Lutein, Zeaxanthin, and Meso-Zeaxanthin

Common Acronyms

CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
HOI	highest observed intake level
ICMR-NIN	Indian Council of Medical Research - National Institute of Nutrition
IOM	Institute of Medicine
IU	international unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KNS	Korean Nutrition Society
LOEL	lowest observed effect level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NIH	National Institute of Health
NOEL	no observed effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Lutein and its structural isomer, zeaxanthin, are lipid-soluble members of the xanthophyll family, a subclass of the carotenoids category possessing antioxidant properties (Alves-Rodrigues and Shao 2004; Thomas and Johnson 2018; Murillo et al. 2019). Lutein and zeaxanthin have identical chemical formulas but differ in the location of one double bond at the end of the cyclic ring (Ravikrishnan et al. 2011; Mrowicka et al. 2022). Zeaxanthin occurs as a mixture of three stereoisomers, including zeaxanthin ((3R,3′R)-zeaxanthin), the predominant form found in nature, and meso-zeaxanthin ((3R,3′S)-zeaxanthin, meso-zeaxanthin), which is absent from fruit,

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vegetable, and liver dietary sources but is present in some foods such as fish and shrimp (Nolan et al. 2014; Murillo et al. 2019).

Lutein, zeaxanthin, and meso-zeaxanthin are common carotenoids found in the human diet that have become increasingly popular ingredients in dietary supplements (Shao and Hathcock 2006; Drake 2023). The main commercial source of lutein for dietary supplements comes from marigold flowers (*Tagetes erecta* L), which are rich in carotenoids, especially lutein, which is mainly present as lutein ester (90–99%) (Olmedilla-Alonso et al. 2024). Supplements derived from *Tagetes erecta* L. also contain zeaxanthin and meso-zeaxanthin at lower concentrations. Known mostly for their role in eye health, consumption and serum levels of these xanthophylls have been investigated for their potential beneficial effects on supporting vision performance of healthy eyes, as well as in the context of ocular diseases, including age-related macular degeneration (AMD), cataracts, and diabetic retinopathy (Bernstein et al. 2016; Drake 2023; Shanaida et al. 2025).

Bioavailability

Xanthophylls may be ingested in either free or esterified forms. The bioavailability and intestinal absorption of xanthophylls, including lutein and zeaxanthin, are influenced by form of xanthophyll (i.e., free vs esterified), dietary factors, release from the food matrix, and digestive enzyme activity (Eisenhauer et al. 2017; Thomas and Johnson 2018; Manikandan et al. 2016). Lutein, zeaxanthin, and meso-zeaxanthin are fat-soluble, and fat is required to facilitate intestinal absorption (Mrowicka et al. 2022). For example, higher fat intake can enhance absorption, whereas dietary fiber may reduce it (Li et al. 2020; Eisenhauer et al. 2017). Simultaneous consumption of multiple xanthophylls can lead to decreased absorption due to competition. Additionally, heating the xanthophylls can potentially increase bioavailability (Eisenhauer et al. 2017). The bioavailability of xanthophyll esters, a common form found in nature, appears to be equal to or higher than that of their corresponding free forms due to an increase in solubility (Shanaida et al. 2025; Olmedilla-Alonso et al. 2024). In general, absorption of xanthophylls can range from 5-50% (Murillo et al. 2019). Data suggest that carotenoid absorption, including that of xanthophylls, by mucosal cells occurs primarily through passive diffusion rather than active transport. After uptake by mucosal cells, they are incorporated into chylomicrons, followed by

entry into the lymphatic system and then the blood (EFSA 2010; Thomas and Johnson 2018). These chylomicrons transport the xanthophylls to the liver, where they are distributed among various lipoprotein fractions (EFSA 2010).

Lutein is one of the most prevalent xanthophylls in human serum (Khachik et al. 1997) and both lutein and the zeaxanthin isomers, specifically RR-zeaxanthin and RS-meso-zeaxanthin, are concentrated in ocular tissues such as the lens and the macula lutea (Yeum et al. 1995; Landrum and Bone 2001; Murillo et al. 2019). Meso-zeaxanthin is not found in circulation but is reported to be a metabolite of lutein that is formed at the macula via metabolic transformation (Murillo et al. 2019; Li et al. 2020).

Safety Considerations

The safety of various carotenoids and xanthophylls have been assessed as part of evaluations for use as food additives (see also *Official Reviews* section).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA 2005) reviewed the available data on lutein extracted from *Tagetes erecta* L. (marigold) and set an acceptable daily intake (ADI) value of 0-2 mg per kg bw per day based on a 90-day oral toxicity study in rats (Pfannkuch et al. 2000, 2001; Kruger et al. 2002). The JECFA Committee noted that lutein extracted from *Tagetes erecta* L. also contains "a smaller proportion of zeaxanthin." The Committee subsequently expanded this ADI to include synthetic zeaxanthin due to the structural and physiological similarities between lutein and zeaxanthin, noting that lutein had a "stronger toxicological database." This group ADI applies only to the synthetic form of zeaxanthin and does not include zeaxanthin extracted from *Tagetes erecta* L. due to the lack of data for a zeaxanthin-rich extract at the time of the Committee's review (JECFA 2005; JECFA 2006). In 2018, the JECFA re-evaluated the group ADI and included several xanthophyll forms such as free lutein, lutein esters, free zeaxanthin, and meso-zeaxanthin, which were all viewed by the Committee as biochemically and toxicologically equivalent (JECFA 2020). Due to the absence of observed toxicity in various non-clinical studies with lutein, zeaxanthin, and meso-zeaxanthin, the Committee established a group ADI of "not specified" for lutein and lutein esters from *Tagetes erecta* L. and synthetic zeaxanthin. JECFA noted that meso-zeaxanthin was not included in this

group ADI as specifications were not available at the time of evaluation (JECFA 2020).

As discussed in more detail below in the *Official Reviews* section, the EFSA evaluated the safety of synthetic zeaxanthin in food supplements (2008, 2012) and re-evaluated the safety of lutein as a food additive (2010, 2011). In its most recent evaluation, the EFSA (2012) Panel concluded that an intake level of 0.75 mg per kg bw per day of synthetic zeaxanthin did "not raise safety concerns" (EFSA 2012). Following its re-evaluation of the safety of lutein, the EFSA (2010) Panel concluded that the 90-day rat study chosen previously by JECFA could be used to derive an ADI value of 1 mg per kg bw per day for lutein and that this ADI "refers to lutein derived from *Tagetes erecta* L. containing at least 80% carotenoids consisting of lutein and zeaxanthin (79 and 5% respectively)." In 2011, the EFSA Panel concluded that the ADI of 1 mg per kg bw per day also applies to lutein with high concentrations of total carotenoids extracted from *Tagetes erecta* L. and present as esters at levels of ≥60% (>93% lutein esters, remainder zeaxanthin esters; EFSA 2011). The safety of meso-zeaxanthin has not been specifically evaluated by the EFSA.

The United States Food and Drug Administration (US FDA) has reviewed Generally Recognized as Safe notifications (GRNs) for various lutein forms (e.g., free lutein, lutein esters, and lutein diacetate) for their intended uses in food (e.g., GRNs 110, 140, 221, 291, 385, 290, 432, 542, and 543).[1] These lutein forms are typically extracts from dried marigold flowers (*Tagetes erecta* L.), which contain both lutein and zeaxanthin at varying concentrations. The FDA has also reviewed GRNs for zeaxanthin and meso-zeaxanthin from various sources (e.g., marigold and paprika) for their intended uses in food (e.g., GRNs 481, 550, 588, and 639). These ingredients also contained varying concentrations and/or combination of zeaxanthin, meso-zeaxanthin, and lutein. Each of these GRAS notifications were successful, having received a letter of no objection from the US FDA.

The ADI values derived by the JECFA and EFSA were based on animal toxicology studies. As noted in CRN's Methodology chapter and its principal points of departure, stronger preference is given to human data over animal data, when available. As such, and consistent with other CRN nutrient chapters, human clinical data were prioritized for evaluation. Based on the availability of

[1] Available at: https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices.

previous authoritative evaluations for these carotenoids (JECFA 2006; EFSA 2008, 2010, 2011, 2012) and CRN's previous assessment of lutein (Shao and Hathcock 2006), updated literature searches included human trials published starting in 2006. Given that these carotenoids occur naturally as a mixture (e.g., from marigold), studies testing mixtures were considered in the determination of CRN's UL values for each. Therefore, the assessments below for lutein, zeaxanthin, and meso-zeaxanthin include approximately 75 studies administrating the carotenoids individually and/or in combination.

Lutein

The only documented side effect of lutein supplementation is carotenoderma, a reversible condition characterized by a yellowish discoloration of the skin resulting from elevated dermal carotenoid levels. Carotenoderma associated with lutein intake has only been reported in two clinical trials, both at daily doses of 15 mg per day for 4–5 months (Granado et al. 1998; Olmedilla et al. 2002). The condition is most often associated with high carotene (e.g., beta-carotene) intake from foods or supplements (>30 mg per day) (Bendich 1988; Drake 2023). Carotenoderma is not considered to be an adverse effect and has been shown to resolve with reduced carotenoid intake (Drake 2023).

CRN's previous derivation of an HOI value for lutein was published in Shao and Hathcock (2006), which reviewed more than thirty peer-reviewed, published human clinical trials involving lutein.[2] The criteria for study inclusion were study duration (at least 1 week) and lutein dose utilized (greater than 2 mg per day). Relevant double-blind, randomized, controlled trials reviewed in the previous assessment involved lutein doses of 8 to 40 mg per day (Granado et al. 1998; Dagnelie et al. 2000; Hughes et al. 2000; Roodenburg et al. 2000; Aleman et al. 2001; Hininger et al. 2001; Olmedilla et al. 2002, 2003; Richer et al. 2004; Thurmann et al. 2005; Zhao et al. 2006; Bahrami et al. 2006). Non-randomized, uncontrolled, and/or open-label clinical trials identified administered lutein doses ranging from 2.4 to 30 mg per day (Berendschot et al. 2000; Dagnelie et al. 2000; Duncan et al. 2002; Bone et al. 2003; Cardinault et al. 2003; Koh et al. 2004). No serious adverse effects were observed or reported across these studies, as described in

[2] Not included in the previous editions of CRN's handbook.

Shao and Hathcock (2006).

Approximately 70 peer-reviewed human trials published since 2006 were identified that met the inclusion criteria for supplemental lutein.[3,4] The clinical trials tested lutein alone or as a combination with other carotenoids (e.g., zeaxanthin and/or meso-zeaxanthin) at doses ranging from 2.5-22.33 mg lutein per day with no serious adverse effects reported. Fifteen of these recent studies administered lutein doses of 20 mg per day for durations ranging from 30 days to two years (e.g., Amin et al. 2019; Sawa et al. 2020; Xu et al. 2013; Yoshida et al. 2023; Yao et al. 2013; Ma et al. 2012). Many of these studies did not specify monitoring for possible adverse side effects in the methods and/or did not report observations regarding adverse effects. A series of publications by Stringham et al. (2016, 2017, 2018, 2019) evaluated the same cohort of patients supplemented with lutein up to 22.33 mg lutein per day concomitantly with 4.7 mg combined zeaxanthin and meso-zeaxanthin. The study duration for each publication ranged from 12 weeks to 12 months with no mention of adverse event monitoring or reports of any side effects or adverse events.

Of note, the EFSA (2010) evaluation discussed the availability of several dietary intervention studies with foods high in lutein (with and without zeaxanthin) at concentrations ranging from 0.4 to 30 mg lutein per day for up to 12 months with no reported side effects, except for Olmedilla (2002). In this study, some participants supplemented for 20 weeks with 15 mg per day lutein from a lutein-rich marigold extract showed carotenoderma, but no changes in biochemical or hematological indices were noted (Olemdilla et al 2002).

Zeaxanthin

CRN has not previously assessed zeaxanthin to derive an UL or HOI value. Fifty peer-reviewed human trials published since 2006 were identified that met the inclusion criteria for supplemental zeaxanthin.[5] The clinical trials tested zeaxanthin alone or as a combination with other carotenoids (e.g., lutein and/or meso-zeaxanthin) at doses ranging from 0.6-26 mg zeaxanthin per day. Similar

[3] Seventy-one publications; some appear to report on the same cohort.
[4] Literature search conducted May 2025.
[5] Literature search conducted May 2025.

to lutein, only a few of the studies monitored for possible adverse side effects, which were primarily identified via self-reporting. Only three clinical studies tested zeaxanthin alone, while 47 studies tested various combinations of related xanthophylls (lutein, zeaxanthin, and/or meso-zeaxanthin).

Three studies administering zeaxanthin at doses of 20 mg per day or higher were identified (Choi et al. 2017; Bovier et al. 2014, 2015). Choi et al. (2017) reported that supplementation with zeaxanthin at doses of 10 or 20 mg per day for 24 months in patients with macular telangiectasia type 2 was "generally safe"; however, the study only included eight participants. Bovier et al. (2014) assessed treatment tolerance in healthy adults administered 20 mg zeaxanthin per day for four months; no related results were mentioned in the publication. Finally, Bovier and Hammond (2015) administered 20 or 26 mg zeaxanthin per day for four months to healthy adults.[6] No adverse effects were reported in this study; however, the methods did not describe monitoring for such.

Meso-Zeaxanthin

CRN has not previously assessed meso-zeaxanthin to derive an UL or HOI value. Approximately 13 peer-reviewed human trials published since 2006 were identified that met the inclusion criteria for supplemental meso-zeaxanthin.[7, 8] The clinical trials tested meso-zeaxanthin in combination with lutein and zeaxanthin at doses ranging from 0.3-17 mg meso-zeaxanthin per day with no serious adverse effects reported.[9] Similar to lutein and zeaxanthin, only a few of the studies monitored for possible adverse side effects, which were primarily via self-reporting. However, Connolly et al. (2011) demonstrated a lack of any effects on renal, liver, lipid, hematological, and inflammatory biomarkers following 10 mg per day supplemental meso-zeaxanthin for 6 months.

Six studies were randomized, blinded, placebo-controlled trials administering meso-zeaxanthin at doses up to 10 mg per day for durations ranging from 6 to 18 months (Connolly et al. 2011;

[6] The material included: 26 mg zeaxanthin, 8 mg lutein, and 190 mg mixed n-s fatty acids.
[7] Fourteen publications; some appear to report on the same cohort.
[8] Literature search conducted May 2025.
[9] No trials identified meeting the inclusion criteria administered meso-zeaxanthin in isolation.

Laughman et al. 2012, 2021; Power et al. 2018; Green-Gomez et al. 2020; Stringham et al. 2024). In the longest of these studies, no serious adverse events were reported during the 18-month trial conducted in 62 patients with open-angle glaucoma (Loughman et al. 2021).

Three randomized, blinded trials were identified that included meso-zeaxanthin at doses up to 17 mg per day; no placebo controls were employed (Meagher et al. 2013; Thurnham et al. 2015; Sabour-Pickett et al. 2014; Akuffo et al. 2015). The studies published by Meagher et al. (2013) and Thurnham et al. (2015) were conducted in healthy adults and those with AMD for 8 weeks. Two publications reported on the Meso-zeaxanthin Ocular Supplementation Trial (MOST) in patients with AMD after 12 and 36 months of supplementation with 10 or 17 mg per day meso-zeaxanthin (Sabour-Pickett et al. 2014; Akuffo et al. 2015). These publications did not report observations regarding adverse events; however, none specified monitoring for such in the methods.

Official Reviews

IOM. The IOM has not derived UL values for lutein, zeaxanthin, or meso-zeaxanthin.

European Food Safety Authority (EFSA 2011, 2012). No UL value has been established by the EC SCF or EFSA for lutein, zeaxanthin, or meso-zeaxanthin. However, ADI values for specific forms as food additives have been derived (see also *Safety Considerations* section).

Previously, the EU SCF (1975) evaluated lutein and zeaxanthin and could not establish an ADI due to a lack of available data but concluded that xanthophylls prepared from natural foods by physical processes are acceptable for use in food. The EFSA (2010, 2011) has since re-evaluated the use of lutein as a food additive. The EFSA (2010) Panel concluded, based on a 90-day rat study (with no effects on reproductive organs), the absence of developmental toxicity and genotoxic effects in available studies, and the fact that lutein is a normal constituent of the diet, that an ADI could be derived. Due to the lack of chronic and multigenerational toxicity studies, the EFSA Panel applied an uncertainty factor of 200 to the NOAEL value of 400 mg per kg bw per day from the 90-day study (Pfannkuch et al. 2000, 2001; Kruger et al. 2002). The resulting ADI value of 1 mg per kg bw per day (corresponding to a daily intake of 60 mg per day in a 60-

kg adult) applies to lutein derived from *Tagetes erecta* L. containing at least 80% carotenoids consisting of lutein and zeaxanthin (79 and 5% respectively). In 2011, the EFSA extended this ADI to lutein with high concentrations of total carotenoids extracted from *Tagetes erecta* L. and present as esters at levels of ≥60% (>93% lutein esters, remainder zeaxanthin esters).

In 2012, the EFSA Panel updated its opinion on the safety of synthetic zeaxanthin as a novel food ingredient in food supplements. The Panel identified a NOAEL value of 150 mg per kg bw per day from a two-generation reproduction toxicity study in rats (Edwards et al. 2006) and reported no concerns in regard to genotoxicity. The Panel applied an uncertainty factor of 200 to this NOAEL, determining that a daily intake level of 0.75 mg per kg bw per day for synthetic zeaxanthin (corresponding to a daily intake of 45 mg per day for a 60-kg adult) does "not raise safety concerns."

Expert Group on Vitamins and Minerals (EVM). The EVM has not derived UL values for lutein, zeaxanthin, or meso-zeaxanthin.

Chinese Nutrition Society (CNS 2023). The CNS derived an UL value of 60 mg per day for lutein (no age group or other demographic specified) but has not set an UL for zeaxanthin or meso-zeaxanthin.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN 2020). The ICMR-NIN has not derived UL values for lutein, zeaxanthin, or meso-zeaxanthin.

Korean Nutrition Society (KNS 2020). The KNS published its general approach to evaluating data for setting DRI values; lutein, zeaxanthin, or meso-zeaxanthin were not included in this assessment.

CRN Recommendations

Similar to Shao and Hathcock (2006), no adverse effects associated with supplemental lutein, zeaxanthin, or meso-zeaxanthin were identified in clinical trials reviewed as part of this

assessment. As such, the goal of the current chapter is to update CRN's supplemental HOI[10] level for lutein and to derive HOI values for zeaxanthin and meso-zeaxanthin. Specific to lutein, this included determining whether more recent human clinical data are available that might impact the conclusions published in Shao and Hathcock (2006), which derived a supplemental HOI value of 20 mg per day for lutein in adults. Studies reporting higher intervention levels of total xanthophylls were limited to Stringham et al. (2016, 2017, 2018, 2019), which administered a total of 27 mg per day (22 mg lutein) and Bovier et al. (2015), which administered 34 mg per day (8 mg lutein, 26 mg zeaxanthin). As such, the body of available clinical research was determined to be insufficient to derive a higher group HOI. Therefore, separate HOI values were derived by CRN for each of the three nutrients individually, as described below.

While not all human clinical trials reviewed were specifically designed to evaluate adverse effects, no trials were identified following CRN's updated methodology that reported any adverse effects associated with the consumption of lutein, zeaxanthin, and/or meso-zeaxanthin. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the HOI are recognized.

CRN's safety methodology for deriving supplemental UL and HOI values prioritizes data from human studies, when available. Approximately 75 human clinical trials published since 2006 were identified and subsequently reviewed that met the inclusion criteria for the current chapter. The tables below summarize the key human clinical studies considered in deriving the supplemental UL or HOI values by CRN according to its principal points of departure for risk assessment (as described in the Methods). A full literature review is outside the scope of this chapter; therefore, only studies identified in the search that are most pertinent[11] based on CRN's methodology are summarized below.

[10] HOI is defined as the highest intake level with adequate data to establish that adverse effects do not occur at intakes up to that level.
[11] Where numerous relevant studies were identified, those most pertinent to the UL/HOI derivation are included in the table as representative studies. Prioritization was given to studies at dose levels informing the UL and studies with higher weighting based on CRN's Methods (e.g., duration, number of participants, randomization, etc.).

Lutein

Key Studies Considered for the CRN HOI for Lutein in Adults

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg/day)	Duration	NOAEL (mg/day)
Key studies from Shao and Hathcock (2006)						
Aleman et al. 2001	Randomized, controlled	Healthy adults and patients with retinal degeneration	29	20	6 months	20
Key studies identified in update						
Sawa et al. (2020)	Prospective, parallel-group comparison, double-blind	Patients with AMD	42	20	6 months	20
Xu et al. (2013)	Randomized, double-blind, placebo-controlled	Patients with early atherosclerosis	65	0, 20	3 months	20
Stringham et al. (2016, 2017, 2018, 2019)	Randomized, double-blind, placebo-controlled	Healthy adults	28 or 59	6.18, 10.86, 22.33	12 weeks to 12 months	22.33

AMD, age-related macular degeneration

CRN's previous assessment concluded that the evidence of safety for lutein supported supplemental intakes up to 20 mg per day (Shao and Hathcock 2006). Although higher levels had been tested without adverse effects, these studies were determined not to be sufficient to serve as the basis of an HOI value. For example, Bahrami et al. (2006) administered 30 mg per day lutein to patients with retinitis pigmentosa. No adverse effects were reported other than self-reported vision changes; however, the disease nature of the subjects limited the relevance of this effect in the general population. In addition, Dagnelie et al. (2000) administered 40 mg per day with no serious adverse events reported beyond self-reported vision changes; however, this study was not a randomized, blinded, or controlled trial.

No serious adverse effects were reported in any human intervention studies published since 2006; these studies included doses ranging from 2.5-22.33 mg lutein per day. For example, human clinical trial studies administering 20 mg lutein per day for three to six months in healthy and diseased patients were without reported adverse effects (e.g., Aleman et al. 2001; Sawa et al.

2020; Xu et al. 2013; Yoshida et al. 2023; Yao et al. 2013; Ma et al.2012). In addition, a series of publications by Stringham et al. (2016, 2017, 2018, 2019) evaluated a cohort of healthy adults administered lutein up to 22.33 mg per day with no adverse effects reported. However, the published methods did not specify that safety or tolerance was monitored for in these studies. The safety conclusions of the JECFA (2020) and EFSA (2010, 2011), which derived ADI values of "not specified" (group ADI) and 1 mg per kg bw per day, respectively, help to address any uncertainty due to the lack of specified monitoring methods in the Stringham et al. studies. For context, the EFSA ADI value is equivalent to 60 mg lutein per day based on a 60-kg adult. Therefore, 22 mg per day from the Stringham et al. studies is identified as the NOAEL for lutein for healthy adults following the CRN process. As described in CRN's Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology, an UF of 1 is applied to yield an HOI of 22 mg per day for adults for supplemental lutein.

The lower CRN HOI value compared to the JECFA and EFSA ADI values is due to differences in methodology, where the CRN process prioritizes human data over animal toxicological data, when available. Based on the lack of any adverse effects reported in human clinical trials, the available authoritative ADI values, and the available toxicological dataset, intakes higher than 22 mg lutein per day may be safe for some individuals.

Quantitative Summary for Lutein in Adults

CRN (2025) HOI, supplemental intake	22 mg/day
IOM	Not evaluated
EFSA (2010, 2011), ADI	1 mg/kg bw/day (lutein derived from *Tagetes erecta* L.) No UL value has been derived.
EVM (2003)	Not evaluated
CNS (2023) UL, total intake	60 mg/day
ICMR-NIN (2020), total intake	Not evaluated
KNS (2020), total intake	Not evaluated

Zeaxanthin

Key Studies Considered for the CRN HOI for Zeaxanthin in Adults

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg/day)	Duration	NOAEL (mg/day)
Choi et al. 2017	Randomized, open-label	Patients with macular telangiectasia type 2 (MacTel)	8	10, 20	24 months	20
Bovier et al. 2014	Randomized, double-blind, placebo-controlled	Healthy patients	92	0, 20	4 months	20
Bovier et al. 2015	Randomized, double-blind, placebo-controlled	Healthy patients	69	0, 20, 26	4 months	26

No serious adverse effects were reported in the identified human intervention studies published since 2006, in which doses ranging from 0.6-26 mg zeaxanthin per day were administered. Human clinical trial studies administering 20 mg zeaxanthin per day for four to 24 months in healthy and diseased patients were reviewed (Choi et al. 2017; Bovier et al. 2014, 2015). In the study by Bovier et al. (2015), no adverse effects were observed in healthy adults administered up

to 26 mg[12] zeaxanthin per day for four months; however, the published methods did not specify that safety or tolerance was monitored for in this study. The safety conclusions of JECFA (2020) and EFSA (2012), which derived ADI values for zeaxanthin of "not specified" (group ADI) and 0.75 mg per kg bw per day, respectively, help to address any uncertainty due to the lack of specified monitoring methods in the Bovier et al. (2015) study. For context, the EFSA ADI is equivalent to 45 mg zeaxanthin per day based on a 60-kg adult. Therefore, based on Bovier et al. (2015), 26 mg per day is identified as the NOAEL for zeaxanthin for healthy adults following the CRN process. As described in CRN's Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology, an UF of 1 is applied to yield an HOI of 26 mg per day for adults for supplemental zeaxanthin.

The lower CRN HOI value compared to the JECFA and EFSA ADI values is due to differences in methodology, where the CRN process prioritizes human data over animal toxicological data, when available. Based on the lack of any adverse effects reported in human clinical trials, the available authoritative ADI values, and the available toxicological dataset, intakes higher than 26 mg zeaxanthin per day may be safe for some individuals.

Quantitative Summary for Zeaxanthin in Adults

CRN (2025) HOI, supplemental intake	26 mg/day
IOM	Not evaluated
EFSA (2012), ADI	0.75 mg/kg bw/day (synthetic zeaxanthin only) No UL value has been derived.
EVM (2003)	Not evaluated
CNS (2023), total intake	Not evaluated
ICMR-NIN (2020), total intake	Not evaluated
KNS (2020), total intake	Not evaluated

[12] The material included: 26 mg zeaxanthin, 8 mg lutein, and 190 mg mixed n-s fatty acids.

Meso-Zeaxanthin

Key Studies Considered for the CRN HOI for Meso-Zeaxanthin in Adults

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg/day)[a]	Duration	NOAEL (mg/day)
Power et al. (2018)	Randomized, double-blind, placebo-controlled	Healthy adults	90	0, 10	12 months	10
Loughman et al. (2021)	Randomized, double-blind, placebo-controlled	Patients with open-angle glaucoma	62	0, 10	18 months	10
Meagher et al. (2013)	Randomized, double-blind	Healthy adults and patients with AMD	54	10, 17	8 weeks	17
Thurnham et al. (2015)	Randomized, double-blind	Healthy adults and patients with AMD	63	0.3, 10, 17	8 weeks	17
Sabour-Pickett et al. (2014); Akuffo et al. (2015)[a]	Randomized, single-blind	Patients with AMD	60	10, 17	12 and 36 months	17

AMD, age-related macular degeneration
[a] Meso-zeaxanthin Ocular Supplementation Trial (MOST)

No serious adverse effects were reported in the identified human intervention studies published since 2006, in which doses ranging from 0.3-17 mg meso-zeaxanthin per day were administered. Six randomized, blinded, placebo-controlled trials administering up to 10 mg meso-zeaxanthin per day for 6 to 18 months were reviewed (Connolly et al. 2011; Laughman et al. 2012, 2021; Power et al. 2018; Green-Gomez et al. 2020; Stringham et al. 2024). In addition, three randomized, blinded trials were identified that included meso-zeaxanthin at doses up to 17 mg per day for 8 weeks and up to 36 months (Meagher et al. 2013; Thurnham et al. 2015; Sabour-Pickett et al. 2014; Akuffo et al. 2015). These studies did not employ a placebo control group, nor did the published methods for each specify monitoring for safety. However, taken together, these studies included a total of 184 participants (heathy adults and/or those with AMD), 67 of which received supplemental meso-zeaxanthin at 17 mg per day for 36 months. Therefore, based on the available data, 17 mg per day is identified as the NOAEL for meso-zeaxanthin for healthy adults following the CRN process. As described in CRN's Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology,

an UF of 1 is applied to yield an HOI of 17 mg per day for adults for supplemental meso-zeaxanthin.

This selection is further supported by the evaluation conducted by the JECFA (2020) on lutein, zeaxanthin, and meso-zeaxanthin that reviewed the available human and animal toxicological data, which were all viewed by the Committee as biochemically and toxicologically equivalent.[13] Based on the lack of any adverse effects in human clinical trials, the higher authoritative ADI values for similar xanthophylls (e.g., lutein and synthetic zeaxanthin), and the available toxicological dataset, intakes higher than 17 mg zeaxanthin per day may be safe for some individuals.

Quantitative Summary for Meso-Zeaxanthin in Adults

CRN (2025) HOI, supplemental intake	17 mg/day
IOM	Not evaluated
EFSA	Not evaluated
EVM (2003)	Not evaluated
CNS (2023), total intake	Not evaluated
ICMR-NIN (2020), total intake	Not evaluated
KNS (2020), total intake	Not evaluated

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[13] The Committee did not include meso-zeaxanthin in the resulting group ADI due to a lack of specifications at the time of evaluation.

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