-zeaxanthin. The FDA has raised no questions regarding the conclusions of the sponsors that the ingredients are generally recognised as safe (*FDA GRAS Notices*)
- The JECFA committee concluded that there were sufficient toxicological data to complete a safety assessment of lutein and lutein esters from Tagetes erecta, synthetic zeaxanthin and *meso*-zeaxanthin. The Committee considered the available toxicological data together with the dietary exposure of the general population. No adverse effects were observed in a broad range of toxicological studies of free lutein, lutein esters and free zeaxanthin and *meso*-zeaxanthin in laboratory animals and in clinical studies in humans. Results from a new 2-generation reproductive toxicity study of zeaxanthin in rats indicated no adverse effects at up to 500 mg/kg per day, the highest dose tested (*WHO Technical Report Series, No. 1014, 2018*).
- In 2010, EFSA published Scientific Opinion on the substantiation of health claims related to *meso*-zeaxanthin and maintenance of vision, stating, "In the human clinical trials, a dosage of 14.9 mg per day of meso-zeaxanthin has been administered for 120 days, without any adverse effects. Rat studies with more than 200 mg per kg per day have shown no – observed-adverse-effect (NOAEL). Ames tests has shown meso-zeaxanthin anti-mutagenic" (*EFSA 2010;8(2):1483*).

Clinical safety data

Connolly *et al* compared the differing serum carotenoid and macular pigment responses reported in several published studies (*Connolly 2010, Connolly 2011*). Two groups consumed one capsule per day for 6 months: intervention group taking 10.6 mg MZ, 5.9 mg L, and 1.2 mg Z (n = 22; male: female = 8:14; age 43±13 years; BMI = 27.2±6.1) and placebo group (n = 22; male: female = 9:13; age 45±12 years; BMI = 26.8±5). The safety of consumption was assessed by analysing blood samples for changes in renal and liver function, as well as lipid profile, hematologic profile, and markers of inflammation. Connolly reported all clinical pathology parameters remained within the normal reference range, with the exception of total cholesterol and LDL, which had a baseline value outside the accepted normal reference range in both the groups compared to baseline. Analysis of fasting blood samples (at baseline and 6 months) revealed that renal and liver function, as well as lipid profile, haematological parameters, and markers of inflammation, are unaffected following supplementation with a formulation containing L, Z and MZ. There were no adverse events recorded or reported by any subject taking part in the study after supplementation with all three macular carotenoids.

Riboflavin (Vitamin B2)

Macushield Original Plus contain Riboflavin (vitamin B2) 0.3mg.

Scientific Background

Riboflavin (vitamin B2) is a water-soluble, yellow, fluorescent compound, chemically specified as a 7,8-dimethyl-10-(1'-D-ribityl)-isoalloxazine. The vitamin is a precursor of certain essential coenzymes. In these coenzyme forms riboflavin functions as a catalyst for oxidation and reduction reactions and electron transport. Riboflavin is thus involved in a wide variety of metabolic pathways, including the biosynthesis and catabolism of amino acids, fatty acids and carbohydrates. One early sign of riboflavin deficiency is a loss of visual acuity. Rarely, neovascularisation and keratitis of the cornea can also occur, causing lacrimation and photophobia. *(EFSA 2010;8(10): 1814).*

Riboflavin and Maintenance of normal vision

In 2010 the European Food Safety Authority (EFSA) Panel published scientific opinion on health claims relating to Riboflavin and concluded that a cause and effect relationship has been established between the dietary intake of riboflavin and maintenance of normal vision. The following supporting rationale is provided by EFSA in the scientific opinion document: *"Riboflavin deficiency can cause conjunctivitis with vascularisation of the cornea and opacity of the lens. Glutathione is important in maintaining the normal clarity of crystallins in the lens and glutathione reductase is a flavoprotein that is particularly sensitive to riboflavin depletion" (EFSA 2010;8(10): 1814).*

Riboflavin and oxidative stress

Unstable molecules, known as free radicals, are produced at the macula because of the high use of oxygen by this tissue in a process known as oxidative stress (this is a normal process of life, known as oxygen metabolism and increases as we age); oxidative stress simply refers to tissue damage caused by free radicals (unstable molecules), which, in turn, are the result of high oxygen metabolism, and it is noteworthy that the human retina is considered to have one of the highest oxygen metabolisms of any tissue in the mammalian world (*Lobo 2010, Wong-Riley 2010, Pham-Huy 2008*).

In 2010 the European Food Safety Authority (EFSA) Panel published scientific opinion on health claims relating to Riboflavin and concluded that a cause and effect relationship has been established between the dietary intake of riboflavin and protection of DNA, proteins and lipids from oxidative damage. The following supporting rationale is provided by EFSA in the scientific opinion document: **"***It is well established that riboflavin participates in a diversity of redox reactions, through the cofactors FMN and FAD, which act as electron carriers. A protective role of riboflavin against lipid peroxidation is provided mainly by the glutathione redox cycle. Glutathione peroxidase requires reduced glutathione, which in turn is generated by glutathione reductase. The glutathione reductase enzyme requires the riboflavin co-enzyme FAD and this enzyme is particularly sensitive to riboflavin deficiency making glutathione reductase enzyme measures most suitable for assessing riboflavin status. Riboflavin deficiency is associated with increased lipid peroxidation, a process that can be inhibited by riboflavin" (EFSA 2010;8(10): 1814).*

References:

- ***Abdel-Aal E-SM**, Akhtar H, Zaheer K, Ali R. Dietary sources of lutein and zeaxanthin carotenoids and their role in eye health. Nutrients. 2013;5(4):1169-85.*
- ***Alvarado-Ramos KE**, De Leon L, Fontes F, Rios-Castillo I. Dietary Consumption of Lutein and Zeaxanthin in Panama: A Cross-Sectional Study. Curr Dev Nutr. 2018;2(9):nzy064. Published 2018 Aug 6. doi:10.1093/cdn/nzy064*
- ***Bernstein PS**, Li B, Vachali PP, Gorusupudi A, Shyam R, Henriksen BS, et al. Lutein, zeaxanthin, and meso-zeaxanthin: The basic and clinical science underlying carotenoidbased nutritional interventions against ocular disease. Prog Retin Eye Res. 2016;50:34-66.*
- ***Bone RA,** Landrum JT, Friedes LM, Gomez CM, Kilburn MD, Menendez E, et al. Distribution of lutein and zeaxanthin stereoisomers in the human retina. Exp Eye Res. 1997;64(2):211-8.*
- ***Bone RA**, Landrum JT, Hime GW, Cains A, Zamor J. Stereochemistry of the Human Macular Carotenoids. Investigative Opthalmology & Visual Science. 1993; 34(6): 2033-2040.*
- ***Bone RA**, Landrum JT, Tarsis SL. Analysis of the Macular Pigment by HPLC: Retinal Distribution and Age Study. Investigative Opthalmology & Visual Science. 1988; 29(6): 843-849.*
- ***Bone RA**, Landrum JT, Tarsis SL. Preliminary identification of the human macular pigment. Vision Res. 1985;25(11):1531-5.*
- ***Britton G,** Liaaen-Jensen S, Pfander H. Carotenoids Handbook. Basel/Boston/Berlin: Birkhäuser Verlag; 2004.*
- ***Connolly EE**, Beatty S, Thurnham DI, Loughman J, Howard AN, Stack J, et al. Augmentation of macular pigment following supplementation with all three macular carotenoids: an exploratory study. Curr Eye Res. 2010;35(4):335-51.*
- ***Connolly, E.,** Beatty, S., Loughman, J., Howard, A., Louw, M., Nolan, J.: Supplementation With All Three Macular Carotenoids: Response, Stability, and Safety. Investigative Ophthalmology & Visual Science, October, 2011, Vol. 52.*
- ***EFSA 2010;8(10): 1814:** Scientific Opinion on the substantiation of health claims related to riboflavin (vitamin B2) and contribution to normal energy-yielding metabolism (ID 29, 35, 36, 42), contribution to normal metabolism of iron (ID 30, 37), maintenance of normal skin and mucous membranes (ID 31, 33), contribution to normal psychological functions (ID 32), maintenance of normal bone (ID 33), maintenance of normal teeth (ID 33), maintenance of normal hair (ID 33), maintenance of normal nails (ID 33), maintenance of normal vision (ID 39), maintenance of normal red blood cells (ID 40), reduction of tiredness and fatigue (ID 41), protection of DNA, proteins and lipids from oxidative damage (ID 207), and maintenance of the normal function of the nervous system (ID 213) pursuant to Article 13(1) of Regulation (EC) No 1924/2006.*
- ***EFSA 2010;8(2):1483:** Scientific Opinion on the substantiation of health claims related to meso-zeaxanthin and maintenance of vision (ID 2096) pursuant to Article 13(1) of Regulation (EC) No 1924/2006, https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2010.1483.*
- ***FDA GRAS Notices -** https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices*
- ***Jaswir I**, Noviendri D, Hasrini R, Octavianti F. Carotenoids: Sources, medicinal properties and their application in food and nutraceutical industry. J Med Plants Res. 2011;5.*
- ***Khachik F.** Separation, identification, and quantification of carotenoids in fruit, vegetables and human plasma by high performance liquid chromotography. Pure and Applied Chemistry. 1991;61(1):71-80.*
- ***Li B**, Ahmed F, Bernstein PS. Studies on the singlet oxygen scavenging mechanism of human macular pigment. Archives of biochemistry and biophysics. 2010;504(1):56-60.*
- ***Lobo, V.,** Patil, A., Phatak, A., Chandra, N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy Review, 2010;4(8):118-126.*
- ***Maoka T**, Arai A, Shimizu M, Matsuno T. The first isolation of enantiomeric and meso-zeaxanthin in nature. Comp Biochem Physiol B. 1986;83(1):121-4.*
- ***National Eye Institute** Website, Eye Health Information, Diagram of the eye [https://nei.nih.gov/health/eyediagram]*
- ***Nolan JM**, Beatty S, Meagher KA, Howard AN, Kelly D, Thurnham DI. Verification of MesoZeaxanthin in Fish. J Food Process Technol. 2014;5(6):335.*
- ***O'Neill ME**, Carroll Y, Corridan B, Olmedilla B, Granado F, Blanco I, et al. A European carotenoid database to assess carotenoid intakes and its use in a five-country comparative study. Br J Nutr. 2001;85(4):499-507.*
- ***Otten** et al. The National Academies Press (Washington DC). Dietary Reference Intakes: The Essential Guide to Nutrient Requirements (DRI) Part III: Carotenoids: p213. 2006.*
- ***Parker RS**. Carotenoids in human blood and tissues. 119(1): p. 101-4. J Nutr. 1989;119(1):101-4.*
- ***Perry A**, Rasmussen H, Johnson EJ. Xanthophyll (lutein, zeaxanthin) content in fruits, vegetables and corn and egg products. . Journal of Food Composition and Analysis. 2009;22(2):9-15.*
- ***Pham-Huy, L.A.**, He, H., Pham-Huy, C. Free Radicals, Antioxidants in Disease and Health. International Journal of Biomedical Science, 2008;4(2):89-96.*
- ***Prado-Cabrero, A.,** Beatty, S., Stack, J., Howard, A., Nolan, J.M. Quantification of zeaxanthin stereoisomers and lutein in trout flesh using chiral high-performance liquid chromatography-diode array detection. J Food Compost Anal. 2016; 50:19-22.*

- ***Public Health England*** *(8th Oct 2018). www.nhs.uk/live-well/eat-well/why-5-a-day. Last accessed 14/10/2019*
- ***Snodderly DM****, Brown PK, Delori FC, Auran JD. The macular pigment. I. Absorbance spectra, localization, and discrimination from other yellow pigments in primate retinas. Invest Ophthalmol Vis Sci. 1984;25(6):660-73.*
- ***Walsh, RP*** *et al. Variation in Carotenoid Content of Kale and Other Vegetables: A Review of Pre- and Post-harvest Effects. Journal of Agricultural and Food Chemistry. 2015.*
- ***Wong-Riley, M.*** *Energy metabolism of the visual system. Eye and Brain. 2010;2:99-116.*
- ***WHO Technical Report Series, No. 1014, 2018:*** *https://apps.who.int/iris/bitstream/handle/10665/279832/9789241210232-eng.pdf#page=51%22%3E. P39-46.*