SCIENTIFIC OPINION

Statement on the safety of synthetic zeaxanthin as an ingredient in food supplements

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)², ³

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to update its opinion on the safety of synthetic zeaxanthin as a novel food ingredient in food supplements in the light of additional information provided by the applicant. In its previous opinion of 2008, the Panel concluded that based on the available data, the safety of zeaxanthin as an ingredient in food supplements at the proposed use level of up to 20 mg/person per day has not been established. In response to the EFSA Opinion of 2008, the applicant provided a two-generation reproduction toxicity study with synthetic zeaxanthin in rats and twenty-two additional references including some mechanistic studies related to carotenoids and lung cancer risk. Although neither animal nor human data on the lung cancer risk of zeaxanthin are available, on the current data available the Panel considers it is unlikely that supplemental intake of zeaxanthin would increase the risk of lung cancer in heavy smokers. The Panel identifies a NOAEL at 150 mg/kg bw per day in the two-generation reproduction toxicity study and has no concerns with regard to genotoxicity. Given the absence of a chronic toxicity/carcinogenicity study, the Panel applies an uncertainty factor of 200 on the NOAEL in the two-generation study. This results in 0.75 mg/kg bw per day for synthetic zeaxanthin corresponding to a daily intake of 53 mg for a person with a body weight of 70 kg. The Panel concludes that based on the available data, intakes of 0.75 mg/kg bw per day for synthetic zeaxanthin, corresponding to a daily intake of 53 mg for a person with a body weight of 70 kg, do not raise safety concerns. Therefore, the use levels proposed by the applicant do not raise safety concerns.

KEY WORDS

Zeaxanthin, carotenoids, xanthophylls, safety, novel food.

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SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to update its opinion on the safety of synthetic zeaxanthin as a novel food ingredient in food supplements in the light of additional information provided by the applicant. Specifically, the Commission asks EFSA if a safety level for synthetic zeaxanthin could be derived on the basis of the additional information provided by the applicant, and in particular to know whether the proposed use level of up to 2 mg per person per day would be safe.

In its previous opinion of 2008, the Panel concluded that based on the available data, the safety of zeaxanthin as an ingredient in food supplements at the proposed use level of up to 20 mg/person per day has not been established. This conclusion was based on the considerations that (i) the proposed levels of use of up to 20 mg/person per day of synthetic zeaxanthin as an ingredient in food supplements would lead to intake levels that would substantially increase the average dietary intake of zeaxanthin, resulting in up to 100 times higher intakes for adults, that (ii) no studies on chronic toxicity and carcinogenicity have been performed using synthetic zeaxanthin; and the toxicological data are not sufficient to derive an acceptable daily intake, and that (iii) on the basis of available data, it is not possible to assess whether additional intake of synthetic zeaxanthin at the proposed level of use would increase the risk of lung cancer in heavy smokers as reported for β-carotene.

In response to the EFSA Opinion of 2008, the applicant provided a two-generation reproduction toxicity study with zeaxanthin and twenty-two additional references including some mechanistic studies related to carotenoids and lung cancer risk.

The effects of high-dose β-carotene observed in animal models of carotenoids research on lung cancer have been mainly attributed to the pro-oxidant properties of β-carotene, being a precursor of vitamin A, its interference with retinoic acid metabolism, and induction of CYP enzymes. There are differences in structure, metabolism and function between zeaxanthin and β-carotene. Contrary to β-carotene, zeaxanthin is more polar and is not a precursor of vitamin A. In particular, it is more stable than β-carotene under pro-oxidant exposure and differs from β-carotene also with regard to its much lower or absent potential of acting as a pro-oxidant in vitro.

Although neither animal nor human data on the lung cancer risk of zeaxanthin are available, based on the current data available the Panel considers it unlikely that supplemental intake of zeaxanthin would increase the risk of lung cancer in heavy smokers. The Panel identifies a NOAEL of 150 mg/kg bw per day in the two-generation reproduction toxicity study with synthetic zeaxanthin in rats and has no concerns with regard to genotoxicity. Given the absence of a chronic toxicity/carcinogenicity study, the Panel applies an uncertainty factor of 200 on the NOAEL in the two-generation study. This results in 0.75 mg/kg bw per day for synthetic zeaxanthin corresponding to a daily intake of 53 mg for a person with a body weight of 70 kg.

The Panel concludes that based on the available data, intakes of 0.75 mg/kg bw per day for synthetic zeaxanthin, corresponding to a daily intake of 53 mg for a person with a body weight of 70 kg, do not raise safety concerns. Therefore, the use levels proposed by the applicant do not raise safety concerns.
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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION


The conclusion of the EFSA Opinion was that based on the existing data, the safety of zeaxanthin as an ingredient in food supplements at the proposed use level of up to 20 mg per person and per day has not been established.

The applicant has now provided additional information, in particular a two generation rat study, and suggests an acceptable daily intake of 1.5 mg/kg bw per day. Together with other information, the applicant is now asking for the use of synthetic zeaxanthin in food supplements at the use level of up to 2 mg/person per day.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In view of the above the Commission requests EFSA to review and update its opinion in the light of the additional information (see annexes). The Commission would be interested to know if a safety level for synthetic zeaxanthin could be derived on the basis of the additional information provided by the applicant, and in particular to know whether the proposed use level of up to 2 mg per person per day would be safe.
ASSESSMENT

1. INTRODUCTION

In 2007, the European Commission asked EFSA to carry out an assessment of the safety of ‘synthetic zeaxanthin as an ingredient in food supplements’ with intended maximum intake of 20 mg per person per day in the context of Regulation (EC) No 258/97. In 2008, the Panel concluded that based on the available data, the safety of zeaxanthin as an ingredient in food supplements at the proposed use level of up to 20 mg/person per day has not been established.

This conclusion was based on the considerations that (i) the proposed levels of use of up to 20 mg/person per day of synthetic zeaxanthin as an ingredient in food supplements would lead to intake levels that would substantially increase the average dietary intake of zeaxanthin, resulting in up to 100 times higher intakes for adults, that (ii) no studies on chronic toxicity and carcinogenicity have been performed using synthetic zeaxanthin; and the toxicological data are not sufficient to derive an acceptable daily intake (ADI), and that (iii) on the basis of available data, it is not possible to assess whether additional intake of synthetic zeaxanthin at the proposed level of use would increase the risk of lung cancer in heavy smokers as reported for β-carotene.

2. ADDITIONAL INFORMATION PROVIDED

To address these considerations expressed by EFSA in 2008, the applicant provided a dossier which includes in total 23 references, two of which were already considered by EFSA in its assessment from 2008 (Hartmann et al., 2004; Schalch et al., 2007). The applicant also referred to the ADI of 1 mg per kg bw per day for a lutein-rich extract from Tagetes erecta (containing also 5 % zeaxanthin) derived by the EFSA Panel on Food Additives and Nutrient Sources added to Food (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010). A publication on profiling the reproductive toxicity of chemicals from multi-generation studies in the toxicity reference database (Martin et al., 2009) is not relevant for the evaluation of synthetic zeaxanthin.

2.1. Toxicological information

2.1.1. Genotoxicity and oral toxicity

One provided publication reported on tests for gene mutations in bacteria (Ames test) and studies on acute and subchronic (90-day) oral toxicity in rats (Ravikrishnan et al., 2011). These studies were performed with a lutein and zeaxanthin enriched product from Marigold flowers (Tagetes erecta L.) containing approximately 54 % lutein and 11 % zeaxanthin. The Panel notes that in 2008 it had no concerns with regards to the genotoxicity of synthetic zeaxanthin, and also the Marigold product was non genotoxic in the Ames test. After administration of the Marigold product at a single oral dose of 2000 mg/kg bw, no toxic effects were observed. In the subchronic oral toxicity study there were no indications of adverse effects up to the highest tested dose of 400 mg/kg bw per day. In the previous evaluation (EFSA Panel on Dietetic Products Nutrition and Allergies, 2008), which was based on studies with highly purified synthetic zeaxanthin, no adverse effects were observed in subchronic studies using mice, rats and dogs up to the highest dose of 1000 mg/kg bw per day. Therefore the additional subchronic oral toxicity study provided by the applicant does not add relevant information to the safety assessment of synthetic zeaxanthin.
2.1.2. Reproduction toxicity

The applicant provided a two-generation reproduction toxicity study with synthetic zeaxanthin (Edwards et al., 2006). This study was carried out in accordance with OECD Guideline 416, and in compliance with the regulations of Good Laboratory Practice (GLP). ‘Zeaxanthin 10 % WS beadlets’ were administered with the diet to groups of 24 male and 24 female rats (Crl:WI(Gix/BRL/Han)BR) at doses of 455, 1364 or 4545 mg/kg body weight (bw) per day. The overall combined intake of zeaxanthin for males and females was 52, 155 and 508 mg/kg bw per day in the low, mid and high dose groups, respectively. One control group received placebo beadlets incorporated in the diet at the same concentration as the zeaxanthin beadlets in the high dose group (placebo control group) and another one a standard rodent diet (conventional control group). In the statistical analyses, data from the test groups as well as the placebo control group were compared to those of the conventional control group. The Panel notes that only the endpoints fertility, fecundity and mating indices were statistically compared between the test and the placebo control group.

Analyses of plasma and liver samples from adults and pups of the P and F\textsubscript{1} generation showed that the zeaxanthin levels increased with the dose, were higher in pups than in adults (plasma: 283 µg/L in pups vs. 110 and 79 µg/L in males and females of the high dose group, respectively) and higher in the liver (23 mg/kg in pups and 2.1 and 3.5 mg/kg in males and females of the high dose group, respectively) than in plasma.

In the parent (P) generation the groups administered zeaxanthin showed no toxicologically relevant differences in mean body weights, body weight gains and food intake compared with the placebo control group. There were no toxicologically relevant differences regarding oestrous cycling data prior to mating, as well as mating, fertility and fecundity indices, duration of gestation, number of implantation sites, number of pups born, pup sex ratio, pup survival and body weight development.

One female in the conventional control group and one in the low dose group showed total embryo-fetal loss, and one female in the conventional control group and two in the high dose group showed total litter loss. No macroscopic findings indicative of an adverse effect of treatment were identified at necropsy of these animals. The only noteworthy difference was a lower post-implantation survival index in the high dose group (87.4 %) compared with the placebo (92.1 % - not statistically analysed) and the conventional control group (94.4 % - not statistically significant). Macroscopic examination of P animals and F\textsubscript{1} pups at necropsy revealed no indications of adverse effects, and there were no toxicologically relevant differences in the weights of selected organs. Microscopic findings were equally distributed between all groups and seminology data for P males were comparable in the groups administered zeaxanthin and placebo. In qualitative testis staging no abnormalities in the integrity of the various cell types present at the different stages of the spermatogenic cycle were identified.

In the F\textsubscript{1} generation two animals died or were killed during the treatment period without identification of treatment-related changes. Compared with the placebo control group, a dose-related decrease in mean body weights and body weight gains of females of the mid and high dose groups was noted in the third week of gestation. Body weights differed by less than 5 % and weight gains were 9 % and 13 % less compared with the placebo control group (not statistically analysed). There were no toxicologically relevant effects of treatment on learning ability, physical development, functional and behavioural development or motor activity of F\textsubscript{1} animals. The high dose group showed a statistically significantly lower mating index compared with the placebo control group (p < 0.05), which was considered by the author to be largely due to atypical oestrous cycling of four females in this group. Slightly fewer pups were born and alive on day 1 and the post-implantation survival index was also slightly lower (not statistically analysed). There were no toxicologically relevant findings regarding F\textsubscript{1} pup body weights, macroscopic findings and organ weights at necropsy of F\textsubscript{1} pups and parent animals, as well as microscopic findings and seminology data for the latter.
In conclusion, compared with the placebo control group, administration of zeaxanthin at a dose of approximately 500 mg/kg bw per day to rats for two successive generations induced a slightly lower post-implantation survival index in the high dose group in the P generation and a slightly lower body weight gain during the gestation period of the F1 generation. There was an adverse effect on fertility of the F1 generation (statistically significantly reduced mating index), slightly fewer pups were born and the post-implantation survival index was also slightly lower. Therefore, the no-observed adverse effect level (NOAEL) was considered to be the nominal dosage of 150 mg zeaxanthin/kg body weight/day.

2.1.3. Risk for lung cancer

In the absence of a study in the smoke-exposed ferret/lung cancer model with zeaxanthin, the applicant provides a study in the ferret model with β-cryptoxanthin (Liu et al., 2011) which he considers as relevant to the perceived potential of zeaxanthin and lutein to be or not to be associated with an increased risk of lung cancer in heavy smokers, as was shown for β-carotene and could be mimicked in the ferret model (Liu et al., 2000).

2.1.3.1. In vitro and animal studies related to the structure and metabolism of β-cryptoxanthin in comparison to zeaxanthin

β-Cryptoxanthin (β,β-carotene-3-ol) is a xanthophyll carotenoid with one half of the molecule (C20 moiety) being identical to zeaxanthin (β,β-carotene-3,3′-diol) and the other half being identical to β-carotene (β,β-carotene). β-Cryptoxanthin therefore yields one molecule vitamin A when metabolised by central cleavage enzyme β,β-carotene-15,15′-monooxygenase (CMO1). The presence of at least one unsubstituted β-ionone ring has been recognized as a requisite for cleavage by CMO1, thus no central cleavage activity was detected when zeaxanthin was used as a substrate (van Vliet et al., 1996).

Zeaxanthin is metabolised by eccentric cleavage through carotene-9′,10′-monooxygenase (CMO2). β-Cryptoxanthin is also metabolised eccentrically through CMO2, which has been identified in humans, mice and ferrets (Hu et al., 2006). CMO2 was characterized as a mitochondrial enzyme which plays a major role in the metabolism of non-provitamin A carotenoids (Amengual et al., 2011). CMO2 has a different expression pattern than CMO1, i.e. in the lung it is the predominant carotened cleavage enzyme in humans and ferrets.

In ferrets, the resulting products from CMO2 metabolism (cleavage at the 9,10 position as well as at 9′,10′) of zeaxanthin are 3-OH-β-apo-10′-carotenal and 3-OH-β-ionone, whereas those of β-cryptoxanthin are 3-OH-β-apo-10′-carotenal, β-ionone, β-apo-10′-carotenal and 3-OH-β-ionone) (Mein et al., 2011); thus two metabolites of β-cryptoxanthin are identical with those resulting from zeaxanthin.

Further, the applicant provided a study suggesting common metabolites of lutein and zeaxanthin in rhesus monkeys (Albert et al., 2008).

The Panel considers that based on structural similarity and the partial overlap of the CMO2 metabolites of β-cryptoxanthin and zeaxanthin, studies on β-cryptoxanthin may be of some relevance for the safety assessment of zeaxanthin.

2.1.3.2. Study with β-cryptoxanthin in smoke-exposed ferret/lung cancer model

In the study by (Liu et al., 2011), a low dose and a high-dose (the latter being five times higher than the average American intake of β-cryptoxanthin of 104 μg/day) were fed to ferrets for three months. The doses were calculated in consideration of the fact that absorption of carotenoids by the ferret is
about five times less than in humans (Wang et al., 1992). β-Cryptoxanthin supplementation significantly dose-dependently increased the concentrations of β-cryptoxanthin in both plasma and lung tissue of the ferrets. The plasma concentrations were in the range of the Western population and were quite low compared to the Japanese population (Xiang et al., 2008). Both low- and high-dose β-cryptoxanthin lowered cigarette smoke-induced lung squamous metaplasia. The reduction was significant for high-dose β-cryptoxanthin and was marginally significant for low-dose β-cryptoxanthin.

The Panel notes that the data in this study with β-cryptoxanthin (Liu et al., 2011) supports the absence of concern for CMO2-produced metabolites of xanthophyll carotenoids at the given doses. However, the doses in this study were rather low, being set relative to the low human intake of β-cryptoxanthin. The highest dose tested was equivalent to 0.5 mg/day for a 70 kg man. Because at most only half of this amount could be theoretically metabolized to the two metabolites common with zeaxanthin, this would correspond to 0.25 mg/day zeaxanthin for a 70 kg man, which is substantially below the 2 mg/day per person applied for use in food supplements. Thus, no conclusions can be drawn from this study on the risk of lung cancer in heavy smokers from supplemental zeaxanthin intake.

2.2. Human studies

2.2.1. Human intervention studies

Further to two studies available already for the assessment in 2008 (Hartmann et al., 2004; Schalch et al., 2007), the applicant reported several additional human intervention studies related to visual function and eye research in which zeaxanthin has been supplemented at doses of up to 20 mg/day for up to 6 months (Carboni et al., 2011; Forma et al., 2011; Huang et al., 2008; Stringham and Hammond, 2008; van de Kraats et al., 2008) or 8 mg/day for a year (Richer et al., 2011) without evidence of adverse effects.

2.2.2. Human observational studies

The applicant points out that from observational studies, negative or weakly negative associations between the intake of zeaxanthin or of lutein plus zeaxanthin and different types of cancer have been observed in several case control studies. Also, as previously cited, the pooled analysis of seven cohort studies indicated that the association between intake of xanthophylls (lutein or lutein plus zeaxanthin) and the risk of lung cancer was negative in smokers and non-smoking subjects (Mannisto et al., 2004).

In a more recent questionnaire based study, associations of supplemental β-carotene, retinol, lutein, and lycopene with lung cancer risk were investigated (Satia et al., 2009). Longer duration of use of individual β-carotene, retinol and lutein supplements was associated with significantly elevated risk of total lung cancer (although the underlying risk increase was small-cell lung cancer in the case of β-carotene and non-small-cell lung cancer in the case of lutein), and the authors concluded that long-term use of these supplements should not be recommended for lung cancer prevention, particularly among smokers. However, the Panel notes that there were only 20 subjects using individual lutein supplements (from a total of 77,126 subjects) and that in these 20 subjects, two lung cancer cases came up. The Panel also notes that this is an observational study in which data on the use of supplements during a 10-year period were collected retrospectively prior to baseline, and that supplemental intake of lutein was very low (respective mean and median daily doses among the users were only 1.5 µg and 1.0 µg) compared to dietary lutein/zeaxanthin intake which ranged from 0.013 to 10.1 mg. The Panel notes that due to the study design, the very small number of lutein supplement users, the low intake levels of lutein and resulting limitations in the explanatory power, this study is not appropriate for safety assessment. Thus, no conclusions can be drawn from this study by Satia et al. (2009) regarding an association between lutein supplementation and lung cancer risk. Moreover,
Despite structural similarity between lutein and zeaxanthin, results obtained with lutein may not per se apply to zeaxanthin.

DISCUSSION

In the previous toxicological evaluation of zeaxanthin (EFSA Panel on Dietetic Products Nutrition and Allergies, 2008), the EFSA NDA Panel assessed studies on acute toxicity in mice and rats, subchronic toxicity studies in mice, rats and dogs, a 52-week study using monkeys, studies on embryotoxicity and teratogenicity in rats and rabbits as well as genotoxicity studies. Based on these data, the Panel concluded that there was no indication for genotoxicity. However, since no studies on chronic toxicity and carcinogenicity were provided, the Panel concluded that the data were not sufficient to derive an ADI. Furthermore, the Panel considered that it is not possible to assess whether additional intake of synthetic zeaxanthin at the proposed level of use would increase the risk of lung cancer in heavy smokers as reported for β-carotene. In 2008, the Panel concluded that the safety of zeaxanthin as an ingredient in food supplements at the originally proposed use level of up to 20 mg per person and per day has not been established. In response to the concerns, the applicant now indicated to the European Commission that the maximum intake as indicated in the original submission should be limited to a maximum intake of synthetic zeaxanthin as a novel food ingredient in food supplements of 2 mg/person per day.

The Panel notes that the applicant has now provided additional toxicological information, in particular a two generation study with synthetic zeaxanthin on reproduction toxicity in rats which showed a NOAEL at 150 mg/kg bw per day.

As regards the risk of lung cancer, no pertinent studies in animals have been provided, notably not in the smoke-exposed ferret/lung cancer model.

Human intervention studies, in which zeaxanthin has been supplemented at doses of up to 20 mg/day for up to 6 months, or 8 mg/day for a year, were without evidence of adverse effects. Available epidemiological studies do not indicate that dietary zeaxanthin is linked to an increased risk of lung cancer.

Concern as regards an increased risk of lung cancer is based on two large intervention studies, where supplemental intakes of 20 mg/d and 30 mg/d β-carotene were associated with a higher lung cancer incidence in heavy smokers (Omenn et al., 1996; The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group, 1994), although supplementation of 50 mg β-carotene on alternate days had no effect on lung cancer incidence in the Physician’s Health Study (Cook et al., 2000; Hennekens et al., 1996).

Experiments conducted in ferrets have provided indications regarding the observed interactions between β-carotene, cigarette smoking and lung tumorigenesis. In ferrets, exposure to cigarette smoke and/or high doses of β-carotene (30 mg/d) was found to induce CYP enzymes in the lungs, to enhance retinoic acid (RA) catabolism, and to decrease levels of retinoic acid receptor β (RAR-β) (Liu et al., 2000; Liu et al., 2003; Wang et al., 1999). It has been proposed that β-carotene, when administered at high doses, has pro-oxidant properties based on its interaction with free radicals in cigarette smoke, particularly in the oxidative environment of a smoker’s lung (Mayne et al., 1996; Arora et al., 2001). The increased formation of oxidative metabolites of β-carotene might lower the levels of RA in the lungs of ferrets exposed to cigarette smoke. It was found in in vitro studies that the eccentric cleavage product of β-carotene, β-apo-13-carotenone, functions as an antagonist of the retinoic X receptor (Eroglu et al., 2010), and in a study by Gradelet et al. (1996) it was demonstrated that CYP enzymes induced by eccentric cleavage breakdown products of β-carotene are involved in the degradation of RA.
Contrary to the findings in animals, studies on archival lung tissue available from 52 men who received a β-carotene supplement or placebo for several years in the ATBC Study, β-carotene supplementation revealed no apparent effect on RAR-β expression (Wright et al., 2010). Similarly, in archival lung tissue samples from patients who were diagnosed with lung cancer in the Physicians’ Health Study, no significant influence on RAR-β of 50 mg β-carotene supplementation on alternate days was observed (Liu et al., 2009).

The Panel notes that several potential mechanisms with regard to an increased risk for lung cancer in heavy smokers taking high dose β-carotene supplements have been derived from studies in animal models, although these still await further elucidation. The transferability of these findings in animals to humans has to be ascertained. Also, these studies provide no information as to whether, or to which extent, the results of β-carotene can refer to zeaxanthin.

The effects of high-dose β-carotene observed in animal models of carotenoids research in lung cancer have been mainly attributed to the pro-oxidant properties of β-carotene, being a precursor of vitamin A, its interference with RA metabolism, and induction of CYP enzymes. There are differences in structure, metabolism and function between zeaxanthin and β-carotene. Contrary to β-carotene, zeaxanthin is more polar and is not a precursor of vitamin A. In particular, it is more stable than β-carotene to pro-oxidant exposure (Siems et al., 1999) and differs from β-carotene also with regard to its much lower or absent potential of acting as a pro-oxidant in vitro (Beutner et al., 2001; Martin et al., 1999; McNulty et al., 2007).

Although neither animal nor human data on the lung cancer risk of zeaxanthin are available, based on the current data available the Panel considers it unlikely that supplemental intake of zeaxanthin would increase the risk of lung cancer in heavy smokers. The Panel identifies a NOAEL at 150 mg/kg bw per day in the two-generation reproduction toxicity study with synthetic zeaxanthin in rats, and has no concerns with regard to genotoxicity. Given the absence of a chronic toxicity/carcinogenicity study, the Panel applies an uncertainty factor of 200 on the NOAEL in the two-generation study. This results in 0.75 mg/kg bw per day for synthetic zeaxanthin, corresponding to a daily intake of 53 mg for a person with a body weight of 70 kg.

CONCLUSION

The Panel concludes that based on the available data, intakes of 0.75 mg/kg bw per day for synthetic zeaxanthin, corresponding to a daily intake of 53 mg for a person with a body weight of 70 kg, do not raise safety concerns. Therefore, the use levels proposed by the applicant do not raise safety concerns.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier “Zeaxanthin – Supplementary information” received on 22/03/2012.

2. Letter from the European Commission to the European Food Safety Authority with the request for an opinion on the safety of ‘Synthetic Zeaxanthin’ as a novel food ingredient in food supplements (DSM Nutritional Products)’. Ref. Ares (2012)300552, dated 14/03/2012.
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or zeaxanthin - the LUXEA (Lutein Xanthophyll Eye Accumulation) study. Arch Biochem Biophys, 458, 128-135.


GLOSSARY / ABBREVIATIONS

ADI         acceptable daily intake
bw          bodyweight
CMO2        β,β-carotene-15,15’-monooxygenase
CMO2        carotene-9’,10’-monooxygenase
CYP         cytochrome P450
GLP         Good Laboratory Practice
NF(I)       novel food (ingredient)
NOAEL       no observed adverse effect level
OECD        Organisation for Economic Co-operation and Development
RA(R)       Retinoic acid (receptor)