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Annex I

Public consultation on the draft scientific opinion on the tolerable upper intake level for preformed vitamin A and β-carotene

European Food Safety Authority (EFSA)

Annex to: EFSA NDA Panel, 2024. Scientific opinion on the Tolerable Upper Intake Level for preformed vitamin A and β-carotene. doi: 10.2903/j.efsa.2024.8814

Annex I – Technical report: Outcome of the public consultation on the draft scientific opinion on the Tolerable Upper Intake Level for preformed vitamin A and β-carotene

Overview

A total of 32 comments and 6 attachments were submitted by seven interested parties from five countries. All the comments are published in open EFSA as received (https://open.efsa.europa.eu/consultations/a0cTk0000008ZWrIAM?status=Closed&search=vitamin+a).

Attachments are included in this report in Appendix A. Comments made therein are addressed under the respective entry. One comment provided as an attachment which includes five comments referring to different sections of the opinion has been split into four entries in this document.

Table 1 depicts the seven interested parties that have participated in the public consultation and the country of origin. These include two food industry associations and/or organisations, two national authoritative bodies, one university affiliate and two persons in their personal capacity.

Among the comments received, one duplicate comment and four comments only requesting to justify the margins of the text in different sections (to be addressed in the publication phase) are not further considered in this report. The remaining comments that have been submitted in relation to this public consultation are addressed below.

EFSA wishes to thank all stakeholders for their valuable contributions.

Table 1. Stakeholders contributing to the public consultation:

Interested party	Country
European Specialist Sports Nutrition Alliance	Belgium
Food Supplements Europe	Belgium
German Federal Institute for Risk Assessment (BfR)	Germany
Laboratory of Dietetics and Clinical Nutrition, University of Pavia	Italy
Spanish Agency for Food Safety and Nutrition (AESAN)	Spain
Submission in Personal Capacity	Spain
Submission in Personal Capacity	Greece

Comments received and replies to comments

Contributor/ Organisation	Section	Comment and Reply
European Specialist Sports Nutrition Alliance (BE)	1. Introduction	**Comment 1.** The European Specialist Sports Nutrition Alliance (ESSNA), the voice of the sports and active nutrition industry in Europe, welcomes the efforts of the European Commission and EFSA to adopt maximum amounts of vitamins and minerals that may be used in food supplements or added to food. ESSNA observed with concern that in the absence of EU-wide maximum permitted levels for vitamins and minerals (MPLs), several EU Member States have set their own MPLs and dietary intake recommendations for vitamin A and β-carotene. This fragmentation of the Single Market has created unjustified barriers to the trade of vitamin A and β-carotene, higher risks of consumer misunderstandings and labelling issues, and an ambiguous legislative landscape – as experienced by many ESSNA members. ESSNA wishes to note that sports nutrition products, including those formulated with vitamin A, often contain high levels of specific vitamins and minerals to cater to the specific dietary needs of sports people, whose needs are different from the ones of the general population. Many sports nutrition products frequently apply vitamin A in products – for instance, in multivitamin tablets, capsules, and other supplements and fortified sports foods. The room for reformulation of products to comply with variating national requirements is small and burdensome for companies operating in the sports and active nutrition sector. With this in mind, ESSNA generally welcomes the harmonisation of UL and MPLs at the EU level in line with scientifically sound and internationally recognised science. Link to attachment **Reply.** The comment addresses risk management issues and is out of the scope of this consultation. No changes to the draft opinion are proposed. **Changes to the opinion based on this comment.** None
German Federal Institute for Risk Assessment (BfR) (DE)	1. Introduction	**Comment 2.** Page 5, lines 21-25 Selenium is missing in the list of substances for which EFSA was requested to update previous opinions. **Reply.** The request from the European Commission to update the Tolerable Upper Intake Level (UL) for selenium was the subject of a previous mandate, as shown in the background and terms of reference of that opinion (EFSA NDA Panel, 2023). **Changes to the opinion based on this comment.** None
Laboratory of Dietetics and Clinical Nutrition, University of Pavia (IT)	1. Introduction	**Comment 3.** • Comment n.1: *Although it is acknowledged that other provitamin A carotenoids (e.g., α-carotene and β-cryptoxanthin) may contribute to total vitamin A intake, their dietary contribution to the overall toxicity of preformed vitamin A is expected to be marginal.* As stated for the protocol (Annex A), the researchers think that a reference should be provided to justify the last sentence, or otherwise to refer to the point in the document where this sentence is justified. In addition, according to the following reference the bioavailability of this compounds is higher than β-

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		carotene. Therefore, the researchers suggest including the following reference in the introduction of the document: Olmedilla-Alonso B, Rodríguez-Rodríguez E, Beltrán-de-Miguel B, Estévez-Santiago R. Dietary β-Cryptoxanthin and α-Carotene Have Greater Apparent Bioavailability Than β-Carotene in Subjects from Countries with Different Dietary Patterns. Nutrients. 2020;12(9):2639. Published 2020 Aug 29. doi:10.3390/nu12092639 • Comment n.4: The researchers believe that the following references could be included in the introduction: Yamaguchi Y, Zampino M, Tanaka T, et al. The Plasma Proteome Fingerprint Associated with Circulating Carotenoids and Retinol in Older Adults. J Nutr. 2022;152(1):40-48. doi:10.1093/jn/nxab340 von Lintig J, Moon J, Lee J, Ramkumar S. Carotenoid metabolism at the intestinal barrier. Biochim Biophys Acta Mol Cell Biol Lipids. 2020;1865(11):158580. doi:10.1016/j.bbalip.2019.158580 Tanumihardjo SA. Vitamin A and bone health: the balancing act. J Clin Densitom. 2013;16(4):414-419. doi:10.1016/j.jocd.2013.08.016 Link to attachment **Reply.** Comment n.1. The Panel agrees to introduce the explanation provided in the protocol to justify the above-mentioned sentence, including the references in supporting the statement. However, the Panel considers that the additional reference suggested by the commenter is not needed or appropriate in that context. Comment n.2. The Panel considers that the references suggested do not belong to the introduction. **Changes to the opinion based on this comment.** The explanation provided in the protocol to justify why the dietary contribution of provitamin A carotenoids other than β-carotene to preformed vitamin A toxicity is expected to be marginal has been incorporated to the opinion in section 1.5.
German Federal Institute for Risk Assessment (BfR) (DE)	1.3. Overview of previous assessments of the UL for preformed vitamin A and β-carotene	**Comment 4.** Page 6, lines 42-49 Selenium is missing in the list of substances for which EFSA was requested to update previous opinions. **Reply.** See reply to comment 2. **Changes to the opinion based on this comment.** None
Spanish Agency for Food Safety and Nutrition (AESAN)	1.3.1. Preformed vitamin A	**Comment 5.** The legends in Table 1 are expressed as: (1), (2) and (3), however, in Tables 2, 7, 8, 9, 10 and 11 they are expressed as: (a) and (b) and in Table 12, by means of asterisks (*). It is suggested to unify criteria. Table 1 (page 7) refers to "d" and "y", while Table 12 (page 61) refers to "days" and "years". It is suggested to unify criteria.

Contributor/ Organisation	Section	Comment and Reply
(ES)		**Reply.** Thank you for the comment. **Changes to the opinion based on this comment.** The suggested editorial changes have been implemented in the opinion.
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	1.4. Other assessments of preformed vitamin A and β-carotene by EFSA	**Comment 6.** Dietary reference values Page 8, line 145: We suggest defining CV (coefficient of variation) here and deleting the definition on page 21, line 871. **Reply.** Thank you for the comment. **Changes to the opinion based on this comment.** The suggested editorial changes have been implemented in the opinion.
German Federal Institute for Risk Assessment (BfR) (DE)	1.5. Interpretation of the Terms of Reference and context of the assessment	**Comment 7.** Pages 9-10, lines 192-197 How could the conclusion that no new supplementation trials have been conducted/published with high doses of β-carotene have been reached already at the beginning when developing the protocol to update the ULs? Wouldn't this rather be something to conclude later on from a literature search? It is also unclear why, in the light of previous study results from RCTs in which β-carotene supplements increased the risk of lung cancer in smokers, the Panel "considered that supplemental β-carotene should be primarily assessed as a source of vitamin A, and therefore for its potential to increase preformed vitamin A toxicity", rather than with regard to the risk of lung cancer? **Reply.** Scoping literature searches were used to develop the protocol. In those literature searches, it became apparent that no new supplementation trials with high doses of β-carotene had been conducted after the evaluations of the SCF (2000) and the EFSA ANS Panel (2012b, 2012a). This conclusion was also supported by several systematic reviews and meta-analyses published in the last years on the effects of β-carotene on cancer risk, including lung cancer (see section 3.6.4.2), where no new intervention studies with supplemental β-carotene had been identified in addition to those considered by EFSA in previous evaluations. After the results of the ATBC and CARET trials became available, some ongoing supplementation trials were terminated for ethical reasons (e.g. WHS), and no new intervention studies with supplemental β-carotene have been undertaken, probably for the same reasons. In this context, and to tailor the time and resources available for the assessment, it was decided at protocol level to investigate the potential contribution of β-carotene to preformed vitamin A toxicity for priority endpoints (i.e. those for which a systematic review of the evidence was conducted), and to address the risk of lung cancer in relation to β-carotene supplementation narratively (non-priority endpoint), as no new evidence from previous assessments was expected to have become available. **Changes to the opinion based on this comment.** None
Spanish Agency for Food Safety and Nutrition (AESAN)	2. Data and Methodologies	**Comment 8.** The legends in Table 2 are expressed as: (a) and (b), as in Tables 7, 8, 9, 10 and 11, however, the legends in Table 1 are expressed as: (1), (2) and (3) and those in Table 12, by means of asterisks (*). It is suggested to unify criteria.

Contributor/ Organisation	Section	Comment and Reply
(ES)		**Reply.** Thank you for the comment. **Changes to the opinion based on this comment.** The suggested editorial changes have been implemented in the opinion.
German Federal Institute for Risk Assessment (BfR) (DE)	2. Data and Methodologies	**Comment 9.** Page 10, lines 211-212 In the sentence "What is the daily intake of total vitamin A from all dietary sources in EU populations?", it is suggested to insert "(including preformed vitamin A and β-carotene)" after "vitamin A" in order to clarify that the intake assessment has been performed for both forms of the vitamin. **Reply.** Thank you for the comment. **Changes to the opinion based on this comment.** The suggested change has been implemented in the opinion.
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	2.1.1. Data	**Comment 10.** 2.1.1.3. Data extraction The second paragraph states that "Intakes of preformed vitamin A were extracted and converted into µg RE/day using the conversion factors depicted in Table 5 (section 3.1)". However, no reference is made to the conversion of β-carotene units, which is mentioned in section 2.2.2.2.1. where it is stated: "Where available, the units of the products identified as containing only β-carotene were kept as milligrams (mg) or were converted from µg RE to mg using a conversion factor of 1:6." **Reply.** Section 2.1.1.3 refers to data extraction from published papers identified through the systematic reviews as being pertinent to the assessment for priority questions in relation to teratogenicity, hepatotoxicity, and bone health, for which the only exposures of interest were preformed vitamin and total vitamin A, not β-carotene alone. Intakes of total vitamin A and provitamin A carotenoids included in the exposure and the conversion factors used by the authors, when available, were extracted. **Changes to the opinion based on this comment.** The above-mentioned explanation on how intakes of total vitamin A were extracted in evidence tables from the published studies identified through the systematic reviews has been added to the opinion (section 2.1.1.3).
Laboratory of Dietetics and Clinical Nutrition, University of Pavia (IT)	2.1.2. Methodologies	**Comment 11.** Comment n.2: *For observational studies, the appraisal addressed six RoB questions, covering five domains*. The researchers wonder why the authors wonder why the RoB was used for the quality assessment of the included observational studies. They think that a tool validated for observational studies would have been preferable (such as the Newcastle-Ottawa Scale for the quality assessment of observational studies). Link to attachment

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		Reply. The Office of Health Assessment and Translation (OHAT) risk of bias (RoB) tool developed by the US National Toxicology Program (NTP) (OHAT/NTP, 2015) has been validated and allows the appraisal of all study designs which are usually found in EFSA's risk assessments, including observational studies. **Changes to the opinion based on this comment.** None.
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	2.2.1. Data	**Comment 12.** EFSA's databases Under "Food composition data" it is stated that food and beverage composition data are collected, including β-carotene in food additive form, however, under "Food composition data" in 2.2.1.2 ("Other data sources") it is stated that composition data are collected for fortified foods and food supplements and β-carotene in food additive form is excluded. 2.2.1.2. Other data sources In the "Food consumption data" section, it is indicated that the intake of vitamin A was estimated from natural sources of the vitamin, fortified foods and food supplements. However, the "Food composition data" section only refers to fortified foods and food supplements and excludes β-carotene in food additive form, contrary to what is stated in the "Food composition data" section of section 2. 2.1.1. ("EFSA's databases") and in the section "Intake data - Intake assessment from natural sources" of section 2.2.2.2. where it is stated that data on β-carotene as a food additive were taken into account in the intake assessment. **Reply.** The EFSA's food composition and food consumption databases (described in Section 2.2.1.1) were used to obtain harmonised intake estimates in EU populations of preformed vitamin A and β-carotene from the background diet. Such intake estimates include the use of β-carotene as food additive, as analytical data used to compile the EFSA Food composition database cannot differentiate between this and the natural content in foods. Section 2.2.1.2 describes "other data sources" including the Mintel GNPD on food composition, in which food products in which vitamin A (as β-carotene) is used as an additive (food colour) were excluded. **Changes to the opinion based on this comment.** The above-mentioned explanation has been incorporated to section 2.2. of the opinion for clarity.
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	3.1. Chemistry of vitamin A and β-carotene and definition of terms	**Comment 13.** Suggestion: write in bold "Carotenoids" (line 535) in the same way that "Preformed vitamin A" is written (lines 533 and 534). Table 5 (page 20) is cut off. It is suggested that it appear on the same page. We recommend justifying the margins of the text. **Reply.** Thank you for the comment. **Changes to the opinion based on this comment.** The suggested editorial changes have been implemented in the opinion.
Laboratory of Dietetics and Clinical Nutrition, University of Pavia (IT)	3.3. Biomarkers of intake for vitamin A, including β-carotene (sQ2)	**Comment 14.** Comment n.3: The researchers suggest that the following references could be useful for addressing vitamin A stores in the liver stores and/or plasma retinyl esters: 1. Valentine AR, Davis CR, Tanumihardjo SA. Vitamin A isotope dilution predicts liver stores in line with long-term vitamin A intake above the current Recommended Dietary Allowance for young adult women. Am J Clin Nutr. 2013;98(5):1192-1199. doi:10.3945/ajcn.113.063867 2. Green MH, Green JB, Ford JL. Vitamin A Absorption Efficiency Determined by Compartmental Analysis of Postprandial Plasma Retinyl Ester Kinetics in Theoretical Humans. J Nutr. 2020;150(8):2223-2229. doi:10.1093/jn/nxaa176

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		3. Ford JL, Green JB, Haskell MJ, et al. Use of Model-Based Compartmental Analysis and a Super-Child Design to Study Whole-Body Retinol Kinetics and Vitamin A Total Body Stores in Children from 3 Lower-Income Countries. J Nutr. 2020;150(2):411-418. doi:10.1093/jn/nxz225 4. Lopez-Teros V, Ford JL, Green MH, et al. The "Super-Child" Approach Is Applied To Estimate Retinol Kinetics and Vitamin A Total Body Stores in Mexican Preschoolers. J Nutr. 2020;150(6):1644-1651. doi:10.1093/jn/nxaa048 Link to attachment **Reply.** Studies on the relationship between the intake of preformed vitamin A and biomarkers of intake have not been systematically reviewed. For the narrative review, the Panel relied on previous opinions by authoritative bodies, systematic reviews, pooled analyses and meta-analysis, and key publications as appropriate. The Panel considers that the publications mentioned above do not add information relevant to this section. **Changes to the opinion based on this comment.** None
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	3.5.1. Intake assessment for preformed vitamin A	**Comment 15.** 3.5.1.1. Sources of dietary preformed vitamin A In the "Food supplements" section, we suggest writing 'vitamin A' (line 1055) in quotation marks, as well as 'vitamin A' in line 1039. On the other hand, in line 1061 the following text would be superfluous: "(Error! Reference source not found.)." 3.5.1.2. EFSA's assessment of background intake for preformed vitamin A The legends of Tables 7 and 8 are expressed as: (a), (b) and (c), as in tables 2, 9, 10 and 11, however, the legends of Table 1 are expressed as: (1), (2) and (3) and those of Table 12 are expressed by means of asterisks (*). It is suggested to unify criteria. Table 8 (page 34) is cut off. It is suggested that it appear on the same page. Table 7 (page 34) describes intakes in the 95th percentile of up to 8210 µg RE/day for preformed Vitamin A, well above the established UL of 3000 µg RE/day. This data, moreover, is presented without considering dietary supplements, which in some countries such as Denmark account for up to 60% of intake (Table 9). We believe that this very high intake data should be commented on. 3.5.1.3. Data on intake of preformed vitamin A from food, including fortified foods The title of this section could be misleading as we consider that the term "food" includes not only natural sources of vitamin A and fortified foods, but also food supplements, which are dealt with in a separate section (point 3.5.1.4.). 3.5.1.4. Data on intake of preformed vitamin A from food supplements The legends in Table 9 are expressed as: (a), (b) and (c), as in Tables 2, 7, 8, 10 and 11, however, the legends in Table 1 are expressed as: (1), (2) and (3) and those in Table 12 by asterisks (*). It is suggested to unify criteria.

Contributor/ Organisation	Section	Comment and Reply
		Reply. The term 'vitamin A' in inverted commas is a left over and will be replaced throughout the opinion. Thank you for the editorial comments regarding the harmonization of table legends and the error in the formatting of a reference. The Panel agrees that the title of sections 3.5.1.3 and 3.5.2.3 could be misleading. The reasons for the very high intake estimates from the background diet using the EFSA's food composition and consumption databases are discussed in section 3.5.1.2, including the derivation of intake scenarios adjusting for the frequency of consumption that could provide more accurate intake estimates. This aspect is also discussed in the conclusions of the intake assessment for preformed vitamin A in section 3.5.1.5. **Changes to the opinion based on this comment.** The suggested editorial changes regarding the harmonization of table legends and the error in the formatting of a reference have been implemented in the opinion. The term "vitamin A" has been removed and replaced by preformed vitamin A and β-carotene for clarity. The title of sections 3.5.1.3 and 3.5.1.4 have been changed to read "Data on the intake of preformed vitamin A excluding food supplements" and "Data on the intake of preformed vitamin A including food supplements, respectively. The same adjustments have been applied to the title of sections 3.5.2.3 and 3.5.2.4 on β-carotene.
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	3.5.2. Intake assessment for β-carotene	**Comment 16.** 3.5.2.2. EFSA's assessment of background intake of β-carotene The legends in Table 9 are expressed as: (a), (b) and (c), as in Tables 2, 7, 8, 10 and 11, however, the legends in Table 1 are expressed as: (1), (2) and (3) and those in Table 12, by means of asterisks (*). It is suggested to unify criteria. 3.5.2.3. Data on β-carotene intake from food, including fortified foods. The title of this section could be misleading since the term "food" includes not only natural sources of vitamin A and fortified foods, but also food supplements, which are dealt with in a separate section (point 3.5.2.4.). 3.5.2.4. Data on β-carotene intake from food supplements The legend of Table 11 is expressed as: (a), as in Tables 2, 7, 8, 9 and 10, however, the legends of Table 1 are expressed as: (1), (2) and (3) and those of Table 12, by means of asterisks (*). It is suggested to unify criteria. **Reply.** Thank you for the editorial comments regarding the harmonization of table legends. In relation to the title of section 3.5.2.4, please see reply to comment 15. **Changes to the opinion based on this comment.** The suggested editorial changes have been implemented in the opinion.
Submission on Personal Capacity (EL)	3.5.2. Intake assessment for β-carotene	**Comment 17.** I have a comment concerning lines 1408-1409 in Chapter 3.5.2.5 This concerns also Appendix D: According to the Greek Codex for Food and Beverages (article 78, paragraph 5d) there is a provision for the addition of Vitamin A and beta-carotene in margarines and spreadable fats up to a level of 7500 ug/kg (the total amount may be a mixture of Vitamin A and carotene). https://www.aade.gr/himeio/trofima-ylika-se-epafi-me-trofima/himeio/kodikas-trofimon-kai-poton **Reply.** Thank you for the comment.

Contributor/ Organisation	Section	Comment and Reply
		Changes to the opinion based on this comment. The information provided by the commenter has been added to Appendix D of the opinion.
Submission on Personal Capacity (ES)	3.5.2. Intake assessment for β-carotene	**Comment 18.** I would like to contribute to this project on vitamin A and b-carotene with data from Spain. I have attached a file with vitamin A intake data (individual assessment of retinol, b-carotene, a-carotene and b-cryptoxanthin) from a representative sample of the adult population in Spain. These data were obtained using data on food consumption data from the National Dietary Intake Survey in Spain (2009–2010), published by the Spanish Agency for Food Safety and Nutrition (AESAN) in 2011. A 24-h food recall, 3-day food diary and a software application containing HPLC analysis data were used. I am willing to provide any other information if needed. Link to attachment **Reply.** The paper contains data on the intake of β-carotene for the whole survey population and results are not provided by age group or sex. Estimated intakes are only for food sources, excluding fortified foods, and do not include the contribution from food supplements. They will be extracted and published in Annex E but will not be used for quality check purposes, as they are not comparable with the EFSA's intake estimates. **Changes to the opinion based on this comment.** None
German Federal Institute for Risk Assessment (BfR) (DE)	3.5.2. Intake assessment for β-carotene	**Comment 19.** Page 36, lines 1158-1164 The Panel refers to Annex E and indicates that estimates of vitamin A and β-carotene intake, respectively, from foods including fortified foods are available from national consumption surveys from various countries in the EU. However, looking at the details presented in Annex E, it becomes evident that those national consumption surveys comprised very heterogenous age ranges, i. e. with respect to β-carotene, the EsKiMo II survey from Germany included only children from 6 to 17 years, while the survey from Sweden refers to children aged 4, 9 and 12 years, and intake data from Austria include the population from 7 to 14 and from 19 to 80 years of age. This should in our view be made transparent in the text. Page 41, lines 1351-1356 Furthermore, the Panel explains that "for surveys that did not clearly indicate whether fortified foods were included in the estimates, it was assumed that they were included." We would like to question this for the following reason: In our view it is very difficult to derive reliable data about the consumption of fortified foods as many food composition tables do not (or only incompletely) include fortified foods. This is further complicated by frequent markets changes, but also by the fact that consumers are often unaware that the foods they consume are fortified. Therefore, if no information is provided in a consumption survey as to whether fortified foods are included or not, we believe it is more likely that this is not the case than that it is. **Reply.** Intake estimates from the national food consumption surveys included in Annex E are not harmonised and differ in several other characteristics than the age ranges considered (e.g. food composition databases and dietary assessment methods used). Details are given in Annex E. The fact that these intake estimates are not harmonised has been clarified in section 2.2 of the opinion. See also reply to comment 12.

Contributor/ Organisation	Section	Comment and Reply
		In relation to the comment on fortified foods, several attempts were made by EFSA to contact Member States asking for clarification about whether fortified foods had been included/excluded in intake estimates conducted at national level. In reply, most data providers acknowledged that they were not able to exclude fortified foods from the intake estimates for the same reasons that the commenter finds difficult to include them. The Panel acknowledges, however, that this concept should be clarified in the opinion. **Changes to the opinion based on this comment.** The text in reply to comment 12 has been incorporated to section 2.2. of the opinion. In addition, it has been clarified in the opinion (sections 3.5.1.3 and 3.5.2.3) that, for national surveys that did not clearly indicate whether fortified foods were included/excluded in the intake estimates, it was assumed that they were not excluded.
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	3.6.1. Teratogenicity (sQ3)	**Comment 20.** In figure 3, the indication "Legend to figure 3" includes the abbreviations, as occurs in figures 4, 5, 6 and 7. However, in figures E1, E2, E3, E4, E5, E6, E7 and E8, the indication "Legend to figure ..." does not include the abbreviations, which are explained in "Abbreviations" at the bottom of the figure. Something similar occurs in other tables of the document. **Reply.** Thank you for the comment. **Changes to the opinion based on this comment.** The suggested editorial changes have been implemented in the opinion.
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	3.6.3. Bone health (sQ5)	**Comment 21.** 3.6.3.3. BMD (sQ5b) It is suggested that the title should include the full name and not just the abbreviation: "Bone Mineral Density (BMD) (sQ5b)". The legend of Table 12 is expressed by means of asterisks (*), however, the legends of Tables 2, 7, 8, 9, 10 and 11 are expressed as (a), (b) and (c) and those of Table 1 are expressed as: (1), (2) and (3). It is suggested to unify criteria. **Reply.** Thank you for the comment. **Changes to the opinion based on this comment.** The suggested editorial changes have been implemented in the opinion.
Laboratory of Dietetics and Clinical Nutrition, University of Pavia (IT)	3.6.3. Bone health (sQ5)	**Comment 22.** Comment n.5: The researchers suggest that the following references might be added in the introduction and/or outcome analysis for vitamin A/β-carotene and bone health: 1. Li X, Liu X. Associations of serum vitamins levels with bone mineral density in the different race-ethnicities US adults. BMC Musculoskelet Disord. 2021;22(1):137. Published 2021 Feb 4. doi:10.1186/s12891-021-03997-0 2. Cao WT, Zeng FF, Li BL, Lin JS, Liang YY, Chen YM. Higher dietary carotenoid intake associated with lower risk of hip fracture in middle-aged and elderly Chinese: A matched case-control study. Bone. 2018;111:116-122. doi:10.1016/j.bone.2018.03.023 3. Li XB, Liu T, Fan L, et al. Circulating serum level of retinoic acid and hip fractures among postmenopausal women. J Am Geriatr Soc. 2019;67(2):336-341. doi:10.1111/jgs.15667 4. Zhang X, Huang J, Zhou Y, et al. Vitamin A Nutritional Status Is a Key Determinant of Bone Mass in Children. Nutrients. 2022;14(21):4694. Published 2022 Nov 6. doi:10.3390/nu14214694

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		5. Navarro-Valverde C, Caballero-Villarraso J, Mata-Granados JM, et al. High Serum Retinol as a Relevant Contributor to Low Bone Mineral Density in Postmenopausal Osteoporotic Women. Calcif Tissue Int. 2018;102(6):651-656. doi:10.1007/s00223-017-0379-8 6. Teigmo MSW, Gundersen TE, Emaus N, Grimnes G. Distribution and determinants of retinol in Norwegian adolescents, and its relation to bone mineral density: the Tromsø Study: Fit Futures. Eur J Clin Nutr. 2018;72(10):1373-1384. doi:10.1038/s41430-018-0193-z Link to attachment **Reply.** The suggested references are not pertinent to the opinion because the exposures addressed have been excluded from the assessment. Serum retinol and serum retinoic acid are not appropriate markers of preformed vitamin A intake (see section 3.3.3 and the protocol in Annex A) and carotenoids *per se* have not been assessed in relation to bone health. **Changes to the opinion based on this comment.** None
Food Supplements Europe (BE)	3.7.2. Derivation of the UL	**Comment 23.** Food Supplements Europe thanks EFSA for the opportunity to comment on the proposed opinion. Our comments specifically relate to evidence underlying the conclusion that, based on available data, no safe level of intake can be established for supplemental β-carotene. We believe that this conclusion does not reflect the totality of evidence and conveys an unwarranted message for risk managers i.e. that supplemental β-carotene is unsafe at any level. There is a significant body of scientific literature that supports the safety of β-carotene supplementation at levels below those associated with increased risk of lung cancer. We would therefore ask EFSA to review the following scientific criteria and convey how these aspects have been taken into account in assessing the evidence base. 1. The studies assessed for the risk of lung cancer and β-carotene supplementation focus on cohorts of current or former cigarette smokers and workers exposed to the lung carcinogen, asbestos. Both the ATBC and CARET investigations examined populations at high risk for lung cancer. Smoking remains the strongest risk factor for lung cancer, which is a key aspect worthy of consideration in the context of the interpretation of the data. We would ask that the opinion clarifies why the Panel justifies that the effects of β-carotene derived from data obtained in these narrower cohorts with predisposed risk factors for lung cancer, are relevant and generalisable to the wider, non-exposed population. This is crucially important to enable risk managers to appreciate if, and to what extent, risks apply to various sub-groups in the population, but importantly to avoid unnecessary restrictions to the wider population. Where risk is limited to specific cohorts, this can be addressed by refined and targeted risk-management measures. 2. Several RCT intervention studies show that for non-smokers, supplementation with β-carotene does not appear to increase the risk of cancer. We would ask that the opinion justifies why the below elements are not considered sufficient to establish a safe intake for the general population, and in particular for people that do not smoke. o The Physicians' Health Study identified no harmful effects in non-smokers as well as smokers consuming β-carotene every other day, over a period of 12 years. In this study, current smokers made up 11% of the cohort and former smokers 39%. o The CARET study did not suggest increased risks for lung cancer among former smokers. o In the ATBC study, the increased risk for lung cancer appeared to be confined to people smoking a minimum of 20 cigarettes daily, whilst no effect on risk was found for those smoking

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		between 5-19 cigarettes per day. o In EFSA's former statement on the safety of β-carotene use in heavy smokers (1) which reviews the scientific literature in terms of the relationship between β-carotene supplementation and cancer, it was concluded that the negative effects observed in heavy smokers in the ATBC and CARET studies were not seen in any other intervention study. The authors of that review concluded that the increased lung cancer incidence in β-carotene supplemented smokers has been demonstrated to be highly specific and likely to be correlated to individuals who smoke more than 20 cigarettes daily over many years. o Epidemiological evidence does not support the association of increased lung cancer incidence in heavy smokers using supplemental doses of β-carotene ranging from 6-15 mg/, over a period of 5 and up to 10 years. (2,3,4) o Line 2377 of the draft EFSA opinion notes that co-supplementation with additional vitamins and minerals precludes conclusions on the effect of β-carotene alone. However, both the ATBC and CARET studies from which data were used to inform lung cancer risk, included concurrent supplementation with other vitamins (see below). Furthermore, the dose of Vitamin A in CARET study was in excess of the tolerable upper intake level, which confounds and significantly limits the applicability of the findings. Intervention Dose Administered: ATBC Trial 20 mg Beta carotene and / or 50 IU Alpha Tocopherol CARET Trial 30 mg Beta carotene and 7500 ug RE of Retinyl Palmitate o In humans, β-carotene has been used to treat patients with erythropoietic protoporphyria to reduce the severity of photosensitivity reactions (i.e. as an ultraviolet screen). As noted in the 2000 Scientific Committee on Food opinion, these patients are treated for years with β-carotene at doses of 180 mg/day without serious side effects and no long-term toxicity reported. (5) 3. The increased incidence of lung cancer in smokers was observed at doses of 20 mg β-carotene or more. According to the β-carotene supplement intake data reported in line 1414 of the draft opinion, the majority of supplements on the EU market have β-carotene levels ≤ 5 mg per daily dose and only 2% of all products exceeded 15 mg per day (with a maximum of 18 mg). This is below the doses that have shown any adverse effects or increased risks for lung cancer. We would ask that the opinion clarifies how this information was taken into consideration in terms of exposure assessment as part of the risk assessment. 4. The conclusion that no safe intake level for β-carotene can be derived is contradictory in view of the established nutritional role of β-carotene as a precursor to retinol, and with a lower-risk profile (When vitamin A status is good, β-carotene is not cleaved into vitamin A. Hence, there is no risk of excess of vitamin A due to intake of β-carotene). The fact that the use of supplemental β-carotene (i.e., in fortified foods and/or food supplements) by the general population should be limited to the sole purpose of meeting vitamin A requirements also presupposes that a safe level of intake should exist for the general population, and one that could be derived from the data and arguments presented above. We would ask that the opinion clarifies why this is not considered a sufficient ground for establishing a safe level. It is important that the conclusions drawn, duly inform risk managers on the balance of evidence. EFSA's conclusions of not being able to establish a safe intake level for β-carotene is likely to be interpreted as a summation that β-carotene is unsafe at any level, which does not reflect the totality of scientific evidence. References: 1 Statement on the safety of β-carotene use in heavy smokers. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); EFSA Journal 2012;10(12):2953 2 Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst. 1993 Sep 15;85(18):1483-92. doi: 10.1093/jnci/85.18.1483. PMID: 8360931 3 Yong LC, Brown CC, Schatzkin A et al., Intake of vitamins E, C, and A and risk of lung cancer. The NHANES I epidemiologic followup study.

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		First National Health and Nutrition Examination Survey. Am J Epidemiol. 1997 Aug 1;146(3):231-43. doi: 10.1093/oxfordjournals.aje.a009258. PMID: 9247007 4 Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A, Briançon S. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med. 2004 Nov 22;164(21):2335-42. doi: 10.1001/archinte.164.21.2335. Erratum in: Arch Intern Med. 2005 Feb 14;165(3):286. PMID: 15557412 5 Opinion of the Scientific Committee on Food on the tolerable upper intake level of beta carotene (expressed on19 October 2000) We would thank EFSA in advance for consideration of the above. **Reply.** The conclusion that, based on available data, no safe level of intake can be established for supplemental β-carotene means that the available evidence does not allow identifying the highest level of intake where there is reasonable confidence in data on the absence of adverse effects, and not that supplemental β-carotene is unsafe at any level. On this respect, please see also the changes introduced to the opinion based on comment 28. As discussed in the SCF (2000) opinion, two studies in hamsters (Beems, 1987; Wolterbeek et al., 1995) and one in ferrets (Wang et al., 1999), which are animal models that partially mimic the absorption and tissue metabolism of β-carotene in humans, describe the potential enhancement of chemically-induced respiratory tract tumourigenesis by β-carotene. The study in ferrets (Wang et al., 1999) is extensively described, as it was specifically designed to mimic the human trials regarding the dose of ß-carotene administered and the exposure to smoking. The results clearly showed that a strong proliferative response in lung tissue was observed in all β-carotene-supplemented animals (exposed and not exposed to tobacco smoke), and this response was enhanced by exposure to tobacco smoke. This information has been incorporated to section 3.6.4.2. of the opinion when describing the conclusions of the SCF on supplemental β-carotene lung cancer risk based on animal and human data. In humans, the Panel took as sources of evidence intervention studies which allowed to isolate the effect of β-carotene from that of other co-interventions, as is the case of studies with factorial designs (ATBC, PHS, WHS and WACS) for lung cancer risk. This is not the case for other intervention studies using supplemental β-carotene at lower doses in combination with antioxidants, as explained in the opinion for the two studies mentioned by the commenter, i.e. the SU.VI.MAX study (Hercberg et al., 2004) and the study conducted in Linxian (Blot et al., 1993). A table summarizing the main characteristics of these studies has been incorporated in section 3.6.4.2. of the opinion for clarity. As shown in that table (Table 13 in the final version of the opinion), higher RRs for lung cancer incidence are reported for supplemental β-carotene vs non-supplemental β-carotene in three out of the four RCTs available. The increased risk of lung cancer was only statistically significant in the ATBC trial of heavy male smokers, possibly the only trial powered for this endpoint owing to the notably higher number of lung cancer cases reported. The ATBC trial also differed from the other three RCTs on the type of supplement administered, the amount of supplemental β-carotene, the pattern of administration, and the plasma concentrations of β-carotene reached. Since supplemental forms of β-carotene have markedly greater bioavailability than β-carotene from foods and its bioavailability can also be variable depending on the formulation, nutritional status of the person or population, and dietary intake pattern, the risk in relation to β-carotene was characterised by the IoM as a function of plasma β-carotene concentrations (IOM, 2000). In the UL draft opinion released for public

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		consultation, plasma concentrations of β-carotene reached with β-carotene supplements in the available RCTs (when reported) and with naturally occurring vs supplemental β-carotene in beverages have been discussed in different sections. The draft opinion has been amended to focus such discussion on section 3.6.4.2 for clarity. In the ATBC and CARET trials, synthetic water soluble β-carotene supplements manufactured by Hoffman-La Roche were administered daily (20 and 30 mg/day, respectively). In the PHS, WHS and WACS, microencapsulated, water-dispersible synthetic all-trans beta-carotene (Lurotin) supplements manufactured by BASF corporation were given every other day. In the ATBC, mean baseline plasma β-carotene concentrations increased from 17 µg/dL to 300 µg/dL (from 0.32 to 5.59 µmol/L) at the 3-year mark, while in the CARET study the median post-intervention plasma concentration of β-carotene was 210 µg/dL (3.91 µmol/L). The PHS trial showed a comparatively lower increase from baseline, reaching a median level of 118 µg/dL (2.19 µmol/L). The increase in plasma β-carotene concentrations in the ATBC and CARET trials significantly exceeded those observed in the PHS, with a respective 17-fold and 12-fold rise from baseline compared to a four-fold increase in the PHS study. The increase in plasma β-carotene concentrations in the ATBC and CARET trials also exceeded the 10-fold increase observed in the Skin Cancer Prevention Study (SCPS), which used 50 mg of Lurotin daily (see sub-section on *Cardiovascular disease incidence and mortality*). The disparity in the achieved plasma β-carotene concentrations may be attributed to a lower bioavailability of supplemental β-carotene in the PHS in comparison to the ATBC, owing to the different formulation used and to the pattern of supplementation. Plasma β-carotene concentrations were not reported in WHS and WACS, which used the same dose, type of supplement and supplementation pattern as PHS. The Panel notes that the mean plasma concentration of β-carotene reached in the ATBC trial is comparable to that reported with daily consumption of a similar amount (21.6 mg/day) of β-carotene as synthetic water dispersible powder in beverages (5.04 µmol/L) and well above the level reached by consuming similar daily amounts (18 mg/day) of β-carotene from non-fortified carrot juice (1.71 µmol/L) ((Thürmann et al., 2002); see section 3.3.4.2). Section 3.7.1.2 on the selection of the critical effect for deriving a UL has been expanded to better explain why lung cancer risk is the critical effect and the reasons why a UL for supplemental β-carotene cannot be derived from the available data. Similarly, section 3.7.2.2. has been amended to clarify that even if an increased risk of lung cancer has been observed among male smokers consuming food supplements at doses of 20 mg/day, no data for supplemental β-carotene given alone are available at doses <20 mg/day in any population group. Supplemental forms of β-carotene have markedly greater bioavailability than β-carotene from foods and its bioavailability can also vary depending on the formulation, administration pattern, and other individual (dietary and non-dietary) factors, and therefore the available data do not allow characterising the hazard or deriving a safe level of intake for supplemental β-carotene (i.e., identifying the highest level of intake where there is reasonable confidence in data on the absence of adverse effects). In section 3.8.2. values of supplemental β-carotene that could be consumed to meet the PRI for vitamin A in adult men and women have been added. The same information has been added to the conclusions. In section 4.2 it has been clarified that the conclusions on β-carotene supplementation for smokers and the general population do not apply to the possible use of supplemental β-carotene for therapeutic purposes under medical supervision (e.g., as source of provitamin A in vitamin A deficiency or for the treatment of erythropoietic protoporphyria). In this respect, as discussed by the SCF (2000), the apparent lack of toxicity of β-carotene observed in high-dose clinical use against erythropoietic photoporphyria (20-180 mg/day and up to 300

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		mg/day for many years), together with the potential benefits in cancer and CVD prevention, justified the large-scale trials previously mentioned. However, the WHS was already early terminated owing to the increased risk and lack of benefit shown in the ATBC and CARET, and the lack of benefit in the PHS. In this context, the no observed toxicity of high doses of supplemental β-carotene in patients with erythropoietic protoporphyria cannot be used as source of data to derive a UL or a safe level of intake of supplemental β-carotene for the general population and this is not discussed in the opinion. Finally, in the context of the conclusions that no UL or safe level of intake can be derived for supplemental β-carotene and that the use of supplemental β-carotene by the general population should be limited to the purpose of meeting vitamin A requirements (corresponding to 4.5 and 3.9 mg/day of β-carotene for adult males and females, respectively), the Panel notes in the risk characterisation that the β-carotene content of some fortified foods and food supplements available on the EU market exceeds the PRIs for vitamin A for several population groups (section 3.5.2.1). Data collected from the Mintel GNPD on fortified foods and food supplements is not compared against the 20 mg/day given in the ATBC trial as proposed by the commenter because that value is not a UL or a safe level of intake, as the potential sources of heterogeneity for the effect of supplemental β-carotene on lung cancer risk cannot be characterised, and no data for supplemental β-carotene given alone are available at doses <20 mg/day in any population group. **Changes to the opinion based on this comment.** The text in sections 3.6.4.2 (other endpoints), 3.7.1.2 (selection of the critical effect), 3.7.2.2 (derivation of the UL), 3.8.2 (risk characterization) and 4.2 (conclusions) on β-carotene has been amended as explained in the reply to clarify the basis for the conclusions, the amounts of β-carotene that would be required to meet vitamin A requirements for adult males and females, and the population groups to which the conclusions do not apply.
European Specialist Sports Nutrition Alliance (BE)	4. Conclusions	**Comment 24.** ESSNA is of the opinion that, the safe level intake of 3,000 µg RE/day for adults is suitable to allow the sports and active nutrition industry to continue to cater to the needs of the physically active population with sufficient vitamin A supplementation, without changing the status quo and reflecting internationally recognised science. ESSNA wishes to emphasise that vitamin A is prominent among physically active consumers as well as athletes, who have different dietary requirements from the general population. The key role of vitamin A in catering to the specific needs of the active population is well-documented in scientific literature (https://www.ncbi.nlm.nih.gov/books/NBK222318/#:~:text=Vitamin%20A%20is%20important%20for,%2C%20growth%2C%20and%20immune%20function.) and recognised in existing EU legislation, as reflected in numerous EFSA-approved health claims: o Vitamin A contributes to normal development and function of the immune system o Vitamin A (including β-carotene) contributes to normal vision, skin, hair, and mucous membranes o Vitamin A contributes to the maintenance of bone, teeth, and nails Despite the proven benefits of vitamin A in supporting healthy and active lifestyles, the physically active population can suffer from vitamin A deficiencies. For instance, research has shown that vitamin A levels are particularly low among endurance athletes. As a consequence, many sports nutrition products, including those sold by ESSNA members, typically contain high doses of vitamin A. As an example, some ESSNA members offer products containing up to 800 µg RE /day. While ESSNA generally welcomes the Panel's decision to maintain the UL for vitamin A. ESSNA wishes to emphasise that the final MPL will depend on the calculation model that is currently being finalised at the

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		European Commission level. Despite the reasonably high UL, there is a risk that the conversion factor for ULs into MPLs will lead to a de facto low MPLs for vitamin A. With this in mind, ESSNA invites the Panel to recognise the physically active population and their dietary needs as an important sub-group of the general population, and ensure that the specificities of specialist foods like sports foods are taken into consideration in the setting of a UL for vitamin A. Link to attachment **Reply.** The comment is out of the scope of the current assessment, which addresses ULs for vitamin A and not Dietary Reference Values (DRVs). **Changes to the opinion based on this comment.** None
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	4.1. Preformed vitamin A	**Comment 25.** Perhaps it could be specified whether this is the UL for vitamin A from all dietary sources, including fortified foods and food supplements or only from fortified foods and food supplements. In the case of β -carotene, the following is indicated: "Based on the available data, no UL or safe level of intake can be established for supplemental β-carotene.", referring to supplementation only. The table in this section is not numbered. **Reply.** The Panel agrees with the comments. **Changes to the opinion based on this comment.** The table in the conclusions has been numbered. Both the text and the new table heading have been amended to clarify that ULs are established for the intake of preformed vitamin A from all sources, including fortified foods and food supplements.
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	4.2. β-Carotene	**Comment 26.** It is suggested in the conclusions section "4.2. β-Carotene" to refer to the vulnerability of the smoking population described throughout the report. **Reply.** The Panel agrees with the comment. **Changes to the opinion based on this comment.** A sentence clarifying that smokers should avoid consuming food supplements containing β-carotene has been added to the conclusions.
European Specialist Sports Nutrition Alliance (BE)	4.2. β-Carotene	**Comment 27.** Despite no UL being established for β-carotene, there are no particular concerns, and overall ESSNA welcomes EFSA's position. **Reply.** Thank you for the comment. **Changes to the opinion based on this comment.** None. Please see also replies to comments 23 and 28.
German Federal Institute for Risk Assessment (BfR)	4.2. β-Carotene	**Comment 28.** Page 74, lines 2663-2666 EFSA concluded that "there is no indication that β-carotene intake from the background diet, including its use as food additive for technological purposes, is associated with adverse health effects", and that – on the basis of the available data, "no UL or safe level of intake can be established for supplemental β-carotene". Such a conclusion would, in our view, be difficult to implement in practice. Moreover, the conclusion as it is currently written gives the impression as if there is no health risk

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(DE)		associated with supplemental β-carotene. To take into account that there are RCTs in which β-carotene supplementation of ≥ 20 mg/day was associated with an increased risk for lung cancer in smokers, the sentence quoted on p. 73 (lines 2651-2654) from EFSA's 2015 opinion, i. e. "The Panel considers that smokers should avoid consuming food supplements containing β-carotene. The Panel also considers that the use of supplemental β-carotene (i.e., in fortified foods and/or food supplements) by the general population should be limited to the purpose of meeting vitamin A requirements (EFSA NDA Panel, 2015).", should in our view be also inserted in the Conclusion. Besides, it would be helpful to indicate the amounts of β-carotene needed to meet vitamin A requirements or rather to achieve the dietary reference intake values for vitamin A. As EFSA (2015) has set Population Reference Intakes for vitamin A of 750 µg RE/day for adult men and 650 µg RE/day for adult women, using a conversion factor of 6:1, the equivalent intake of β-carotene would be 3.9 and 4.5 mg β-carotene, respectively. Based on the conclusion drawn, a level of 4.5 mg β-carotene would thus have to be considered as the daily limit for use of supplemental β-carotene. **Reply.** The Panel agrees with the suggestion of clarifying in the conclusions that smokers should avoid consuming food supplements containing β-carotene and with the suggestion of providing an indication on the daily amounts of beta carotene that would cover the PRI for vitamin A for adult men and women. However, setting daily limits for the use of β-carotene is outside EFSA's remit and is in the remit of risk managers. **Changes to the opinion based on this comment.** The above-mentioned sentence on β-carotene has been added to the conclusions. Also, a sentence indicating the daily amounts of β-carotene that would cover the PRI for vitamin A for adult men and women has been added to the section on risk characterisation (3.8.2) and to the conclusions (section 4.2).
Spanish Agency for Food Safety and Nutrition (AESAN) (ES)	References and Appendices	**Comment 29.** In general the document shows great scientific soundness, supported by a large amount of up-to-date data and scientific articles reviewed, as well as an excellent level of interpretation of them for the preparation of the final conclusions and recommendations. The Spanish Agency for Food Safety and Nutrition (AESAN) has set up an expert group to review the draft scientific opinions on the Tolerable Upper Intake Level for nutrients and to provide comments on them, as appropriate. The AESAN thanks the EFSA Panel for their excellent work in this area and for facilitating this open public consultation. In "References" section: Unify the format of the bibliographic references (the name of the journals is sometimes in extenso and sometimes abbreviated...). Page 81. In the reference "Bohn, T. 2018" the pages should be revised, it says "p.0". Page 82. The reference "EC (European Commission)" appears as unpublished. Although it has not been published it would be advisable to put the year in which it was written. Pages 159 and 163 the citation "Sugiera et al., 2016" should be corrected to "Sugiura et al., 2016". Page 45, Figure 3. The citations "Johanssen et al., 2008b" and "Mills et al., 1997a" should be corrected to "Johanssen et al., 2008" and "Mills et al, 1997". We recommend justifying the margins of the text. Appendix B – Evidence tables B.3. Intervention studies reporting on hepatotoxicity In the Tables of appendix B: on page 157 "months" and "mo" appear. It is suggested to unify criteria. Appendix D – National provisions on the mandatory and voluntary addition of 'vitamin A' to foods and national nutritional guidelines/recommendations for supplementing the diet with 'vitamin A' In Table D3 (page 163) Vitamin A is expressed in mg/kg while throughout the document it is expressed in µg/mg; it is suggested to unify criteria to avoid misleading.

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		Reply. Thank you for the editorial comments. **Changes to the opinion based on this comment.** The suggested editorial comments have been implemented in the opinion, except for the harmonization of vitamin A units in Annex D, which have been kept as reported by the European Commission.
Laboratory of Dietetics and Clinical Nutrition, University of Pavia (IT)	Appendices	**Comment 30.** the comments to the appendices are attached as a word document Link to attachment **Reply.** All the comments provided in the attachment do not refer to the appendices of the opinion but to the Annexes, which were not open for comments in the public consultation. However, these comments are addressed below. **Comments in relation to Annex A (protocol).** Comment A1): See reply to comment 3. Comment A2): Thank you for the comment, which allowed us identifying an internal note left in the draft of the protocol. The sentence has been removed from the protocol with no impact on the opinion. Comment A3): The absorption of preformed vitamin A is extensively addressed in the opinion (section 3.2.1.1). **Comments in relation to Annex B.** Comment B1) The suggested Banca Dati per la composizione degli Alimenti per gli studi epidemiologici in Italia Food composition database (BDA-IEO) is not freely available, as a contribution needs to be paid to obtain an electronic extraction of data. The Centro di Ricerca Alimenti e la Nutrizione (CREA) Italian database has been used instead as source of food composition data (Marletta and Camilli, 2019). Comment B2) Limitations of dietary assessment methods to estimate intakes of preformed vitamin A are discussed in section 3.4 of the opinion and limitations of the EFSA food consumption database in this respect are discussed in section 3.5.1.2. Annex B describes the EFSA food consumption database used to estimate the background intake for all nutrients. **Comment in relation to Annex C.** Thank you for the editorial comment. **Comment in relation to Annex H.** Only preformed vitamin A and total vitamin A, but not β-carotene alone, were exposures of interest in relation to bone health, as no adverse effects on bone has been reported for β-carotene (see section 3.6.3.1).

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		Changes to the opinion based on this comment. The editorial changes suggested for Annex C have been implemented and the sentence related to comment A2 has been removed from the protocol with no impact on the opinion.

Abbreviations

AESAN	Spanish Agency for Food Safety and Nutrition
ATBC	The Alpha-Tocopherol, Beta Carotene Cancer Prevention study
BE	Belgium
BMD	Bone Mineral Density
CARET	the β-Carotene and Retinol Efficacy Trial
CV	Coefficient of Variation
DE	Germany
DRV	Dietary Reference Value
EC	European Commission
EFSA	European Food Safety Authority
EL	Greece
ES	Spain
ESSNA	European Specialist Sports Nutrition Alliance
EU	European Union
HPLC	High-Performance Liquid Chromatography
IT	Italy
IU	International Units
MPLs	Maximum Permitted Levels
NDA Panel	EFSA Panel on Nutrition, Novel Foods and Food Allergens
RCT	Randomised controlled trial
RE	Retinol Equivalent
RoB	Risk of Bias
sQ	Sub-question
UL	Tolerable Upper Intake Level

Appendix A – Attachments to comments received

Attachment to comment 1

ESSNA European Specialist Sports Nutrition Alliance | The voice of the sports & active nutrition sector in Europe

ESSNA's comments on the European Food Safety Authority's (EFSA) draft scientific opinion on the tolerable upper intake level (ULs) for vitamin A and β-carotene

March 2024

Introduction, lines 12-16: Article 6 of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods and Article 5 of Directive 2002/46/EC on the approximation of the laws of the Member States relating to food supplements provide that maximum amounts of vitamins and minerals added to foods and to food supplements shall be set.

- The European Specialist Sports Nutrition Alliance (ESSNA), the voice of the sports and active nutrition industry in Europe, welcomes the efforts of the European Commission and EFSA to adopt maximum amounts of vitamins and minerals that may be used in food supplements or added to food.
- ESSNA observed with concern that in the absence of EU-wide maximum permitted levels for vitamins and minerals (MPLs), several EU Member States have set their own MPLs and dietary intake recommendations for vitamin A and β-carotene. This fragmentation of the Single Market has created unjustified barriers to the trade of vitamin A and β-carotene, higher risks of consumer misunderstandings and labelling issues, and an ambiguous legislative landscape – as experienced by many ESSNA members.
- ESSNA wishes to note that sports nutrition products, including those formulated with vitamin A, often contain high levels of specific vitamins and minerals to cater to the specific dietary needs of sports people, whose needs are different from the ones of the general population. Many sports nutrition products frequently apply vitamin A in products – for instance, in multivitamin tablets, capsules, and other supplements and fortified sports foods. The room for reformulation of products to comply with variating national requirements is small and burdensome for companies operating in the sports and active nutrition sector.
- With this in mind, ESSNA generally welcomes the harmonisation of UL and MPLs at the EU level in line with scientifically sound and internationally recognised science.

For more information, please contact:
ESSNA Secretariat

Email: laura@essna.com
Website: www.essna.com

Attachment to comments 3, 11, 14 and 22

DRAFT OPINION – UPPER LEVEL VITAMIN A

Comment 1) *Although it is acknowledged that other provitamin A carotenoids (e.g., α-carotene and β- cryptoxanthin) may contribute to total vitamin A intake, their dietary contribution to the overall toxicity of preformed vitamin A is expected to be marginal.*

As stated for the protocol (Annex A), the researchers think that a reference should be provided to justify the last sentence, or otherwise to refer to the point in the document where this sentence is justified. In addition, according to the following reference the bioavailability of this compounds is higher than β-carotene. Therefore, the researchers suggest including the following reference in the introduction of the document:
Olmedilla-Alonso B, Rodríguez-Rodríguez E, Beltrán-de-Miguel B, Estévez-Santiago R. Dietary β-Cryptoxanthin and α-Carotene Have Greater Apparent Bioavailability Than β-Carotene in Subjects from Countries with Different Dietary Patterns. Nutrients. 2020;12(9):2639. Published 2020 Aug 29. doi:10.3390/nu12092639

Comment 2) *For observational studies, the appraisal addressed six RoB questions, covering five domains.*

The researchers wonder why the authors wonder why the RoB was used for the quality assessment of the included observational studies. They think that a tool validated for observational studies would have been preferable (such as the Newcastle-Ottawa Scale for the quality assessment of observational studies).

Comment 3) Chapter 3.3. "Biomarkers of intake for vitamin A, including β-carotene" (sQ2). The researchers suggest that the following references could be useful for addressing vitamin A stores in the liver stores and/or plasma retinyl esters:

1. Valentine AR, Davis CR, Tanumihardjo SA. Vitamin A isotope dilution predicts liver stores in line with long-term vitamin A intake above the current Recommended Dietary Allowance for young adult women. Am J Clin Nutr. 2013;98(5):1192-1199. doi:10.3945/ajcn.113.063867
2. Green MH, Green JB, Ford JL. Vitamin A Absorption Efficiency Determined by Compartmental Analysis of Post-prandial Plasma Retinyl Ester Kinetics in Theoretical Humans. J Nutr. 2020;150(8):2223-2229. doi:10.1093/jn/nxaa176
3. Ford JL, Green JB, Haskell MJ, et al. Use of Model-Based Compartmental Analysis and a Super-Child Design to Study Whole-Body Retinol Kinetics and Vitamin A Total Body Stores in Children from 3 Lower-Income Countries. J Nutr. 2020;150(2):411-418. doi:10.1093/jn/nxz225
4. Lopez-Teros V, Ford JL, Green MH, et al. The "Super-Child" Approach Is Applied To Estimate Retinol Kinetics and Vitamin A Total Body Stores in Mexican Preschoolers. J Nutr. 2020;150(6):1644-1651. doi:10.1093/jn/nxaa048

Comment 4) The researchers believe that the following references could be included in the introduction:

1. Yamaguchi Y, Zampino M, Tanaka T, et al. The Plasma Proteome Fingerprint Associated with Circulating Carotenoids and Retinol in Older Adults. J Nutr. 2022;152(1):40-48. doi:10.1093/jn/nxab340
2. von Lintig J, Moon J, Lee J, Ramkumar S. Carotenoid metabolism at the intestinal barrier. Biochim Biophys Acta Mol Cell Biol Lipids. 2020;1865(11):158580. doi:10.1016/j.bbalip.2019.158580
3. Tanumihardjo SA. Vitamin A and bone health: the balancing act. J Clin Densitom. 2013;16(4):414-419. doi:10.1016/j.jocd.2013.08.016

Comment 5) Chapter 3.6.3. "Bone health". The researchers suggest that the following references might be added in the introduction and/or outcome analysis for vitamin A/β-carotene and bone health:

1. Li X, Liu X. Associations of serum vitamins levels with bone mineral density in the different race-ethnicities US adults. BMC Musculoskelet Disord. 2021;22(1):137. Published 2021 Feb 4. doi:10.1186/s12891-021-03997-0
2. Cao WT, Zeng FF, Li BL, Lin JS, Liang YY, Chen YM. Higher dietary carotenoid intake associated with lower risk of hip fracture in middle-aged and elderly Chinese: A matched case-control study. Bone. 2018;111:116-122. doi:10.1016/j.bone.2018.03.023
3. Li XB, Liu T, Fan L, et al. Circulating serum level of retinoic acid and hip fractures among postmenopausal women. J Am Geriatr Soc. 2019;67(2):336-341. doi:10.1111/jgs.15667
4. Zhang X, Huang J, Zhou Y, et al. Vitamin A Nutritional Status Is a Key Determinant of Bone Mass in Children. Nutrients. 2022;14(21):4694. Published 2022 Nov 6. doi:10.3390/nu14214694
5. Navarro-Valverde C, Caballero-Villarraso J, Mata-Granados JM, et al. High Serum Retinol as a Relevant Contributor to Low Bone Mineral Density in Postmenopausal Osteoporotic Women. Calcif Tissue Int. 2018;102(6):651-656. doi:10.1007/s00223-017-0379-8
6. Teigmo MSW, Gundersen TE, Emaus N, Grimnes G. Distribution and determinants of retinol in Norwegian adolescents, and its relation to bone mineral density: the Tromsø Study: Fit Futures. Eur J Clin Nutr. 2018;72(10):1373-1384. doi:10.1038/s41430-018-0193-z

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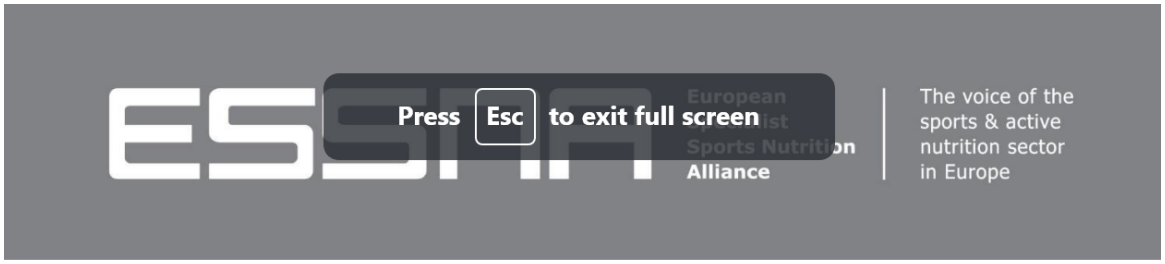
Attachment to comment 18

The PDF of the following reference was attached to the comment: Beltrán-de-Miguel, B., Estévez-Santiago, R., & Olmedilla-Alonso, B. (2015). Assessment of dietary vitamin A intake (retinol, α-carotene, β-carotene, β-cryptoxanthin) and its sources in the National Survey of Dietary Intake in Spain (2009-2010). *International journal of food sciences and nutrition*, *66*(6), 706–712. https://doi.org/10.3109/09637486.2015.1077787

Attachment to comment 24



ESSNA's comments on the European Food Safety Authority's (EFSA) draft scientific opinion on the tolerable upper intake level (ULs) for vitamin A and β-carotene

March 2024

Overall conclusion on intake level for preformed Vitamin A, lines 2589-2592: The Panel proposes to retain the UL of 3,000 µg RE/day for adults, based on a NOAEL for teratogenicity (section 3.7.1.1). This UL applies to men and women, including women of child-bearing age, pregnant and lactating women, and post-menopausal women.

- ESSNA is of the opinion that, the safe level intake of 3,000 µg RE/day for adults is suitable to allow the sports and active nutrition industry to continue to cater to the needs of the physically active population with sufficient vitamin A supplementation, without changing the status quo and reflecting internationally recognised science.

- ESSNA wishes to emphasise that vitamin A is prominent among physically active consumers as well as athletes, who have different dietary requirements from the general population.

- The key role of vitamin A in catering to the specific needs of the active population is well-documented in scientific literature and recognised in existing EU legislation, as reflected in numerous EFSA-approved health claims:
  - Vitamin A contributes to normal development and function of the immune system
  - Vitamin A (including β-carotene) contributes to normal vision, skin, hair, and mucous membranes
  - Vitamin A contributes to the maintenance of bone, teeth, and nails

- Despite the proven benefits of vitamin A in supporting healthy and active lifestyles, the physically active population can suffer from vitamin A deficiencies. For instance, research has shown that vitamin A levels are particularly low among endurance athletes. As a consequence, many sports nutrition products, including those sold by ESSNA members, typically contain high doses of vitamin A. As an example, some ESSNA members offer products containing up to 800 µg RE /day.

- While ESSNA generally welcomes the Panel's decision to maintain the UL for vitamin A. ESSNA wishes to emphasise that the final MPL will depend on the calculation model that is currently being finalised at the European Commission level. Despite the reasonably high UL, there is a risk that the conversion factor for ULs into MPLs will lead to a de facto low MPLs for vitamin A. With this in mind, ESSNA invites the Panel to recognise the physically active population and their dietary needs as an important sub-group of the general population, and ensure that the specificities of specialist foods like sports foods are taken into consideration in the setting of a UL for vitamin A.

Overall conclusion on intake level for β-carotene, line 2606-2609: In the absence of adequate data to characterise a dose–response relationship and identify a reference point for supplemental β-carotene in relation to lung cancer risk, no UL for supplemental β-carotene intake can be established for any population group.

- Despite no UL being established for β-carotene, there are no particular concerns, and overall ESSNA welcomes EFSA's position.

ESSNA European Specialist Sports Nutrition Alliance | The voice of the sports & active nutrition sector in Europe

For more information, please contact:
ESSNA Secretariat

Email: laura@essna.com
Website: www.essna.com

Attachment to comment 30

Comments to EFSA's Public Consultation on the Upper Levels for Vitamin A and β-carotene

From the Laboratory of Dietetics and Clinical Nutrition (LDNC), Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Italy

ANNEX A: PROTOCOL

Comment A1) Pag. 4 *Throughout this protocol, total vitamin A refers to, specifically preformed vitamin A (retinol and retinyl esters) and the provitamin A β-carotene. Although it is acknowledged that other provitamin A carotenoids (α-carotene and β-cryptoxanthin) may contribute to total vitamin A intake, their contribution to the overall toxicity of vitamin A is expected to be marginal.*

The researchers think that a reference should be provided to justify the last sentence, or otherwise to refer to the point in the document where this sentence is justified.
In addition, according to the following reference the bioavailability of this compounds is higher than β-carotene. Therefore, the researchers suggest mentioning the following reference in the introduction of the document: Olmedilla-Alonso B, Rodríguez-Rodríguez E, Beltrán-de-Miguel B, Estévez-Santiago R. Dietary β-Cryptoxanthin and α-Carotene Have Greater Apparent Bioavailability Than β-Carotene in Subjects from Countries with Different Dietary Patterns. Nutrients. 2020;12(9):2639. Published 2020 Aug 29. doi:10.3390/nu12092639

Comment A2) pag.5 *Several interactions between the intake of preformed vitamin A supplement and different drugs have been described (e.g. anticoagulants, hepatotoxic drugs, retinoids). Vitamin A supplementation in patients under medical treatment with these drugs requires medical advice.*

The researchers believe that references should be provided to readers in order to justify these phrases. Also, they believe that adding a sentence to expand the second concept would be beneficial.

Comment A3) pag.6 *Preformed vitamin A is efficiently absorbed in the small intestine over a wide range of intake (~ 70–90 %).*

Being vitamin A a liposoluble vitamin, its absorption depends also on the amount of dietary fat provided by the meal. Therefore, the researchers suggest including this consideration and suggest the following reference: Carazo A, Macáková K, Matoušová K, Krčmová LK, Protti M, Mladěnka P. Vitamin A Update: Forms, Sources, Kinetics, Detection, Function, Deficiency, Therapeutic Use and Toxicity. Nutrients. 2021;13(5):1703. Published 2021 May 18. doi:10.3390/nu13051703

ANNEX B: METHODOLOGICAL CONSIDERATIONS IN THE CALCULATION OF INTAKE ESTIMATES FOR PREFORMED VITAMIN A AND B-CAROTENE FROM THE BACKGROUND DIET IN EU COUNTRIES

Comment B1) pag.1 *For gap-filling and cross-checking the quality of the available data, additional publicly available national databases from the following countries were consulted:*
For preformed vitamin A: Denmark (Frida, 2022), Estonia (NutriData, 2022), France (Anses, 2020), Netherlands (NEVO, 2021), Norway (Norwegian Food Safety Authority, 2022) and Sweden (The Swedish Food Agency, 2022).
For β-carotene: Denmark (Frida, 2022), Estonia (NutriData, 2022), Finland (Fineli, 2019), France (Anses, 2020), Netherlands (NEVO, 2021), Portugal (PortFIR, 2021), Sweden (The Swedish Food Agency, 2022), Italy (Marletta and Camilli, 2019).

The researchers wonder why the BDA-IEO (Banca Dati per la composizione degli Alimenti per gli studi epidemiologici in Italia Food composition database) food composition database was not included. It is a freely accessible Italian and nationwide used database for the clinical practice and epidemiological studies. It provides data on both preformed vitamin

A (retinol) and β-carotene content, as well as the retinol equivalent content. Link to access: https://bda.ieo.it/?page_id=96 (last accessed on 17/03/24)

Comment B2) pag.5 *Consumption data were collected using repeated 24-hour dietary recalls or dietary records covering from two to nine days per subject.*

The researchers suggest including at least a reference indicating how many days are needed to be able to estimate vitamin A intake appropriately and representatively through intake assessment measures (e.g., 24-h recalls). As an example, they provide the following references on the days needed to appropriately estimate vitamin A intake:

	Early childhood		Pre-schoolers		School-age children		Adults	
Reference	Giovannini et al, 1995		Nelson et al, 1989		Miller et al, 1991		Willet, 1990	
	Variance*	Number of days	Variance*	Number of days	Variance*	Number of days	Variance*	Number of days
Vitamin A	0,93	55	4.6	20	7.57	14	3.28	105

* Ratio between inter-individual variance and intra-individual variance.

Source: Scaglioni S. & Turconi G "Metodi di valutazione dei consumi alimentari" IN: Diagnostica Nutrizionale, 1997

ANNEX C: EFSA'S INTAKE ASSESSMENT FOR PREFORMED VITAMIN A

Comment C1) Foglio 1 "Information to the readers", column "Table title".

Table 7: *Specific food categories on ontributing to preformed vitamin A intake*
Table 10: *Specific food categories on ontributing to preformed vitamin A intake in the no offal scenario*
Table 13*: Specific food categories on ontributing to preformed vitamin A intake in the offal consumers only scenario*

For all these cells, the researchers highlight the following typing error: "on ontributing"

ANNEX H: Studies excluded at full-text screening and during data extraction

Comment 1) Considering the search strategies applied, the researchers wonder why the following reference do not appear among the excluded study: Charkos TG, Liu Y, Oumer KS, Vuong AM, Yang S. Effects of β-carotene intake on the risk of fracture: a Bayesian meta-analysis. BMC Musculoskelet Disord. 2020;21(1):711. Published 2020 Oct 31. doi:10.1186/s12891-020-03733-0

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Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY and et al., 1993. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst, 85:1483-1492. doi: 10.1093/jnci/85.18.1483

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2012a. Scientific Opinion on the re-evaluation of mixed carotenes (E 160a (i)) and beta-carotene (E 160a (ii)) as a food additive. EFSA Journal 2012; 10(3):2593. [67 pp.] doi:10.2903/j.efsa.2012.2593.

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2012b. Statement on the safety of β-carotene use in heavy smokers. 10(12):2953. [7 pp.] doi:10.2903/j.efsa.2012.2953. 2953 pp.

EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), 2023. Scientific opinion on the tolerable upper intake level for selenium. EFSA Journal 2023; 21(1):7704, 194 pp.

Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A and Briançon S, 2004. The SU.VI.MAX Study: A Randomized, Placebo-Controlled Trial of the Health Effects of Antioxidant Vitamins and Minerals. Archives of Internal Medicine, 164:2335-2342. doi: 10.1001/archinte.164.21.2335

IOM (Institute of Medicine Panel on Dietary, Antioxidants Related, Compounds), 2000. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. (US) NAP and reserved. CbtNAoSAr

OHAT/NTP (Office of Health Assessment and Translation, Division of the National Toxicology Program), 2015. OHAT Risk of Bias Rating Tool for Human and Animal Studies. 37 pp. pp.

SCF (Scientific Committee on Food), 2000. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Beta Carotene.

Thürmann PA, Steffen J, Zwernemann C, Aebischer C-P, Cohn W, Wendt G and Schalch W, 2002. Plasma concentration response to drinks containing β-carotene as carrot juice or formulated as a water dispersible powder. European Journal of Nutrition, 41:228-235. doi: 10.1007/s00394-002-0381-3

Wang XD, Liu C, Bronson RT, Smith DE, Krinsky NI and Russell M, 1999. Retinoid signaling and activator protein-1 expression in ferrets given beta-carotene supplements and exposed to tobacco smoke. J Natl Cancer Inst, 91:60-66. doi: 10.1093/jnci/91.1.60

Wolterbeek AP, Schoevers EJ, Bruyntjes JP, Rutten AA and Feron VJ, 1995. Benzo[a]pyrene-induced respiratory tract cancer in hamsters fed a diet rich in beta-carotene. A histomorphological study. J Environ Pathol Toxicol Oncol, 14:35-43