

# Lutein and Zeaxanthin



Lutein and zeaxanthin are members of the large group of carotenoids, which are lipophilic plant pigments responsible for the yellow to red colours in nature, as in fruit, vegetables, flowers, and autumn leaves. For example, the bright yellow colour of corn (maize) is due to lutein and zeaxanthin.

Based on their chemical composition, carotenoids can be divided into hydrocarbons – carotenoids comprising only carbon (C) and hydrogen (H), such as  $\beta$ -carotene or lycopene – and into xanthophylls. The latter contain oxygen (O), in addition to carbon and hydrogen. Lutein and zeaxanthin belong to the group of xanthophylls (see figure 1 for the molecular structures of  $\beta$ -carotene, vitamin A (retinol), lutein, zeaxanthin, and meso-zeaxanthin, a derivative of lutein only found in the retina of the eye).

Further, carotenoids can be distinguished into those with provitamin A activity, and those without provitamin A activity. Lutein and Zeaxanthin do not have any provitamin A activity, i.e., they cannot be used by humans as a source of vitamin A.

Interest in lutein and zeaxanthin is focusing on their role in the eye: they are highly and selectively accumulated in the retina, especially in the macula lutea, the site of highest visual acuity. There, lutein and zeaxanthin form the so-called macular pigment, protecting the retina against light-induced damage, and thus contribute to healthy vision throughout life.



## IMPORTANCE FOR HEALTH

The roles of lutein and zeaxanthin in humans may be considered both in terms of 'generic' effects – effects displayed by all other carotenoids - and in terms of effects specific to lutein and zeaxanthin.

### General health benefits

As with all carotenoids, lutein and zeaxanthin are effective antioxidants, protecting important biomolecules and cells against damage induced by free radicals. For example, lutein and other carotenoids are proven to act as antioxidants in blood <sup>1</sup> and to reduce the skin's sensitivity against UV-induced erythema ('sunburn') <sup>2</sup>. Further, as diets high in fruit and vegetables provide lutein and zeaxanthin, these two carotenoids contribute to the health benefits observed with such diets, for example in relation to heart disease and cancer <sup>3</sup>.

### Eye health

Effects specific for lutein and zeaxanthin are their roles in the retina and the lens of the eye. Here, lutein and zeaxanthin are selectively accumulated. None of the other carotenoids typically found in blood and tissues are present in retina and lens. It is because of this specific feature that lutein and zeaxanthin have been associated with healthy vision throughout life and favourable effects related to two age-related eye diseases: Age-related Macular Degeneration and Cataract.

In the eye, lutein and zeaxanthin act both as blue light filters and as antioxidants. Blue light is the part of the visible light spectrum with the highest energy, and the retina has long been known to be especially vulnerable to blue light ('blue light hazard'). The localisation of the macular pigment (MP) within the retina - like a shield between incoming light and the photoreceptors - and its capacity to absorb blue light makes it ideal for protection. Antioxidant protection is critically important to the eye: due to its high level of exposure to light, all structures in the eye are at high risk of damage from light induced free radicals. High

levels of blood (and thus oxygen) supply, together with the high levels of polyunsaturated fatty acids in photoreceptor membranes make the retina even more susceptible to oxidative damage. Indeed, high levels of lutein and zeaxanthin in the retina have been demonstrated to protect photoreceptor cells against light-induced damage <sup>16</sup>.

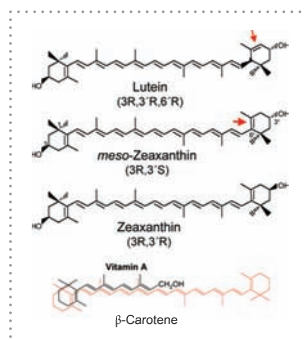


Figure 1

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For cataracts, epidemiological data suggest a reduced disease risk with high intakes of lutein and zeaxanthin and/or of foods which are high in these carotenoids, and also with higher blood levels. Further, there is a relation between clarity of the lens and MP density: in people above 50 years of age, a clearer lens was related to higher MP density, suggesting that lutein and zeaxanthin in the eye may retard ageing of the lens <sup>4</sup>.

Age-related macular degeneration (AMD) affects the *macula lutea*, the centre of the retina and site of highest visual acuity, needed for activities such as reading. AMD is characterised by loss of central vision and is the leading cause of irreversible blindness in western countries. Currently, there is no cure, and only a few treatment strategies are available. As with many degenerative diseases, these strategies aim at slowing down disease progression, not at improving disease status, and they cannot be applied to all patients. The main risk factor for AMD is age. Thus, options for prevention appear very important, especially in the ageing western societies.

The rationale for the macular pigment - lutein and zeaxanthin – in prevention of AMD is based on the idea that high MP density throughout life reduces damage to retinal structures, which would otherwise accumulate over decades and become manifest as symptoms of AMD later in life. Strong support comes from data on primates which were raised on a diet devoid of lutein and zeaxanthin: lutein and zeaxanthin levels in blood and tissues were not detectable in these animals. Further,

they did not develop a macular pigment, but experienced changes in the retina which were similar to those observed in the early stages of AMD <sup>16</sup>.

In humans, lower MP density has been observed in AMD patients as compared to controls, and this was established to be the cause of the disease, rather than its consequence <sup>16</sup>. Additional data from epidemiological studies suggest lower disease risk with higher intakes and/or higher blood levels of lutein and zeaxanthin, although such associations were not observed in all studies. However, the relations between intake, blood levels and levels in the macula (MP density) are complex, and correlations between these parameters are poor, so that absence of associations between lutein and zeaxanthin and AMD risk in epidemiologic studies may be due to confounding factors concealing this association <sup>5</sup>. Evidence on the effects of lutein supplementation on disease progression in patients with early AMD will be developed in AREDS III<sup>i</sup>, a study conducted by the US National Institutes of Health (NIH).

In addition, some physicochemical features of lutein and zeaxanthin imply that they may have ‘short term effects’, i.e., effects on measures of visual function, such as visual acuity, glare and contrast sensitivity <sup>6</sup>. Data from some pilot trials and a one year placebo-controlled human intervention trial proved that these effects do occur: MP-density increased, and visual acuity and contrast sensitivity improved <sup>11</sup>.

i AREDS: Age-Related Eye Disease Study

## DIETARY SOURCES AND INTAKE OF LUTEIN AND ZEAXANTHIN

### Sources

Lutein and zeaxanthin occur in nature as yellow pigments in vegetables, fruit and flowers. A diet rich in vegetables and fruit supplies between 1 to 2 mg of lutein per day. Individual lutein intakes however vary greatly depending on individual dietary patterns. Kale, spinach, broccoli, sweet corn, yellow peppers and pumpkins have been identified as some of the best sources. Other rich sources are egg yolks, and lutein also occurs in grains and potatoes (*Table 1*). In nature, both lutein and zeaxanthin occur in ‘free’ form – as in green vegetables – and in the form of their fatty acid esters, usually in yellow to orange vegetables and fruit.

**Table 1: Lutein and zeaxanthin content in selected foods (mg/100g)**

	Lutein*	Zeaxanthin
Kale	14.7 – 39.6	n.a.
Spinach	4.5 – 15.9	0.2 – 0.3
Broccoli	0.8 – 2.4	n.a.
Peas	1.1 – 2.4	n.a.
Corn	0.4 – 1.9	0.3 – 0.9
Carrots	0.2 – 0.3	n.a.
Pepper (yellow/red)	< 0.1 – 8.2	1.5 – 16.8
Oranges	0.1 – 0.2	0.07
Peaches	< 0.1	< 0.01
Apples	< 0.1	< 0.01
Eggs	0.1 – 2.1	0.1 – 1.6
Potatoes	0.02 – 0.05	< 0.01 – 0.11
Grains	0.02 – 0.14	< 0.01 – 0.03

\*For analytical reasons lutein and zeaxanthin are often reported together. n.a. not available

1 Yeum KJ. et al. The activities of antioxidant nutrients in human plasma depend on the localization of attacking radical species. *J Nutr* 2003; 133:2688-2691

2 Heinrich U. et al. Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema. *J Nutr* 2003; 133:98-101

3 Rock CL. Relationship of carotenoids to cancer. And: Sesso HD. et al. Heart and vascular diseases. In: *Carotenoids in Health and Disease* (Krinsky NI, Mayne ST, Sies H, eds). Marcel Dekker, New York, 2004: 373-408, 473-490

4 Berendschot TT. et al. Lens aging in relation to nutritional determinants and possible risk factors for age-related cataract. *Arch Ophthalmol* 2002; 120:1732-1737, Hammond BR Jr. et al. Density of the human crystalline lens is related to the macular pigment carotenoids, lutein and zeaxanthin. *Optom Vis Sci* 1997; 74:499-504

5 Gruber M. et al. Correlates of serum lutein + zeaxanthin: findings from the Third National Health and Nutrition Examination Survey. *J Nutr* 2004; 134:2387-2394

6 Hammond BR. et al. Carotenoids in the retina and lens: possible acute and chronic effects on human visual performance. *Arch Biochem Biophys* 2001; 1:385:41-46



Marigold flowers (*Tagetes erecta*) have been the source of commercial lutein preparations since the late 1960s. These have a long history of use in animal feed, where they are added to the feed of chicken to enhance the colour of both egg yolks and skin, the latter being desirable for an attractive appearance of roasted chicken. Lutein extracts from *Tagetes* are also approved as food colour (E 161b), the main uses being in dairy products,

non-alcoholic drinks, bakery products, and ice-cream. Highly purified marigold extracts, either containing 'free' lutein or lutein esters, are also marketed as ingredients for food supplements and fortified foods for the beneficial effects of lutein on human health. All commercial marigold-derived lutein preparations contain 5 - 10% zeaxanthin, due to its natural presence in marigolds.

## Intake

Most food composition tables do not distinguish between lutein and zeaxanthin, but report them together. However, lutein is more abundant in the human diet, and zeaxanthin intakes have been reported to be 0.1 – 0.2 mg/day, i.e., approx 10% of the lutein intakes<sup>7</sup>. Table 2 gives typical lutein intakes in various European countries.

**Table 2. Lutein Intakes in Europe (mg/day)<sup>8</sup>**

Country	Median	Range (interquartile range*)
Spain (n = 70)	3.25	1.75 – 4.34
France (n = 76)	2.50	1.71 – 3.91
UK (n = 71)	1.59	1.19 – 2.37
Republic of Ireland (n = 76)	1.56	1.14 – 2.1
The Netherlands (n = 75)	2.01	1.42 – 3.04

\*Interquartile range: statistical parameter, describing the difference between upper quartile (Q<sub>3</sub>, 75th percentile) and lower quartile (Q<sub>1</sub>, 25th percentile), i.e., the lowest 25% of intakes and the highest 25% of intake are not included.

## Recommended intake

No dietary reference intakes (DRIs) or recommended dietary allowances (RDAs) have yet been set for lutein or zeaxanthin, because such values exist only for vitamins and minerals and other essential nutrients. Based on data on beneficial effects observed in some epidemiological studies, intakes of approx. 6 mg lutein/day seem desirable for healthy people<sup>9</sup>.

Increases in MP density have been observed – although not in all individuals - with supplemental intakes as low as 2.4 mg lutein given daily over a period of several months<sup>10</sup>. Beneficial

effects on various parameters of vision were observed in patients with early forms of AMD with 10 mg lutein/day<sup>11</sup>. However, studies usually used only one dose, and dose-response data are not available yet.

Newborn babies get their lutein and zeaxanthin from their mother's milk. Compared to breast milk, lutein and zeaxanthin levels in commercial infant formulas are usually much lower<sup>12</sup>, and it has been hypothesised whether inadequate supply of lutein and zeaxanthin early in life may have serious consequences<sup>13</sup>.

## ABSORPTION AND METABOLISM

The absorption of lutein and zeaxanthin follows the same pathway as that of all other fat soluble dietary compounds – for example, triglycerides, cholesterol, vitamin E – i.e. fat is necessary for proper absorption. In brief, lutein and zeaxanthin are incorporated into micelles formed with dietary fats and bile acids in the small intestine, and taken up into the cells lining the intestinal wall. There, lutein and zeaxanthin are incorporated into chylomicrons which transport the newly absorbed carotenoids via the lymph into the blood circulation and to the

liver for incorporation into other lipoproteins. Lutein esters are hydrolysed (cleaved) prior to absorption, and only the free lutein is absorbed and appears in blood.

Lutein and zeaxanthin are two of the six major carotenoids found in human blood. Their blood concentrations depend on dietary intake, and, consequently, can be raised by increasing intake, either via diet or supplementation. However, blood concentrations achieved from a given intake of lutein depend on many other factors and will vary considerably among individual people.

7 Garcia-Closas R. et al. Dietary sources of vitamin C, vitamin E and specific carotenoids in Spain. *Br J Nutr* 2004; 91:1005-1011

8 O'Neill ME. et al. A European carotenoid database to assess carotenoid intakes and its use in a five-country comparative study. *Br J Nutr* 2001; 85:499-507

9 Seddon JM. et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA*. 1994; 272:1413-1420

10 Bone RA. et al. Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. *J Nutr* 2003; 133:992-998

11 Richer S. et al. 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*. 2004; 75:216-230

12 Jewell VC. et al. A comparison of lutein and zeaxanthin concentrations in formula and human milk samples from Northern Ireland mothers. *Eur J Clin Nutr* 2004; 58:90-97

13 Sommerburg O. et al. Carotenoid supply in breast-fed and formula-fed neonates. *Eur J Pediatr* 2000; 159:86-90

In blood, lutein and zeaxanthin are transported in lipoproteins – in both LDL and HDL - to target tissues. Adipose tissue and liver may be regarded as storage sites. Functional, highly selective accumulation occurs in the macular region of the retina of the eye, and, to a lesser extent, in the lens. In Europe, typical concentrations in blood are around 0.4 µmol/L for lutein and 0.1 µmol/L for zeaxanthin (see also Table 3), with high variation due to dietary habits and other factors <sup>14</sup>.

Concentration in the centre of the retina, the site of highest visual acuity, are so much higher that lutein and zeaxanthin are macroscopically visible and have given the centre of the retina its name: *Macula lutea*, which is latin for 'yellow spot'. Lutein and zeaxanthin in the macular region are also termed 'macular pigment', and the amount of macular pigment is referred to as 'macular pigment density' or 'MP density'. Today, it is established that the macular pigment consists solely of lutein, zeaxanthin and meso-zeaxanthin (see figure 1 for structural formulas). Meso-zeaxanthin is derived from lutein and is found exclusively in the macula and retina of the eye <sup>15</sup>.

The levels of lutein and zeaxanthin – the MP density – can be modified by changing the intake of lutein and zeaxanthin, with dietary measures as well as by supplementation <sup>16</sup>.

**Table 3: Lutein and Zeaxanthin Plasma Levels in Men in Europe (µmol/L, mean and standard deviation) <sup>14</sup>**

Site	Lutein	Zeaxanthin
Varese/Turin, IT (n = 99)	0.60 ± 0.24	0.13 ± 0.06
Florence, IT (n = 97)	0.56 ± 0.21	0.11 ± 0.06
Ragusa/Naples, IT (n = 92)	0.61 ± 0.26	0.11 ± 0.05
Athens, GR (n = 95)	0.51 ± 0.21	0.11 ± 0.04
Granada, ES (n = 97)	0.40 ± 0.16	0.10 ± 0.04
Murcia, ES (n = 99)	0.37 ± 0.17	0.11 ± 0.05
Northern Spain, ES (n = 97)	0.36 ± 0.15	0.12 ± 0.05
UK vegetarians, UK (n = 99)	0.38 ± 0.17	0.09 ± 0.05
Cambridge, UK (n = 98)	0.26 ± 0.12	0.06 ± 0.04
Potsdam, DE (n = 98)	0.27 ± 0.13	0.07 ± 0.03
Heidelberg, DE (n = 99)	0.29 ± 0.12	0.08 ± 0.04
The Netherlands, NL (n = 97)	0.28 ± 0.12	0.07 ± 0.03
Denmark, DK (n = 99)	0.28 ± 0.13	0.05 ± 0.03
Malmö, SE (n = 99)	0.28 ± 0.13	0.06 ± 0.03
Umea, SE (n = 99)	0.27 ± 0.11	0.05 ± 0.02

**SAFETY**

The long history of consumption of foods rich in lutein and zeaxanthin provides evidence that these carotenoids are safe. In addition, no adverse effects have been observed in intervention studies involving supplementation with high doses of lutein (up to 30 mg/day) for extended periods of time <sup>11,17</sup>.

Both lutein and lutein esters have completed the GRAS (Generally Recognized As Safe) self-affirmation as well as the GRAS notification process according to the requirements of the US FDA. This includes a formal safety assessment by scientific expert panels. Furthermore, after assessing similar information, the Joint Expert Committee on Food Additives of the FAO/WHO<sup>ii</sup> (JECFA) established an acceptable daily intake (ADI) level for lutein and zeaxanthin of up to 2 mg/kg body weight, equivalent to 120 mg/day for a 60 kg person.

Using recently developed risk assessment procedures for nutrients for which a Tolerable Upper Intake Level (UL) could not be derived, an Observed Safe Level (OSL) of 20 mg/d has been suggested for lutein <sup>18</sup>.

In Europe, foods and/or food ingredients which have not been consumed in significant amounts prior to May 1997 – the date when the Novel Food Regulation came into force – need to undergo the approval process as outlined in the Regulation if they do not have a history of safe food use. Lutein and lutein esters derived from *Tagetes erecta* have been widely used as active ingredient in food supplements in Member States of the European Union before May 1997. Also they have a history of safe use as approved food additives in Europe and as GRAS approved food ingredients in the US. Further, a competent authority in one of the EU Member States (Agence Française de Sécurité Sanitaire des Aliments, AFSSA) authorised the use of an extract from *Tagetes erecta* (consisting mainly of lutein and zeaxanthin) as a food supplement ingredient thus confirming implicitly that lutein is not considered Novel Food <sup>19</sup>.

<sup>ii</sup> Food and Agriculture Organization of the United Nations and World Health Organization

14 Al-Delaimy WK, et al. Plasma levels of six carotenoids in nine European countries: report from the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2004; 7:713-722

15 Johnson EJ, et al. Nutritional manipulation of primate retinas. III: Effects of lutein or zeaxanthin supplementation on adipose tissue and retina of xanthophyll-free monkeys. Invest Ophthalmol Vis Sci. 2005; 46:692-702

16 Krinsky NI, et al. Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. Annu Rev Nutr 2003; 23:171-201.

17 Landrum JT, et al. A one year study of the macular pigment: the effect of 140 days of a lutein supplement. Exp Eye Res 1997; 65:57-62

18 Shao A, Hathcock JN. Risk assessment for the carotenoids lutein and lycopene. Regul Toxicol Pharmacol. 2006 Jun 28; [E-pub ahead of print]

19 AFSSA. Avis favorable relative à l'évaluation de l'emploi d'un extrait d'œillet d'Inde en tant qu'ingrédient dans un complément alimentaire dated Nov 15, 2001 http://www.afssa.fr