



**EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to a combination of lutein and zeaxanthin and improved vision under bright light conditions pursuant to Article 13(5) of Regulation (EC) No 1924/2006**

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## SCIENTIFIC OPINION

### **Scientific Opinion on the substantiation of a health claim related to a combination of lutein and zeaxanthin and improved vision under bright light conditions pursuant to Article 13(5) of Regulation (EC) No 1924/2006<sup>1</sup>**

**EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)<sup>2,3</sup>**

European Food Safety Authority (EFSA), Parma, Italy

#### **ABSTRACT**

Following an application from DSM Nutritional Products and Kemin Foods, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of lutein and zeaxanthin and improved vision under bright light conditions. The Panel considers that the food is sufficiently characterised. Improved vision under bright light conditions is a beneficial physiological effect. The applicant provided a total of 10 published and one unpublished human intervention studies as being pertinent to the health claim. Five studies investigated the effects of lutein and/or zeaxanthin on macular pigment optical density, but did not assess vision, whereas two studies investigated the effects of lutein only. Two further studies had already been evaluated by the Panel in a previous assessment. No conclusions could be drawn from one further small (no effect) study. In a further trial with a large number of missing data owing to drop-out/non-compliance of study subjects, a combination of lutein and zeaxanthin had no effect on any outcomes of visual function in the population of subjects completing the protocol as planned. In weighing the evidence, the Panel took into account that the one study from which conclusions could be drawn did not show an effect of lutein plus zeaxanthin on vision. The Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of lutein and zeaxanthin and improved vision under bright light conditions.

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#### **KEY WORDS**

lutein, zeaxanthin, vision, visual performance, contrast sensitivity, health claims

<sup>1</sup> On request from the Competent Authority of France following an application by DSM Nutritional Products and Kemin Foods, Question No EFSA-Q-2013-00875, adopted on 25 June 2014.

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## SUMMARY

Following an application from DSM Nutritional Products and Kemin Foods, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of lutein and zeaxanthin and improved vision under bright light conditions.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

The food that is the subject of the health claim is a combination of lutein and zeaxanthin. Lutein and zeaxanthin are xanthophyll carotenoids naturally present in food, especially in green leafy vegetables. Lutein and zeaxanthin can be measured in foods by established methods. The Panel considers that the food, a combination of lutein and zeaxanthin, which is the subject of the health claim is sufficiently characterised.

The claimed effect relates to improved visual performance, in particular under bright light conditions. The target population proposed by the applicant is the general healthy population. The Panel considers that improved vision under bright light conditions is a beneficial physiological effect.

The applicant provided a total of 10 published and one unpublished human intervention studies as being pertinent to the health claim.

Five studies investigated the effects of lutein and/or zeaxanthin on macular pigment optical density, but did not assess vision, whereas two studies investigated the effects of lutein only, and not of the combination of lutein plus zeaxanthin that is the subject of the health claim, on visual outcomes. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

Three published and one unpublished human intervention studies investigated the effects of lutein, either alone or in combination with zeaxanthin, on measures of vision. Two of these studies were already evaluated by the Panel in relation to a claim on lutein and maintenance of normal vision. The Panel considered that no conclusions could be drawn from these two studies for the scientific substantiation of the claim owing to important methodological limitations.

In a randomised, single-blind, placebo-controlled, parallel study, 36 subjects were randomly assigned to consume daily for six months (i) 20 mg lutein and 2 mg zeaxanthin, (ii) 10 mg lutein, 2 mg zeaxanthin and 10 mg meso-zeaxanthin, or (iii) a placebo. The outcome measures included visual acuity, contrast sensitivity, glare disability and photostress recovery. No significant differences were observed between the lutein plus zeaxanthin group and the placebo group for any measure of vision. The Panel notes the small sample size of the study and considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In a randomised, double-blind, placebo-controlled, parallel trial, 115 subjects were randomised to consume daily for one year 10 mg lutein plus 2 mg zeaxanthin or a placebo. The primary outcome of the study, on which power calculations were based, was changes in macular pigment optical density. Secondary outcomes included measures of visual function, i.e. contrast sensitivity, glare sensitivity/tolerance and photostress recovery time. According to the statistical analysis plan, a repeated measures analysis of variance was foreseen to analyse the data. However, during a blind data review, the authors decided that a linear mixed model regression was more appropriate, owing to a “substantial number of unbalanced missing values”. In total, 34 subjects dropped out of the study. In the statistical analysis, the following three study populations were considered: (i) the “baseline set” (intention to treat, ITT); (ii) “intention to treat” (modified intention to treat, mITT); (iii) “protocol compliant” (per protocol, PP). When the ITT and mITT populations were considered, a significant improvement in contrast sensitivity and photostress recovery was reported in the lutein plus

zeaxanthin group compared with the placebo group, whereas no significant changes between groups were observed for glare sensitivity. No significant differences were observed between groups for contrast sensitivity, photostress recovery or glare sensitivity when the analysis was performed in the PP population. The Panel notes that a combination of lutein and zeaxanthin had no effect on any outcomes of visual function in the population of subjects completing the protocol as planned (i.e. PP population), that at least 50 % of the subjects considered for the ITT and the mITT analyses had missing data owing to drop-out/non-compliance of study subjects, and that no evidence was provided that could justify the discrepancy of the results obtained from the different analyses. The Panel also notes that the statistical analysis was not carried out according to the statistical analysis plan, that measures of visual function were secondary outcomes in this study and that multiplicity of outcomes was not considered in the statistical analyses. The Panel considers that this study does not show an effect of a combination of lutein and zeaxanthin on vision.

In weighing the evidence, the Panel took into account that the one study from which conclusions could be drawn did not show an effect of lutein plus zeaxanthin on vision.

The Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of lutein and zeaxanthin and improved vision under bright light conditions.

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## BACKGROUND

Regulation (EC) No 1924/2006<sup>4</sup> harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

## STEPS TAKEN BY EFSA

- The application was received on 29/10/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.
- The scientific evaluation procedure started on 11/12/2013.
- On 05/03/2014, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 25/03/2014 and was restarted on 09/04/2014, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 11/04/2014, EFSA received the requested information (which was made available to EFSA in electronic format on 08/04/2014).
- During its meeting on 25/06/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to a combination of lutein and zeaxanthin and improved vision under bright light conditions.

## TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: a combination of lutein and zeaxanthin and improved vision under bright light conditions.

## EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of a combination of lutein and zeaxanthin, a positive assessment of its safety, nor a decision on whether a combination of lutein and zeaxanthin is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

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<sup>4</sup> Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

## INFORMATION PROVIDED BY THE APPLICANT

### Applicants' names and addresses

DSM Nutritional Products France, Le Véronèse, 19/21 Avenue Dubonnet, 92400 Courbevoie, France.

Kemin Foods, L.C., Campo Grande, 35-8° D, 1700-087 Lisboa, Portugal.

The application includes a request for the protection of proprietary data for one unpublished study (DSM Nutritional Products Ltd and Kemin Foods L.C., 2013), in accordance with Article 21 of Regulation (EC) No 1924/2006.

### Food/constituent as stated by the applicant

According to the applicant, the food that is the subject of the health claim is a combination of lutein and zeaxanthin.

### Health relationship as claimed by the applicant

According to the applicant, the consumption of lutein together with zeaxanthin leads to an increase in macular pigment optical density, which, in turn, is claimed to improve visual performance, in particular under bright light conditions. The applicant indicated that the improved visual performance is brought about, and can be measured, by a faster recovery from photo bleaching, higher tolerance against the “veiling effect” of glare and improved contrast sensitivity in a high luminance field of view.

### Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: “Lutein together with zeaxanthin helps maintain clarity and contrast of sight in bright light conditions”.

### Specific conditions of use as proposed by the applicant

The applicant has proposed an intake of 10 mg lutein plus 2 mg zeaxanthin per day. The proposed target population is the general healthy population.

## ASSESSMENT

### 1. Characterisation of the food/constituent

The food that is the subject of the health claim is a combination of lutein and zeaxanthin.

Lutein and zeaxanthin are xanthophyll carotenoids naturally present in food, especially in green leafy vegetables such as spinach and kale. Lutein and zeaxanthin can be measured in foods by established methods.

The applicant indicated the Chemical Abstracts Service (CAS) numbers for both lutein (127-40-2) and zeaxanthin (144-68-3) and provided monographs (JECFA, 2004, 2006) which the ingredients comply with.

An overview of the manufacturing process and information regarding stability and reproducibility of batches were provided. The applicant also submitted two bioavailability studies (Hartmann et al., 2004; Evans et al., 2013) on the formulations of the lutein and zeaxanthin used in the human study (DSM Nutritional Products Ltd and Kemin Foods L.C., 2013, unpublished) claimed as proprietary by the applicant.

The Panel considers that the food, a combination of lutein and zeaxanthin, which is the subject of the health claim, is sufficiently characterised.



## 2. Relevance of the claimed effect to human health

The claimed effect relates to improved visual performance, in particular under bright light conditions. The target population proposed by the applicant is the general healthy population.

Vision is a defined function of the eye and nervous system. An increase in vision, maintenance of vision or reduced loss of vision is a beneficial physiological effect for the general population. Visual function can be measured by using standard tests of visual acuity and contrast sensitivity under specific light conditions, e.g. under bright light conditions.

Changes in macular pigment optical density (MPOD) have been proposed as outcome measures for the scientific substantiation of claims on the maintenance of vision. To this end, the applicant provided four observational studies which reported on the relationship between MPOD and photophobia light threshold (Wenzel et al., 2006), heterochromatic luminance contrast (Renzi and Hammond, 2010), photostress recovery, glare disability and visual discomfort (Stringham et al., 2011), and photostress recovery, glare disability and chromatic contrast (Hammond et al., 2013). The Panel notes that MPOD is not a measure of visual function and considers that the available evidence (including the four observational studies provided by the applicant) does not establish that changes in MPOD predict changes in visual function. Therefore, the Panel considers that MPOD is not a suitable outcome measure for the scientific substantiation of claims related to increased vision, maintenance of vision or reduced loss of vision (EFSA NDA Panel, 2012b).

The Panel considers that improved vision under bright light conditions is a beneficial physiological effect.

## 3. Scientific substantiation of the claimed effect

A claim on lutein in combination with zeaxanthin and maintenance of normal vision has already been assessed by the Panel with an unfavourable outcome (EFSA NDA Panel, 2011).

The applicant performed a literature search in PubMed using the search terms (“lutein” or “zeaxanthin”) and (“macular pigment” or “vision”) restricted to “humans”, and (“lutein” or “zeaxanthin”) restricted to “clinical trial”. The search was carried out on 20 December 2012, with an update for studies published thereafter until 20 July 2013. Only studies carried out in healthy populations were included. Studies which were concerned with MPOD in relation to neuronal processing were excluded.

The applicant provided a total of 10 published human intervention studies and one unpublished human intervention study as being pertinent to the health claim.

Five studies investigated the effects of lutein and/or zeaxanthin on MPOD, but did not assess vision (Schalch et al., 2007; Johnson et al., 2008; Bone and Landrum, 2010; Graydon et al., 2012; Landrum et al., 2012), whereas two studies (Ma et al., 2009; Yao et al., 2013) investigated the effects of lutein only, and not of the combination of lutein plus zeaxanthin that is the subject of the health claim, on visual outcomes. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

Three published human intervention studies (Kvansakul et al., 2006; Rodriguez-Carmona et al., 2006; Loughman et al., 2012) and one unpublished human intervention study (DSM Nutritional Products Ltd and Kemin Foods L.C., 2013) investigated the effects of lutein, either alone or in combination with zeaxanthin, on measures of vision. Two of these studies (Kvansakul et al., 2006; Rodriguez-Carmona et al., 2006) were already evaluated by the Panel in relation to a claim on lutein and maintenance of normal vision (EFSA NDA Panel, 2012a). The Panel considered that no conclusions could be drawn from these two studies for the scientific substantiation of the claim owing to important methodological limitations.



In a randomised, single-blind, placebo-controlled, parallel study (Loughman et al., 2012), 36 subjects (19 male, 17 female, mean age  $51 \pm 13$  years) were randomly assigned to consume daily for six months (i) 20 mg lutein and 2 mg zeaxanthin ( $n = 12$ ), (ii) 10 mg lutein, 2 mg zeaxanthin and 10 mg meso-zeaxanthin ( $n = 12$ ) or (iii) a placebo ( $n = 12$ ). The outcome measures, which were assessed at baseline and at months 3 and 6, included visual acuity, contrast sensitivity, glare disability, photostress recovery, ocular stray light, MPOD and serum concentrations of lutein and total carotenoids. Four subjects dropped out of the study. Between-group comparisons were carried out with a repeated measures analysis of variance (RM-ANOVA) followed by Tukey's test. No significant differences were observed between the lutein plus zeaxanthin group and the placebo group for any measure of vision. It was indicated in the publication that "this exploratory study had adequate statistical power to detect only large within-group or between group differences". The Panel notes the small sample size of the study and that post-hoc power calculations indicated that the study was underpowered. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In a randomised, double-blind, placebo-controlled, parallel trial (DSM Nutritional Products and Kemin Foods, 2013, unpublished; claimed as proprietary by the applicant), 115 subjects (67 female, 48 male) recruited from the University of Georgia (USA) were randomised to consume daily for one year 10 mg lutein plus 2 mg zeaxanthin ( $n = 57$ ) or a placebo (cellulose;  $n = 58$ ). Subjects were included if they were healthy, between 18 and 40 years and had a body mass index (BMI) of 20-30 kg/m<sup>2</sup>. Smokers were excluded from the study. The participants were asked to abstain from eating dark-green leafy vegetables and all other sources with high xanthophyll content during the whole study period. No information on the compliance with this requirement was provided. No assessment of the background diet was performed. The study was approved by the Institutional Review Board at the University of Georgia. The primary outcome of the study, on which power calculations were based, was changes in MPOD. Secondary outcomes were serum xanthophyll concentrations and measures of visual function, i.e. contrast sensitivity, glare sensitivity/tolerance and photostress recovery time. The outcomes were measured at baseline and at months 3, 6, 9 and 12. According to the statistical analysis plan, a RM-ANOVA was foreseen to analyse the data. However, during a blind data review, the authors decided that a linear mixed model regression was more appropriate, owing to a "substantial number of unbalanced missing values". In total, 34 subjects dropped out of the study. In the statistical analysis, the following three study populations were considered: (i) the "baseline set" (intention to treat, ITT), i.e. all subjects who were randomised ( $n = 115$ ); (ii) "intention to treat" (modified intention to treat, mITT), defined by the applicant as all subjects who participated at baseline and had at least one subsequent visit ( $n = 109$ ); (iii) "protocol compliant" (per protocol, PP), defined by the applicant as all randomised subjects who had complete data sets for all visual measurements and who were at least 80 % compliant with the study products ( $n = 55$ ). When the ITT and mITT populations were considered, a significant improvement in contrast sensitivity ( $p = 0.028$  and  $p = 0.030$  for the ITT and mITT, respectively) and photostress recovery ( $p = 0.015$  and  $p = 0.013$ , respectively) was reported in the lutein plus zeaxanthin group compared with the placebo group, whereas no significant changes between groups were observed for glare sensitivity. No significant differences were observed between groups for contrast sensitivity, photostress recovery or glare sensitivity when the analysis was performed in the PP population ( $p = 0.75$ ,  $p = 0.48$  and  $p = 0.85$ , respectively). Upon EFSA's request for clarification on the discrepancy of the results between the ITT and mITT populations and the PP population, the applicant argued that the absence of significant effects of the intervention on outcomes of visual function in the PP population could be the result of "(i) a loss of power in the per protocol subgroup, (ii) random differences between the per protocol population and the other subjects or (iii) a systematic bias between the per protocol population and the other subjects". The Panel considers that the absence of significant effects in the PP population could not be explained by a lack of power and notes that no evidence was provided to indicate that random differences or a systematic bias could explain the absence of effects in the PP population. The Panel notes that a combination of lutein and zeaxanthin had no effect on any outcomes of visual function in the population of subjects completing the protocol as planned (i.e. PP population), that at least 50 % of the subjects considered for the ITT and the mITT analyses had missing data or were not compliant with the protocol, and that no evidence was provided that could justify the discrepancy of the results obtained from the different analyses. The

Panel also notes that the statistical analysis was not carried out in accordance with the statistical analysis plan, that measures of visual function were secondary outcomes in this study and that multiplicity of outcomes was not considered in the statistical analyses. The Panel considers that this study does not show an effect of a combination of lutein and zeaxanthin on vision.

In weighing the evidence, the Panel took into account that the one study from which conclusions could be drawn did not show an effect of lutein plus zeaxanthin on vision.

The Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of lutein and zeaxanthin and improved vision under bright light conditions.

## CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food, a combination of lutein and zeaxanthin, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect relates to improved visual performance, in particular under bright light conditions. The target population proposed by the applicant is the general healthy population. Improved vision under bright light conditions is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of a combination of lutein and zeaxanthin and improved vision under bright light conditions.

## DOCUMENTATION PROVIDED TO EFSA

Health claim application on a combination of lutein and zeaxanthin and improved vision under bright light conditions pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0399\_FR). October 2013. Submitted by DSM Nutritional Products Ltd and Kemin Foods.

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## ABBREVIATIONS

BMI	body mass index
CAS	Chemical Abstracts Service
ITT	intention to treat
mITT	modified intention to treat
MPOD	macular pigment optical density
PP	per protocol
RM-ANOVA	repeated measures analysis of variance