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Safety of astaxanthin for its use as a novel food in food supplements

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Abstract

Following a request from the European Commission, the Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the safety of astaxanthin when used as a novel food in food supplements at maximum levels of 8 mg/day, taking into account the overall cumulative intake of astaxanthin from all food sources. In 2014, the NDA Panel assessed the safety of the novel astaxanthin-rich ingredient derived from microalgae *Haematococcus pluvialis* in the context of an application submitted under Regulation (EC) No 258/1997. In that opinion, the NDA Panel considered that the acceptable daily intake (ADI) for astaxanthin was 0.034 mg/kg body weight (bw) set by the EFSA FEEDAP Panel in 2014. In 2019, the FEEDAP Panel adopted an opinion which concerned the renewal of the authorisation of dimethyldisuccinate-astaxanthin and a new use of the additive for crustaceans and other fish than salmonids. In that assessment, the FEEDAP Panel derived a new ADI of 0.2 mg astaxanthin/kg bw which replaced the ADI of 0.034 mg/kg bw established in 2014. By taking into account an updated exposure assessment for astaxanthin from the background diet (fish and crustaceans) in combination with 8 mg from food supplements, the NDA Panel concludes that (i) such combined exposure to astaxanthin is safe for adults, (ii) 14 to < 18 years old adolescents reach the ADI, and (iii) the ADI is exceeded by 28% in children aged 10 to < 14 years and up to 524% in infants aged 4–6 months.

Keywords: astaxanthin, xanthophylls, carotenoids, *Haematococcus pluvialis*, acceptable daily intake, ADI

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

Astaxanthin (ATX) is a pink colour extract from the alga *Haematococcus pluvialis* and is widely used in the food and feed industry as a colour.

Under Commission Implementing Regulation (EU) 2017/2470 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283, an ATX-rich oleoresin from *Haematococcus pluvialis* algae is authorised in food supplements at levels of up to 40–80 mg/day which correspond to a maximum authorised level of 8 mg ATX per day.

The first authorisation of ATX in food supplements at the maximum levels of 8 mg/day was granted in Sweden in 1995, before the cut-off date of 15 May 1997 when the first EU novel food regulation ((EC) No 258/1997) came into effect. Subsequently, a number of notifications of ATX pursuant to Article 5 of Regulation (EC) No 258/1997 on novel foods were notified to the Commission based on substantial equivalence to the Swedish authorisation from 1995.

More recently, in 2014, an application for the safety of ATX as a novel food ingredient under Regulation (EC) No 258/1997 at maximum cumulative consumption levels of 4 mg/day coming from its use in fermented liquid dairy products, non-fermented liquid dairy products, fermented soya products and fruit drinks for healthy adults was evaluated by the EFSA NDA Panel.[1] Using the ADI of 0.034 mg/kg bw per day set by the FEEDAP Panel in its 2014 opinion of ATX as a feed additive,[2] the NDA Panel concluded that the intake of ATX from these uses would exceed the ADI at least two-fold. Consequently, the Panel concluded that safety of ATX for these uses could not be established.

In light of the above, it would seem that the intake from the authorised use levels of 8 mg/day of ATX in food supplements would exceed the ADI and thus may not be in accordance with the conditions set out in Article 7 of Regulation (EU) 2015/2283. In addition, there seem to be other sources of exposure to ATX which would contribute to the overall intake. On the other hand, during the public consultation of the draft Implementing Regulation establishing the Union list,[3] food business operators who are placing ATX on the market in food supplements or in other approved food uses in other regions (i.e. outside of the EU), claim that there is a substantial body of evidence on the safety of ATX.

In accordance with Article 29(1) of Regulation (EC) No 178/2002, the EC tasked EFSA to evaluate whether the safety of ATX used as a NF in food supplements at maximum levels of 8 mg/day is still in accordance with the requirements of Regulation (EU) 2015/2283,[4] taking into account the overall, cumulative intakes of ATX from all sources, including from its approved uses in food supplements and in other foods. In doing so, EFSA should solicit and make use of the most recent toxicological and exposure evidence which may be available to business operators and in the public domain.

2. Data and methodologies

2.1. Data

The data considered in this assessment are (i) previous assessments of ATX by EFSA Panels in 2014 (EFSA NDA Panel, 2014; EFSA FEEDAP Panel, 2014a,b), (ii) information received by the European Commission during the public consultation of the draft Union list (European Commission, 2017), (iii) an updated safety assessment by the EFSA FEEDAP Panel from 2019 on synthetic ATX dimethyldisuccinate (DMDS) (EFSA FEEDAP Panel, 2019), (iv) information received from a public call for data by EFSA,[5] and (v) information retrieved by EFSA from an extensive literature search.

2.2. Methodologies

The extensive literature search on ATX consulted the following scientific databases: 'Scopus', 'Pubmed', 'Scifinder' and 'Web of Science'. The search was targeted to identify scientific evidence

[1] EFSA Journal 2014; 12(7):3757. https://www.efsa.europa.eu/it/efsajournal/pub/3757
[2] EFSA Journal 2014; 12(6):3274. https://www.efsa.europa.eu/it/efsajournal/pub/3724
[3] https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-4851094/feedback_de?p_id=119856
[4] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32015R2283&from=EN
[5] https://www.efsa.europa.eu/en/consultations/call/180725

available in peer-reviewed scientific papers in relation to ATX and toxicological data and studies reporting adverse health outcomes in humans.

3. Assessment

In 2014, the NDA Panel assessed the safety of the Novel Food (NF) ATX-rich ingredient derived from microalgae *Haematococcus (H.) pluvialis* in the context of an application submitted under Regulation (EC) No 258/1997 (EFSA NDA Panel, 2014). In that opinion, the Panel noted that the proposed maximum daily intake of 4 mg ATX (0.06 mg/kg bodyweight (bw) for an adult weighing 70 kg) from the NF would exceed the acceptable daily intake (ADI) for ATX of 0.034 mg/kg bw per day (corresponding to approximately 2.4 mg for an adult person) established by the EFSA FEEDAP Panel (2014a).

In 2019, the FEEDAP Panel adopted an opinion on the safety and efficacy of ATX-DMDS (dimethyldisuccinate (EFSA FEEDAP Panel, 2019), a colouring feed additive, for salmonids, crustaceans and other fish.[6] This Opinion addressed mainly the renewal of the authorisation of ATX-DMDS[7] (aimed at demonstrating that the additive remains safe for the target species, consumer, user[8] and environment) and the new use of the additive for crustaceans and other fish than salmonids. For that assessment, the FEEDAP Panel considered previous risk assessments performed by EFSA (EFSA, 2005; EFSA FEEDAP Panel, 2007, 2014a,b; EFSA NDA Panel, 2014) and data from a structured literature search performed by the applicant. This literature search was not limited to synthetic ATX-DMDS but was designed to identify also data on ATX produced by microorganisms. Furthermore, the FEEDAP Panel was provided with data from stakeholders responding to the EFSA call for data who gave their consent that the FEEDAP Panel can make use of this information for its reassessment.

In their reassessment of the toxicological profile of ATX, the FEEDAP Panel confirmed that ATX was neither mutagenic nor carcinogenic and established an ADI of 0.2 mg ATX/kg bw per day by applying an uncertainty factor of 200 to an lowest observed adverse effect level (LOAEL) of 40 mg/kg bw per day for the increased incidence of multinucleated hepatocytes observed in a 2-year carcinogenicity study in rats. The FEEDAP Panel repealed the ADI of 0.034 mg/kg bw established in 2014.

The FEEDAP Panel noted that no new repeated-dose toxicological studies were provided with the application on synthetic ATX-DMDS. However, the FEEDAP Panel referred to six repeated-dose toxicity studies which were not considered in their previous assessment from 2014 (Takahashi et al., 2004; Stewart et al., 2008; Katsumata et al., 2014; Tago et al., 2014; Buesen et al., 2015; Lin et al., 2017). According to the FEEDAP Panel, these studies did not affect the assessment because they were either conducted with non-synthetic sources of ATX or their no observed adverse effect levels (NOAELs) were higher than the one established for subchronic studies in the 2014 opinion (EFSA FEEDAP Panel, 2014a,b). Two of these studies (Takahashi et al., 2004; Stewart et al., 2008) concerned ATX from *H. pluvialis* and were already considered in the safety assessment of 2014 by the NDA Panel (EFSA NDA Panel, 2014). Two oral subchronic toxicity studies in rats (Katsumata et al., 2014; Lin et al., 2017) concerned ATX produced by bacteria for which NOAELs were derived at the highest doses tested in both studies, i.e. 1,000 mg/kg bw and 750 mg/kg bw, respectively. The study of Tago et al. (2014) reported that ATX produced by *Phaffia rhodozyma* was not genotoxic in a bacterial reverse mutation test and in an *in vivo* micronucleus test and that the NOAEL in a subacute oral toxicity study in rats was the highest dose tested (i.e. 1,000 mg/kg bw). An oral subchronic toxicity study in rats with synthetic ATX reported an NOAEL at the highest dose tested of 700–920 mg/kg (Buesen et al., 2015). The NDA Panel considers that the results from these studies have no impact on its previous conclusions regarding genotoxicity and repeated dose toxicity for ATX produced from *H. pluvialis* (in the light of chronic and carcinogenicity studies with synthetic ATX).

The information submitted to EFSA by in total six stakeholders who responded to the public call for data, included published data from the literature on human studies, mechanistic, kinetic and toxicological studies, opinions from experts contracted by stakeholders, reviews on the regulatory status of ATX and new unpublished experimental *in vitro* data. These data were considered in the

[6] In accordance to Article 4(1) (authorisation of a feed additive or new use of a feed additive), under Article 13(3) (modification of the authorisation of a feed additive) and under Article 14(1) (renewal of the authorisation) of Regulation (EC) No 1831/2003.

[7] Commission Regulation (EC) No 393/2008 of 30 April 2008 concerning the authorisation of astaxanthin dimethyldisuccinate as a feed additive. OJ L 117, 1.5.2008, p. 20.

[8] 'Users' are defined as the persons who may be exposed to the additive while handling it, when incorporating it into premixtures or feedingstuffs or using a feedingstuff supplemented with the additive. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2012.2539

assessment by the FEEDAP Panel (2019). One stakeholder did not give consent to make these data available to the FEEDAP Panel, but this information is now addressed in this Opinion.

The information submitted by this stakeholder concerned an expert view on the two EFSA Opinions from 2014 (EFSA FEEDAP Panel, 2014a,b; EFSA NDA Panel, 2014), which focused on mechanistic considerations on the observed effects in the liver of female rats in a 1-year chronic and a 2-year carcinogenicity study considered by both EFSA Panels in 2014. According to that expert view, the observed effects in the liver should not be considered as adverse, but rather as rat-specific adaptive responses, i.e. resulting from chronic induction of cytochrome P450. In order to support the suggested underlying mechanism, the stakeholder provided two *in vitro* studies with primary female human and rat liver cell cultures. These studies aimed to investigate the hypothesis of rat-specific induction of cytochrome P450 and potential quantitative differences between ATX from *H. pluvialis* vs. synthetic ATX regarding induction of liver enzymes.

The FEEDAP Panel (2019) discussed chronic induction of cytochrome P450 as a possible mechanism for the observed hepatocellular hypertrophy and noted that: *'[…] in the presence of histopathological hepatocellular changes indicative of liver toxicity, such as an increased incidence of (single) cell necrosis and multinucleated cells, hepatocellular hypertrophy might be an initial step in the development of hepatocellular tumours.'* The NDA Panel concurs with the view that chronic induction of cytochrome P450 would not disprove the adversity of the observed liver effects. The NDA Panel considers that the two provided *in vitro* studies, although supportive to the proposed mechanism for hepatocellular hypertrophy in rats, do not alter the conclusions for the *in vivo* toxicity of synthetic and algal ATX in rats or humans. The NDA Panel, therefore, considers that the updated ADI (i.e. 0.2 mg/kg bw) derived by the FEEDAP Panel in 2019, also applies to ATX from *H. pluvialis*.

In its Opinion, the FEEDAP Panel also provided an updated consumer exposure assessment for ATX residues in fish (including consumption of salmon and trout) and crustaceans following the methodology described in the Guidance on the safety of feed additives for consumers (Table 1) (EFSA FEEDAP Panel, 2017).

Table 1: Chronic dietary exposure of consumers to ATX based on residue data in salmonids and crustaceans – Summary statistics across European dietary surveys (EFSA FEEDAP Panel, 2019)

Population class	Number of surveys	Highest exposure estimate (mg/kg bw per day)[(a)]	% of the ADI (0.2 mg/kg bw)
Infants	6	0.053	27
Toddlers (1 to < 3 years)	10	0.146	73
Other children (3 to < 10 years)	18	0.101	51
Adolescents (10 to < 18 years)	17	0.071	36
Adults (≥ 18 years)	17	0.060	30
Elderly (≥ 65 years)	14	0.056	28

(a): Highest values of the P95 among the surveys, except for toddlers where the P90 from one survey was the highest value (higher than the P95 of all other surveys with toddlers).

Estimates for combined intake levels for ATX from the background diet (salmonids and crustaceans) and from 8 mg ATX from food supplements and how such a combined exposure scenario relates to the ADI of 0.2 mg/kg bw are provided in Table 2.

Table 2: Combined chronic dietary exposure scenario for ATX from the diet and supplements and its relation to the ADI of 0.2 mg/kg bw

Population class	Highest exposure estimate (mg/kg bw per day)[(a)]	Default body weight[(b)]	8 mg ATX from FS[(c)] (mg/kg bw per day)	Combined exposure estimate[(d)] (mg/kg bw per day)	Exceedance of the ADI with Combined exposure	
					mg/kg bw	%[(e)]
Infants (4 to < 6 months)	0.053	6.7	1.194	1.247	1.047	524
Infants (6 to < 12 months)		8.8	0.909	0.962	0.762	381

Population class	Highest exposure estimate (mg/kg bw per day)[a]	Default body weight[b]	8 mg ATX from FS[c] (mg/kg bw per day)	Combined exposure estimate[d] (mg/kg bw per day)	Exceedance of the ADI with Combined exposure	
					mg/kg bw	%[e]
Toddlers (1 to < 3 years)	0.146	11.9	0.672	0.818	0.618	309
Other children (3 to < 10 years)	0.101	23.1	0.346	0.446	0.246	123
Adolescents (10 to < 14 years)	0.071	43.3	0.185	0.256	0.056	28
Adolescents (14 to < 18 years)		61.3	0.131	0.202	0.002	1
Adults (≥ 18 years)	0.060	70.0	0.114	0.174	−0.026	−13[e]
Elderly (≥ 65 years)	0.056	70.0	0.114	0.170	−0.030	−15[e]

(a): ATX exposure from consumption of fish and crustaceans.
(b): Default body weights derived from EFSA Scientific Committee (2012).
(c): Theoretical exposure to ATX FS (= food supplements) per kg bw when using default body weights from (b).
(d): Combined exposure estimate from the diet and FS.
(e): Combined exposure estimate is 13 and 15%, respectively, below the ADI.

4. Discussion

When considering an exposure to ATX from the background diet together with 8 mg ATX per day from food supplements, adults with a default body weight of 70 kg are exposed to ATX at 0.174 mg/kg bw per day, which is about 13% below the ADI. Such a combined exposure scenario for adolescents aged 14 to < 18 years with a default body weight of 61.3 kg results in an exposure of approximately 0.2 mg/kg bw per day which corresponds to the ADI. Adolescents aged 10 to < 14 years (with a default body weight of 43.3 kg) exceed the ADI of 0.2 mg/kg bw per day by 0.056 mg/kg bw per day (exceedance of the ADI by 28%) at such combined exposure scenarios. The exceedance for children below 10 years of age ranges approximately from 0.25 to 1 mg per kg bw per day (exceeding the ADI by 123–524%).

5. Conclusion

The Panel concludes that an intake of 8 mg ATX per day from food supplements is safe for adults even in combination with the high exposure estimate to ATX from the background diet.

Adolescents at 14 to < 18 years of age reach the ADI in a combined exposure scenario when 8 mg ATX from food supplements are consumed in combination with high dietary background intake estimates.

In such a combined intake scenario of 8 mg ATX from food supplements and high exposure estimates from the background diet, the ADI is exceeded in children below 14 years of age (from 28% in children aged 10 to < 14 years and up to 524% in infants aged 4–6 months).

Documentation provided to the EFSA call for data

1) Response for call for data relevant to the safety assessment of ATX in the framework of Regulation 2283/2015 – EFSA-Q-2018-00595 (valuation report of public literature on ADME, mechanistic studies on liver effects, animal toxicity studies and human studies on ATX together with original studies referenced therein) submitted on 12 February 2019 by Algalif Iceland ehf.
2) Response for call for data relevant to the safety assessment of ATX in the framework of Regulation 2283/2015 – EFSA-Q-2018-00595 (Evaluation report of data used for the previous EFSA opinions and two new in vitro studies on ATX commissioned to HepaPredict AB); Follow-up study to quantify the inductive liability of ATX in primary rat hepatocytes in 2D cultures (carried out by HepaPredict AB); Study on the quantification of the inductive liability of ATX in primary human hepatocytes in 2D cultures (carried out by HepaPredict AB)) submitted on 13 February 2018 by Intertek on behalf of AstaReal Co. Ltd.

3) Information to the specific call for data (EFSA-Q-2018-00595) on ATX from Haematococcus pluvialis algae (Evaluation report on previous EFSA opinions on ATX, including mechanistic considerations and human data and a new in vitro study, original studies referenced therein); In vitro study on the quantification of the inductive liability of ATX in 2D cultures of primary hepatocytes from rat, mouse and human (carried out by HepaPredict AB) – Confidential final results report and Confidential study protocol); Evaluation of the rodent findings regarding their relevance to humans (carried out by Toxicology Knowledge Team Sweden AB (TKT)) submitted by Medfiles Ltd. on 15 February 2018 on behalf of Oriflame Cosmetics Global SA Luxembourg.
4) Submission concerning the safety assessment of ATX (Evaluation of regulatory status and evaluation of the isomeric differences between nATXn and sATXs, evaluation of 85 clinical studies with ATX) submitted on 15 February 2018 by PlantaPhile Ltd.
5) AVIS de l'Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail relatif au risque de toxidermie induit par la consommation de lutéine et de zéaxanthine dans les compléments alimentaires. ANSES – Saisine n° 2010-SA-0242, Maisons-Alfort, le 25 février 2011.

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Abbreviations

ADI	Acceptable Daily Intake
ATX	Astaxanthin
bw	Body weight
DMDS	Dimethyldisuccinate
FEEDAP	EFSA Panel on Products or Substances used in Animal Feed
LOAEL	Lowest Observed Adverse Effect Level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NF	Novel food
NOAEL	No observed adverse effect level