Annex A

Public consultation on the Scientific Opinion of the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) on the relationship between intake of alpha-lipoic acid (thioctic acid) and the risk of developing insulin autoimmune syndrome

European Food Safety Authority (EFSA)[1]

Abstract

The European Food Safety Authority (EFSA) has launched a public consultation to receive input from the scientific community and all interested parties on the draft Scientific Opinion on the relationship between intake of alpha-lipoic acid (thioctic acid) and the risk of developing insulin autoimmune syndrome (IAS), endorsed by the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) for public consultation at its Plenary meeting on 21 January 2021. The written public consultation for this document was open from 28 January 2021 to 25 February 2021. EFSA received comments from six interested parties. EFSA and its NDA Panel wish to thank all stakeholders for their contributions. This report, which summarises the outcome of the public consultation, includes a brief summary of the comments received and how the comments were addressed. The NDA Panel considered the comments received and prepared an updated version of the Scientific Opinion. The Scientific Opinion was discussed and adopted at the NDA Plenary meeting on 8 April 2021 and is published in the EFSA Journal.

[1] Acknowledgements: EFSA wishes to thank the members of the Working Group on Alpha-lipoic acid: Daniele Cappellani, Richard Ijzerman, Alexandre Maciuk and Hendrik Van Loveren, and the EFSA staff members: Ester Artau Cortacans, Céline Dumas, Charlotte Salgaard Nielsen and Ariane Titz for the support provided to the development of this document.

Table of contents

1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

The Danish authorities requested the Commission to initiate the procedure under Article 8 of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods[2] for the intake of alpha-lipoic acid in food supplements because of the potential risk to health associated with the intake of this substance. Safety concerns associated with the use of alpha-lipoic acid in food supplements have been outlined in a scientific opinion by the Danish National Food Institute (DTU) on the safety of alpha-lipoic acid use in food supplements[3], and in an expert opinion on the safety of placing dietary supplements with alpha-lipoic acid on the market for the general population[4] by the Belgian Superior Health Council.

The above-mentioned scientific assessments lay out the possible harmful effects associated with the use of alpha-lipoic acid in food supplements, in particular a potential risk for Insulin Autoimmune Syndrome and reports in clinical studies of several adverse effects.

Consequently, the Commission has initiated the procedure under Article 8 (2) of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods, for the intake of alpha-lipoic acid in food supplements.

In accordance with Article 29(1)(a) of Regulation (EC) No 178/20024, the European Commission asks EFSA to:

– Review the existing scientific data on the possible link between the intake of alpha-lipoic acid and Insulin Autoimmune Syndrome.

– Provide advice on a dietary intake of alpha-lipoic acid intentionally added to foods that does not give rise to concerns about Insulin Autoimmune Syndrome for the general population, and as appropriate, for vulnerable subgroups of the population.

1.2. Interpretation of the Terms of Reference

In line with EFSA policy on openness and transparency, and in order for EFSA to receive comments from the scientific community and stakeholders, EFSA shall release the draft Scientific Opinion on the relationship between intake of alpha-lipoic acid (thioctic acid) and the risk of insulin autoimmune syndrome (IAS, Hirata's disease) for public consultation.

The comments resulting from the public consultation shall be published together with the adopted Scientific Opinion. The Scientific Opinion shall address the relevant comments received from the public consultation.

1.3. Additional information

Upon request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA Panel) developed a draft Scientific Opinion on the relationship between intake of alpha-lipoic acid (thioctic acid) and the risk of IAS. In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key issues. Accordingly, for addressing this request, EFSA has carried out a public consultation:

- The draft Scientific Opinion was published on EFSA's website for comments (28 January to 25 February 2021) (see Appendix A). The NDA Panel prepared an updated version

[2] OJ L 404, 30.12.2006, p. 26.

[3] 'Safety of alpha-lipoic acid use in food supplements', Danish National Food Institute, DTU Doc nr. 17/14450, 10.10.2017.

[4] Avis du Conseil Supérieur de la Sante N. 9274, 'Innocuité de l'acide alpha-lipoïque dans les compléments alimentaires', 4.06.2015.

of the draft Scientific Opinion, taking into account the relevant comments received. The updated draft Scientific Opinion was discussed and adopted at the NDA Plenary meeting on 8 April 2021 and is published in the EFSA Journal. EFSA is committed to publishing the comments received during the public consultation, as well as this technical report on the outcome of the public consultation.

2. Data and Methodologies

2.1. Data

EFSA received comments from six interested organisations and individuals through the electronic form accessible on the EFSA website (Table 1). No comments were received by email.

Table 1: List of organisations and individuals submitting comments by means of the electronic form on the EFSA website

Organisation[(a)]/individual	Category	Country
Individual	Personal capacity	IT
RIVM (National Institute for Public Health and the Environment)	University/public research institute	NL
Uriach Consumer Healthcare S.L.	Private sector (e.g. industry, consultancy, etc.)	ES
EHPM – European Federation of Associations of Health Products Manufacturers	Private sector (e.g. industry, consultancy, etc.)	BE
Alfasigma	Private sector (e.g. industry, consultancy, etc.)	IT
Food Supplements Europe	Private sector (e.g. industry, consultancy, etc.)	BE
Submissions from organisations		5
Submissions from individuals		1
Total		6

IT: Italy; NL: The Netherlands; ES: Spain; BE: Belgium

(a): As indicated by the commenters

2.2. Methodologies

All comments are summarised and addressed below in the following order: risk management aspects, comments on the abstract, comments on source, production process, stability and type of formulations available, comments on the absorption, distribution, metabolism and excretion (ADME) of alpha-lipoic acid (ALA), comments on genetic determinants of IAS, comments on the pathophysiology of IAS and comments on case reports. Similar comments received from the same or different parties are grouped together and addressed only once. All written individual comments are listed, as received, in Appendix B. Names of individuals and personal information such as personal email addresses and phone numbers have been blackened for data protection reasons.

In the following sections, extracted sentences from the Scientific Opinion are written in *italic* and changes are highlighted in **bold**.

3. Assessment

3.1. Risk management

Comment(s) received

1. Some comments relate to the level of risk that might be acceptable for a food. One commenter drew parallels to other diseases in which food supplements containing certain nutrients would be contraindicated (e.g. iron and haemochromatosis), while these supplements are still commonly used by the general population. Also, labelling of food supplements was proposed with respect to a statement that a health care professional should be consulted if symptoms indicative of hypoglycaemia occurred.

Panel consideration of comments received

Ad 1. The Panel considers that these comments address risk management aspects, i.e. the level of risk that is acceptable for the European population and the management of this risk by e.g. labelling. These comments relate to aspects outside the remit of EFSA and are under the remit of risk managers (European Commission, European Parliament, Member States). Therefore, these comments are not further addressed in this technical report. **No change has been made to the Opinion**.

3.2. Abstract

Comment(s) received

2. It was recommended to state in a clearer way in the abstract that the scope of the current Scientific Opinion is limited to the link between ALA intake and IAS.

3. EFSA was asked to elaborate more on the lack of evidence linking ALA naturally occurring in foods and IAS.

Panel consideration of comments received

Ad 2. A statement, as requested, has been included in the abstract: '**A review of all possible adverse effects associated with consumption of ALA was not requested.'**

Ad 3. The Panel intended to convey that no publication had been identified that suggested a link between ALA naturally occurring in foods and IAS. The abstract and conclusions have been revised accordingly: '**No publication linking the intake of ALA naturally occurring in foods to IAS was identified**.'

3.3. Sources of alpha-lipoic acid, production process, stability and type of formulations available

Comment(s) received

4. The Panel was asked to clarify why the Panel assumes that most industrially produced ALA is a racemic mixture rather than the *S-(-)* form (Section 3.1.).

Panel consideration of comments received

Ad 4. The Panel is aware that both the pure *R-(+)*-enantiomer as well as the racemic mixture are used in ALA-containing products. The *S-(–)* form is formed during the industrial production of ALA by chemical synthesis. The available information on chemical synthesis routes indicates a racemic synthesis. Therefore, the Panel assumes that most ALA-containing products are marketed as racemic mixture and not in the form of the pure *R-(+)*-enantiomer, which may be more complex to produce. Also, the Panel is not aware of any food supplement that contains only the pure *S-(–)* form. The sentence

was clarified in the Opinion: '*Therefore, the Panel assumes that most industrially produced ALA is a racemic mixture* ***rather than the pure R-(+)-enantiomer***'. The sentence was moved from Section 3.1 to Section 3.2.

3.4. Absorption, distribution, metabolism and excretion of alpha-lipoic acid

Comment(s) received

5. It was proposed to expand this section (3.4) of the Opinion and evaluate any known ADME parameter around dihydrolipoic acid following ALA ingestion.

Panel consideration of comments received

Ad 5. A dedicated literature search on the topic has been conducted by EFSA on 1 March 2021 following public consultation, in order to address the comment received. Section 2.1 (Data) of the Opinion has been updated accordingly, as well as the appendices containing the search strings and the flow charts of the literature searches. The information that was found is described in the Opinion in Section 3.4: '**Only limited data are available on the concentrations of dihydrolipoic acid in human plasma and no publication has been retrieved on its pharmacokinetics of. Khan et al. (2011) reported mean (standard deviation, SD) concentrations in plasma of 15 healthy volunteers (aged 22-25 years) of 173 (4.26) ng/mL for dihydrolipoic acid and of 35 (5.64) ng/mL for ALA. Whether volunteers had received ALA supplements or not, was not explicitly stated. Teichert and Preiss (1992) found dihydrolipoic acid concentrations in plasma of six healthy non-supplemented volunteers of 33-145 ng/mL and ALA concentration of 1-25 ng/mL after acid hydrolysis. In contrast, Haj-Yehia et al. (2000) showed in a chromatogram that concentrations of dihydrolipoic acid in plasma of a volunteer who had received supplemental ALA were lower than ALA concentrations (numeric values not reported). This is similar to what was shown by Khan et al. (2015) for free endogenous ALA from plasma of a most likely non-supplemented individual. The Panel notes that these data on the plasma ratio of dihydrolipoic acid/ALA are limited and insufficient to conclude on which is the major circulating form.'**

3.5. Genetic determinants of insulin autoimmune syndrome

Comment(s) received

6. It was stated that 'glutamine' that was indicated to be present at position 74 in the DRB1*04:03, 04:06, and 04:07 alleles should be glutamate.

7. It was asked whether the DRB1*04:15 allele also includes glutamate at position 74 and whether one could predict bioinformatically the potential for other genotypes to elicit IAS based on the presence of glutamate at position 74.

Panel consideration of comments received

Ad 6. Glutamine has been replaced by **glutamate** in the Opinion (Section 3.5.3.).

Ad 7. In the literature search, the Panel had not retrieved any information in relation to the amino acid sequence of DRB1*04:15. Following the comment from the public consultation, the Panel searched the UniProt database[5] for further information. Also in this database no data related to DRB1*04:15 were available. The following sentence was added in the Opinion in Section 3.5.3: '**The Panel was unable to retrieve data**

[5] https://www.uniprot.org/

on the amino acids that are present at position 74 and 37 in the allele DRB1*04:15.'

Even if bioinformatics could assist in the determination of other alleles implicated in IAS, the Panel considers it out of scope of the present assessment to identify all possible alleles that could theoretically be involved in the development of IAS.

3.6. Pathophysiology of insulin autoimmune syndrome

Comment(s) received

8. It has been indicated that the statement in the Opinion: '*It has been proposed that substances containing sulfhydryl groups may cleave the disulfide bonds between the insulin chains A and B...*' is not entirely correct as it is the intra-A disulfide bond that is reduced by sulfhydryl compounds.

9. It was suggested to expand on the mechanism underlying IAS in order to understand whether ALA and other sulfhydryl-containing compounds work through a threshold or non-threshold mechanism. The mechanism described in the Opinion suggests a non-threshold mechanism for ALA. In this relation, it was also mentioned that there is more information available than what is described in the Opinion, but without providing additional references to underpin this statement.

Panel consideration of comments received

Ad 8. The sentence in the Opinion was changed as follows: *It has been proposed that substances containing sulfhydryl groups may cleave* ***one disulfide bond of insulin, resulting in structural modification and increased immunogenicity*** (Cappellani et al., 2020).

Ad 9. The Panel has described in the Opinion (Section 3.5.4.) all data and information that were retrieved through the literature search on the potential mechanism that underlies the development of IAS. No additional data were provided during the public consultation nor was there any indication that relevant data have been missed in the search. Mostly, the mechanism has been described in the literature in hypothetical terms. The hypothesis seems plausible, but proof is lacking. Therefore, further research leading to the elicitation of the exact mechanism by which ALA may cause IAS in individuals with a genetic predisposition was included by the Panel as a recommendation for research in Section 6 of the Opinion. The Panel would like to note that the intention of the draft Opinion was not to suggest a non-threshold mechanism. The information is not sufficient to conclude on whether such threshold exists and where a possible threshold lies. Therefore, **no changes have been made to the Opinion**.

3.7. Summary of case reports linking alpha-lipoic acid intake with insulin autoimmune syndrome

Comment(s) received

10. Several comments were received that suggested complementing the data derived from published case reports with data from vigilance databases, adverse event reports from clinical trials or using sales data and company internal vigilance data, mainly to establish the incidence of ALA-induced IAS. Also, it was asked to explain why these data were not used even though this had been foreseen in the protocol.

11. It was asked to elaborate more on the case reports, e.g. to provide a summary of how many cases occurred with the known alleles implicated in IAS vs those with unknown

alleles, to describe the severity of adverse events and the reversibility of signs and symptoms. It was also suggested to provide more information on fatalities, disabilities, hospitalisation and proportion of the different signs and symptoms (e.g. loss of consciousness vs mild symptoms such as sweating/weakness).

Panel consideration of comments received

Ad 10. The questions asked to EFSA in the Terms of Reference for this mandate were to review the existing scientific data on the possible link between the intake of ALA and IAS and to provide advice on a dietary intake of ALA intentionally added to foods that does not give rise to concerns about IAS. In this context, the retrieval of more case reports, possibly unpublished, through vigilance databases would not have changed the conclusions of the Panel that were already drawn from 49 published case reports found through a comprehensive literature search, i.e. that the consumption of ALA added to foods, including food supplements, is likely to lead to an increased risk of developing IAS in individuals with certain genetic polymorphisms. More precisely, if no reports in vigilance databases in addition to the published case reports had been found, this would not have led to the conclusion that there is no association between the intake of ALA added to foods and IAS. The identification of more case reports would not have increased the level of certainty in the conclusions on the association based already on a large number of published case reports. Also, including vigilance data would not have helped to estimate the incidence of IAS in Europe (discussed in the comments received) or the risk of developing IAS following ALA consumption, not only because there is considerable uncertainty as to whether all cases of IAS following ALA consumption have been either published in the literature or documented in vigilance databases, but also because IAS may have been underdiagnosed in vigilance notifications. In addition, based on the publicly available information available both from case reports and vigilance notifications, it is not possible to identify with sufficient certainty the overlap between cases published in the literature and those registered in vigilance databases.

Similar considerations apply to adverse event data generated in clinical efficacy trials. For the latter, it also needs to be emphasised that the likelihood that IAS occurs as adverse event in such trials, where the study population is not representative of the general population, is low considering that IAS is a rare disease. The absence of occurrence of IAS in such a trial or in a series of trials is therefore not a proof that there is no association between the intake of ALA added to foods and IAS.

The same is true for any sales data of food business operators presented in the comments received. These were mostly linked to their own post-marketing surveillance systems, listing data on undesirable effects, among which the food business operators did not observe any cases of IAS reported in relation to their products (Appendix C of the technical report).

Therefore, these data sources have not been used. The reasons for not using them, listed above, have been included in the Opinion (Section 3.6.). A paragraph as follows was added: '**As conclusions on an association between the consumption of ALA and an increased risk of development of IAS could be drawn from published case reports, the data retrieval from vigilance databases and adverse event reports from clinical trials was not further pursued as this would not have changed the conclusions of the Panel derived from the case reports. The same applies to sales data and data from food business operators' post-marketing surveillance systems.**'

Ad 11. A summary was included in the Opinion (Section 3.6.) on how many cases experienced loss of consciousness vs other symptoms. These symptoms have also been described. The number of cases per allele has also been indicated in the text.

The new text reads as follows: '*Out of the 49 cases, data on health status, other possible concomitant medication, and HLA class DRB1* genotype were available for 26, 20 and 38 cases, respectively.* **The type of signs and symptoms occurring was reported for 27 cases. In 12 of those cases, subjects lost consciousness or went into hypoglycaemic coma. Other symptoms reported were mostly sweating, tremors, dizziness, fatigue, weakness, confusion, hunger and palpitations.**

Nineteen individuals were identified as carrying the DRB1*04:06 allele, 14 had DRB1*04:03, two DRB1*04:15 and three individuals were identified as subtypes DRB1*04. No cases associated with DRB1*04:07 were found. The predominant allele in the 19 cases of Caucasian origin diagnosed in Europe was DRB1*04:03 (11 cases). The alleles DRB1*04:06 and DRB1*04:15 were found in two cases and one case, respectively. One case was identified as DRB1*04 and in four cases no information was available.'

A statement on the reversibility of the signs and symptoms in the described case reports had already been presented in the Opinion as submitted for public consultation. However, this statement is now repeated in the abstract and in the conclusions of the Opinion. The Panel considers that it is not necessary to specifically express itself on fatalities and disabilities as the reversibility of signs and symptoms has already been described in the Opinion. The information in the case reports is insufficient to make a comprehensive assessment of hospitalisation and the duration thereof. Therefore, this point could not be addressed in the Opinion.

References

Cappellani D, Macchia E, Falorni A and Marchetti P, 2020. Insulin Autoimmune Syndrome (Hirata Disease): A comprehensive review fifty years after its first description. Diabetes, Metabolic Syndrome and Obesity, 13:963-978. doi: 10.2147/DMSO.S219438. eCollection 2020.

Haj-Yehia AI, Assaf P, Nassar T and Katzhendler J, 2000. Determination of lipoic acid and dihydrolipoic acid in human plasma and urine by high-performance liquid chromatography with fluorimetric detection. Journal of Chromatography A, 870:381-388. doi: https://doi.org/10.1016/S0021-9673(99)00857-2

Khan A, Iqbal Z, Watson DG, Khan A, Khan I, Muhammad N, Muhammad S, Nasib HA, Iqbal N, Faiz ur r and Kashif M, 2011. Simultaneous determination of lipoic acid (LA) and dihydrolipoic acid (DHLA) in human plasma using high-performance liquid chromatography coupled with electrochemical detection. Journal of Chromatography B, 879:1725-1731. doi: https://doi.org/10.1016/j.jchromb.2011.04.017

Khan MI, Iqbal Z and Khan A, 2015. Simultaneous determination of the endogenous free α-lipoic acid and dihydrolipoic acid in human plasma and erythrocytes by RP-HPLC coupled with electrochemical detector. In: Armstrong D (ed.). Methods in Molecular Biology. New York Heidelberg Dordrecht London, Humana Press Inc., Springer. pp. 345-360.

Teichert J and Preiss R, 1992. HPLC-methods for determination of lipoic acid and its reduced form in human plasma. International Journal of Clinical Pharmacology, Therapy, and Toxicology, 30:511-512

Abbreviations

ADME	absorption, distribution, metabolism and excretion
ALA	alpha-lipoic acid
BE	Belgium
DTU	Danish National Food Institute
EC	European Commission
EHPM	European Federation of Associations of Health Products Manufacturers
ES	Spain
IAS	insulin autoimmune syndrome
IT	Italy
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NL	The Netherlands
RIVM	National Institute for Public Health and the Environment
SD	standard deviation

Appendix A – Explanatory text for the public consultation on the draft Scientific Opinion on the relationship between intake of Alpha-Lipoic Acid (thioctic acid) and the Risk of Insulin Autoimmune Syndrome

EFSA has launched an open consultation on its draft opinion on alpha-lipoic acid (ALA). Following a request from the European Commission, this document of the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) discusses data on the relationship between intake of alpha-lipoic acid (or thioctic acid) and the risk of insulin autoimmune syndrome (IAS) and investigates whether a dose may be set below which ALA added to foods is not expected to cause IAS in the general population or in vulnerable subgroups. This request refers to the procedure under Article 8 (2) of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods.

Interested parties are invited to submit written comments by 25 February 2021. Please use the electronic template provided to submit comments and refer to the line and page numbers. To submit additional data to support your comments or files, there is an upload feature available in the tool (for a maximum size of 1Mb file). Otherwise you can also contact the Nutrition Unit's functional mailbox nda_admin@efsa.europa.eu.

Please note that comments will not be considered if they:

- are submitted after the closing date of the consultation
- are presented in any form other than what is provided for in the instructions and template
- are not related to the contents of the document
- contain complaints against institutions, personal accusations, irrelevant or offensive statements or material
- are related to policy or risk management aspects, which are out of the scope of EFSA's activity.

EFSA will assess all comments which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA Panel and taken into consideration if found to be relevant.

Copyright-cleared contributions

Persons or organizations participating in a Public Consultation of EFSA are responsible for ensuring that they hold all the rights necessary for their submissions and consequent publication by EFSA. Comments should inter alia be copyright cleared taking into account EFSA's transparency policy and practice to publish all submissions. In case the submission reproduces third-party content in the form of charts, graphs or images, the required prior permissions of the right holder(s) should have been obtained by the PC respondent.

Publication of contributions

Contributions will be published and may be re-used by EFSA in a different context. It should be noted that contributions submitted by individuals in a personal capacity will be published as such, indicating the author's first and family name, unless a substantial justification for protection is provided by the respondent. Contributions submitted on behalf of an organisation are also made publicly available and attributed to the organization in question.

Appendix B – Full list of comments submitted by means of the electronic form on the EFSA website

Chapter name	Organisation	Comment
Abstract	Food Supplements Europe	Food Supplements Europe thanks EFSA for making available the opinion in advance to adoption and for the opportunity to provide further information and views. We strongly welcome this way of working which is highly transparent and ensures that no data or information are overlooked. We note that the scope of EFSA Scientific Opinion is not a full safety assessment of ALA but is only limited to the relationship between ALA intake and Insulin Autoimmune Syndrome (IAS, also known as Hirata disease). We recommend to state this clearly in the abstract. IAS is indeed a rare hypoglycaemic reaction akin to allergy that can occur in response to ALA. It is important to note that this is not dependent on the type of food supplements containing ALA but on factors of the individual (genotype, previous exposure to certain drugs, etc). We believe the opinion can gain more clarity by including or elaborating on three important aspects: 1. Incidence of ALA IAS cases in Europe 2. Elaboration of the mechanism of action 3. Analysis of the reported adverse effects These comments are inserted with reference to the sections and line numbers in the template.
Abstract	RIVM (National Institute for Public Health and the Environment)	RIVM would like to congratulate EFSA on the work that has been done. We also thank EFSA for the opportunity to provide comments on this draft opinion and hope to have provided a useful contribution in doing so. Page 1, line 25 (and Page 20, line 600): EFSA has not identified any evidence of a link between ALA naturally occurring in foods and IAS. In the remainder of the document, it is not described if and how this was studied. Could EFSA elaborate more on this?
1.4 Context of the assessment	Individual 1	In Italy, during the last 18 years, a conservative estimate from sell-out databases (limited to the pharmacy distribution, excluding selling via web or large distribution) suggests that around 4.000.000 boxes of dietary supplements containing alpha-lipoic acid were sold each year. Considering that a part of boxes contains 20 tablets and also assuming that all were consumed for a whole year by single subjects, based on the estimated number of adverse events registered by the Italian pharmacovigilance system during the same time period, we should have an expected rate of people experiencing any kind of suspected adverse events (not only Hirata syndrome) of 0.0029%, independently from the strength of association and of severity [1]. Considering these data only, the possibility to identify a single case of Hirata syndrome is extremely rare even if not detectable by the best pharmacovigilance systems. Even if a spontaneous undereporting could be suspected, this estimation is in line with what reported in the setting of randomized clinical trials, where the description of eventual side effects is

Chapter name	Organisation	Comment
		mandatory. In particular, a recent meta-analyses pooled data from 71 randomized clinical studies, comprising 155 treatment arms, which included 4749 subjects with 2558 subjects treated with ALA and 2294 assigned to placebo, where no incident case of Hirata syndrome was reported.[2] 1. Favari E, Grassi D, Cicero AFG. Interpreting data on alpha-lipoic acid safety considering the number of subjects exposed. Clin Nutr. 2021 Feb;40(2):654. doi: 10.1016/j.clnu.2020.12.003. 2. Fogacci F, Rizzo M, Krogager C, Kennedy C, Georges CMG, Kne_zevi_c T, et al. Safety evaluation of a-lipoic acid supplementation: a systematic review and meta-analysis of randomized placebo-controlled clinical studies. Antioxidants (Basel) 2020 Oct 19;9(10):1011. https://doi.org/10.3390/antiox9101011.
2.1 Data	RIVM (National Institute for Public Health and the Environment)	Page 7, line 275: Another protocol amendment (No 2) concerned signal data (published or unpublished) from vigilance databases that were originally planned to be retrieved in the protocol but were not used. Could EFSA add an explanation why these signal data were not used?
3.1 Identity of alpha-lipoic acid	RIVM (National Institute for Public Health and the Environment)	Page 8, line 316: The R-(+)-enantiomer is the naturally occurring form of ALA (Hermann et al., 2014). It can be synthesized in the body from octanoic acid and cysteine (Bilska and Wlodek, 2005), while the S-(–) form cannot (Ikuta et al., 2016). The S-(–) form is a synthetic product that forms during the industrial production of ALA (Yoon et al., 2016). Therefore, the Panel assumes that most industrially produced ALA is a racemic mixture. Could EFSA explain why it is assumed that most industrially produced ALA is a racemic mixture rather than the S-(-)form?
3.4 Absorption, distribution, metabolism and excretion of ALA	Food Supplements Europe	Lines 398-411: DHLA and ALA are interconvertible physiologically via metabolism as mentioned, so presence of DHLA as an impurity (as mentioned in 3.2) is potentially less important than actual measurements of DHLA in plasma if it needs to react with plasma insulin. We recommend that EFSA expands on the metabolism section on page 10 (lines 398-411) and evaluates any known ADME parameters around DHLA (particularly, do T1/2, plasma AUC, plasma cmax, % converted to DHLA exist?) following ALA ingestion as DHLA seems to be the moiety of interest.
3.5.2 Epidemiology of IAS	Food Supplements Europe	The opinion rightly notes that IAS is an extremely rare condition. We can complement this with data from Italy, a Member State with an important developed market for ALA containing food supplements. From available sales data, it is known that between 2011 and 2020, approximately 70 million boxes of food supplements containing ALA were placed on the market in Italy. Considering that a single person consumes about 4-5 boxes per year, it can be estimated that 12 million people have been exposed to ALA. EFSA reported 14 cases of IAS in Italy over 18 years.

Chapter name	Organisation	Comment
		This confirms that the condition is very rare even though observations of allele frequencies among European countries show that for HLA DRB 04:06 Italy is higher than most other countries with 1% of people carrying the allele. For HLA DRB 03:04 allele frequency in Italy is described as 1-3,2% which is similar to most other European countries (1). Adding the frequency of both alleles for Italy (1% + 3,2% = 4,2%) and comparing those 4,2% to the frequency of IAS (14 people out of 12 million) again underlines how rare this disease is and shows that genotyping of people might not be very helpful to predict the occurrence of IAS. In addition, since the ALA market in other Member States is not as developed as in Italy, the Italian figures cannot be extrapolated to other Member States, where the incidence is likely to be even lower. In some northern Member States, no cases of IAS have been reported, which is congruent with the observation that the genetic predisposition can be regional. Global figures on the low incidence rate of IAS in association with ALA, can be found in data from WHO Vigibase (2). According to a Vigibase data search, we found that there were only 4 reports of Insulin Autoimmune Syndrome out of the 8147 total reports for ALA. Approximately 0.049% of ALA reports are reportedly associated with IAS. The scope of the data is global and spans as far back as 1973. This search was carried out by using the term "alpha lipoic acid" (synonym of "thioctic acid"). In its protocol for the assessment of the relationship between intake of alpha-lipoic acid and the risk of insulin autoimmune syndrome in section 1.1.4 – What is the association between ALA and IAS in humans, EFSA lists two important questions, namely - Are there any additional reports in European Nutravigilance databases of European Member States or the EMA Eudravigilance database, not yet published in the literature? - Are there any cases of IAS reported in clinical trials? EFSA did not address these two questions in their opinion but focused on the documented case reports of IAS in humans that are available in literature. We suggest that EFSA revisits these questions and carries out a detailed analysis of European vigilance databases and the clinical trial literature to consider all available information and to gain a broader picture on the incidence of IAS in relation to ALA consumption. These are data that we do not have access to, but that can be obtained from national authorities. (1) Allele frequencies: http://allelefrequencies.net/hla6006a.asp?hla_locus_type=Classical&hla_locus=DRB1&hla_allele1=DRB1*04%3A03&hla_allele2=DRB1*04%3A03&hla_selection=&hla_pop_selection=&hla_population=&hla_country=&hla_dataset=&hla_region=Europe&hla_ethnic=&hla_study=&hla_order=order_1&hla_sample_size_pattern=equal&hla_sample_size=&hla_sample_year_pattern=equal&hla_sample_year=&hla_level_pattern=equal&hla_level=&standard=a&hla_show=

Chapter name	Organisation	Comment
		(2) http://www.vigiaccess.org
3.5.3 Genetic determinants of IAS	Food Supplements Europe	Lines 452-463: Section 3.5.3 says that "glutamine at position 74 in all three alleles and serine at position 37 (unique to DRB1*04:06) have been proposed to be responsible for this increased predisposition for developing IAS". This does not seem correct. Based on the citation, tracing backwards to the original publication (Uchigata 1995) indicates it is glutamate, not glutamine, that is required at position 74. (3) Based on the hypothesis in the point above, does the 04:15 allele that was seen several times in the summary table harbor the same GLU74 (the paper that found glu74 only looked at 04:03, 04:06, and 04:07)? If not, that means the mechanism needs more work. Could one bioinformatically predict potential for other genotypes to elicit IAS based on the GLU74, which could help drive downstream epidemiology estimations based on genotype (e.g., GLU74 vs non-GLU74). (3) Uchigata Y et al. Differential immunogenetic determinants of polyclonal insulin autoimmune syndrome (Hirata's disease) and monoclonal insulin autoimmune syndrome. Diabetes 1995 Oct; 44(10): 1227-1232
3.5.4 Pathophysiology of IAS	Food Supplements Europe	EFSA concludes that the ALA dose below which IAS is not expected to occur is likely to vary between individuals and cannot be determined based on the available data. We believe that there is more information available and recommend that EFSA expands and emphasizes the mechanistic underpinnings of IAS as it has implications for understanding whether ALA and other sulfhydryl compounds work through a threshold or non-threshold mechanism (to use traditional genotoxicity terminology). With the mechanism as reported, ALA could work in a non-threshold mechanism: 1 dihydrolipoic acid (DHLA) molecule could reduce 1 disulfide bond in an insulin molecule to linearize the insulin peptide and cause autoimmune binding to specific HLA-DRB1 gene products due to its increased affinity. This may have implications for other reducing agents consumed orally, like glutathione or methionine. As a consequence, we recommend EFSA adds or highlights the following: Lines 398-411: See comment included under section 3.4 Lines 476-480: Page 12, lines 476-480 say "It has been proposed that substances containing sulfhydryl groups may cleave the disulfide bonds between the insulin chains A and B…"; reviewing the citation, this does not seem entirely in support of the evidence. What Matsushita 1994 showed was the KKTSICSLYQLENY epitope on the A chain was what separated the selectivity in binding between 04:05 and 04:06. So they hypothesized that the cysteine in the TSICSLYQLENY, which participates in the intra-A disulfide bond, must be reduced by sulfhydryl compounds; they did not directly test or mention the interchain disulfide bonds

Chapter name	Organisation	Comment
		(A and B) as necessary to be reduced, although it may be implied. (4) Regardless, the text should mention the intra-A disulfide bond as a critical bond to reduce. Lines 452-463: See comment included under section 3.5.3 (4) Matsushita S et al. Allele specificity of structural requirement for peptides bound to HLA- DRB1*0405 and -DRB1*0406 complexes: implication for the HLA-associated susceptibility to methimazole-induced insulin autoimmune syndrome. J Exp Med. 1994 Sep 1; 180(3): 873–883
3.6 Summary of case reports linking ALA intake with IAS	Food Supplements Europe	Lines 578-581 Since predisposed individuals do not know they will experience the signs and symptoms, this presents a challenge to the risk managers to adequately contain the issue, given that the vast majority of the general population are not susceptible and thus, can take food supplements containing ALA in a safe way (5). (5) Fogacci F. et al. Safety Evaluation of a-Lipoic Acid Supplementation: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Clinical Studies. Antioxidants 2020, 9, 1011; doi:10.3390/antiox9101011 To help the risk managers to assess the impact of this condition, it would be good if EFSA would be able to draw more detailed conclusions from the analysis of the available data on - the seriousness of the observed adverse events - the reversibility of the signs and symptoms once consumption of ALA has been stopped. - What signs and symptoms would susceptible people need to observe in order to be advised to stop taking ALA (e.g. signs of serious low blood sugar, such as sweating, paleness, chills, headache, dizziness and/or confusion?) In particular relating to Table 1, we would recommend that EFSA addresses the below questions. Some descriptive statistics would help provide context on the risk in relation to doses taken: - No fatalities were reported? - Were permanent disabilities reported? - Were patients hospitalized, and for how long? - What is the proportion of the various signs and symptoms: loss of consciousness on the severe end vs sweating/weakness on the other? - Of all the cases in Table 1 where genotype was reported, can the proportion that had a known mechanistic allele vs an unknown mechanistic allele (e.g., predisposition alleles like 04:03 and 04:06 vs resistance alleles like 04:05) be summarised.

Chapter name	Organisation	Comment
		Is it possible that really the handful of alleles are all that is responsible, we know the required genotype (GLU74), and can predict all genotypes that would/could have a reaction? This would help to investigate the epidemiology of possible IAS responses.
3.6 Summary of case reports linking ALA intake with IAS	EHPM-European Federation of Associations of Health Product Manufacturers	Commenting on chapter 3.6, line 529, page 13: Alpha lipoic acid (thioctic acid) has been extensively used to improve neuropathic symptoms in diabetic patients. The studies with the acronym ALADIN (Alpha Lipoic Acid in Diabetic Induced Neuropathy) were conducted by the pharmaceutical industry. Dosages of 600 mg or 1200 mg were used. The study of Reljanovic et al.(1) shows that a treatment with ALA (thioctic acid) in diabetic patients did not cause serious side effects, such as hypoglycaemic episodes, which are common in people with IAS. The occurrence of IAS seems extremely rare and did also not occur in the researched populations in the meta-analysis of randomized controlled trials by Mijnhout et al.(2) Commenting on line 936, page 30: The study of Parente et al.(3) states: "Our study was carried out with 610 expectant mothers, and showed that ALA oral treatment is completely safe also during pregnancy. ALA was administered without interruptions up to six months at the dose of 600 mg per day. It did not bring out any adverse effect both in mothers and infants.". No adverse effects, like hypoglycaemic episodes, were reported in this study. See annex: (1) Reljanovic, M., et al. ""Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (α-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II)."" Free radical research 31.3 (1999): 171-179. Available here: https://www.tandfonline.com/doi/abs/10.1080/10715769900300721 (2) Mijnhout, Gerritje S., et al. ""Alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials."" International Journal of Endocrinology 2012 (2012). Available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3272801/ (3) Parente, E., et al. ""Safety of oral alpha-lipoic acid treatment in pregnant women: a retrospective observational study."" Eur Rev Med Pharmacol Sci 21.18 (2017): 4219-4227. Available here: https://pubmed.ncbi.nlm.nih.gov/29028075/
4. Conclusions	Uriach Consumer Healthcare S.L.	INTRODUCTION Recently, a safety concern has been raised about the possible association of insulin autoimmune syndrome (IAS) with the use of alpha-lipoic acid (ALA) in medicines and food supplements (DTU memo dated June 7th, 2016; Pharmacovigilance Risk Assessment Committee recommendations on signals, EMA/PRAC/590240/2015). Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the

Chapter name	Organisation	Comment
		relationship between intake of ALA and the risk of IAS. Section 4 (Conclusions) of this Draft Scientific Opinion of NDA mentions the limited availability of data on the risk associated with the development of IAS following consumption of ALA. Uriach Consumer Healthcare S.L. Spain (Uriach CHC Spain), a leading food supplement manufacturer and distributor in Spain, is currently marketing several products containing ALA in Spain. The aim of this document is to evaluate the safety data collected by the Corporate Vigilance System (CVS) of Uriach to aid in the characterization of the possible association between ALA and IAS, as well as to outline the opinion of Uriach Consumer Healthcare S.L. in this issue. DISCUSSION Based on the potential benefits and the good safety profile described for ALA, Uriach CHC Spain has been marketing in Spain since 2017 two different families of food supplements containing ALA in different presentations and concentrations: Tiobec and Sinopol. In these 4 years, Uriach CHC has sold to pharmacies a total of 142.433 packs of these products. Following the internal SOPs, at Uriach CHC Spain all the adverse events of the different types of products (drugs, medical devices, cosmetics or food supplements) are processed in the same way and all their safety information is centralized in a Corporate Vigilance System (CVS) that receives, analyzes and performs the follow-up of all these events. Regarding the post-marketing experience since the Uriach CHC Spain products containing ALA (Tiobec and Sinopol) were first commercialized, and up to 15 February 2021, only one adverse event has been received. The case corresponds to an adverse reaction to Tiobec 400 in a female consumer (Localized Itching/Pruritus) that bears not apparent relation with IAS. In addition to Uriach CHC, several other companies commercialize ALA in Spain, and more than 1 million units were sold to consumer in pharmacies in the past 4 years (HMR, 2001, sell-out data, Spain, pharmacy channel). No cases of IAS associated to ALA consumption were found in Spain in a dedicated search of the scientific literature in that period, and only one previous case in 2015, already cited in the NDA draft opinion, has been reported (ref. Michalopoulou, 2015, in the NDA draft opinion). Taken together, our internal sales data and the supportive data coming from global ALA market sales to consumer in Spain, as well as reported cases in the literature, did not permit to identify any signal or concern regarding a major incidence of IAS by ALA in Spain. CONCLUSIONS 1. Alpha-lipoic acid has been widely used as food supplement, showing a good safety profile. 2. Uriach CHC has been marketing two different families of products including alpha-lipoic acid as one of the components in their formulation since 2017: Tiobec and Sinopol. 3. In the post marketing surveillance activities of these products, only one case including one adverse reaction without relation to IAS has been reported. 4. To date, both products, Tiobec and Sinopol, have shown a positive safety profile and no case of IAS has been received at Uriach CHC Spain with these products.
5. Uncertainties	Individual 1	The commission should have a really hard job in creating a warning on the use of alpha-lipoic acid as related to Hirata syndrome. In fact, we could have very similar conditions when considering the risk of hemochromatosis in subjects genetically sensible to iron supplementation, or the risk of Wilson Syndrome in those sensible to cupper supplementation, or also the risk to develop early and severe atherosclerosis in subjects affected by Familial Sitosterolemia assuming foods enriched with phytosterols. All

Chapter name	Organisation	Comment
		these conditions are very rare, usually dangerous and related to specific genetic patterns, and their clinical impairment could be related to the exposition to very common dietary supplements (iron, cupper, phytosterols, as examples of supplements whose use is perhaps supported by EFSA health claim).
6. Recommendation	EHPM-European Federation of Associations of Health Product Manufacturers	To inform the small population group at risk which in rare cases can have symptoms associated with the insulin autoimmune syndrome at postprandial hypoglycemic episodes, the following label warning could be made mandatory: ""Stop using the product and consult a healthcare professional, if you experience symptoms of low blood sugar, such as sweating, paleness, chills, headache, dizziness and/or confusion."". This procedure is already successfully in action via the Marketed Health Products Directorate in Canada for ALA Health Products since 30.06.2016 (see annex 4 & 5) (4) Summary Safety Review-Alpha Lipoic Acid Assessing the Potential Risk of Low Blood Sugar (Hypoglycemic Episodes) (5) Health Product Info Watch with the review article: Alpha-lipoic acid and serious hypoglycemic episodes
Other comments	EHPM-European Federation of Associations of Health Product Manufacturers	IQVIA Market Data on sales quantity of Alpha Lipoic Acid for Italy from 2018-2020. MAT July 2020* Year 2018: Unit Sold**: 4.967.989 Year 2019: Unit Sold**: 5.075.496 Year 2020: Unit Sold**: 4.915.175 Total 2018-2020: Unit Sold**: 14.958.660 C.A.G.R % * : 2020 vs 2018: -0,5% * MAT: Moving Annual Total, C.A.G.R.: Compound annual growth rate ** Absolute quantities of sales from wholesaler to pharmacies ('Sell out'). These numbers refer to units (packages which contain in general 20 or 40 servings). In general, these products are used daily, at doses ranging from 100-600 mg, for 2-4 weeks, 2-3 times per year. Based on current data we can not confirm the total number of individual doses used per year yet. The EFSA opinion indicates a total of 6 cases of IAS reported between 2018-2020 (5 Caucasian and 1 Asian subject, p.17-18). The the total units sold in Italy alone over these 3 years is nearly 15 million. Do to the very limited time constraints we have not been able to collect similar data for other Member states. A view on the total number of units sold and number of consumers would certainly put the very small incidence of IAS further into perspective.

Chapter name	Organisation	Comment
		(6) Recently published study: Fogacci F, Rizzo M, Krogager C, Kennedy C, Georges CMG, Knežević T, Liberopoulos E, Vallée A, Pérez-Martínez P, Wenstedt EFE, Šatrauskienė A, Vrablík M, Cicero AFG. Safety Evaluation of α-Lipoic Acid Supplementation: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Clinical Studies. Antioxidants (Basel). 2020 Oct 19;9(10):1011. doi: 10.3390/antiox9101011. PMID: 33086555; PMCID: PMC7603186. Available at https://pubmed.ncbi.nlm.nih.gov/33086555/ This meta-analysis of extracted data suggested that supplementation with ALA was not associated with an increased risk of any treatment-emergent adverse event (all p > 0.05).
Supporting documents attached to comments	Alfasigma	see SUPPORTING INFORMATION **Lipoic_Acid_EFSA_Public_consultation**
Supporting documents attached to comments	EHPM-European Federation of Associations of Health Product Manufacturers	Reljanovic, M., et al. ""Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (α-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II)."" Free radical research 31.3 (1999): 171-179. Available here: https://www.tandfonline.com/doi/abs/10.1080/10715769900300721 Mijnhout, Gerritje S., et al. ""Alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials."" International Journal of Endocrinology 2012 (2012). Available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3272801/ Parente, E., et al. ""Safety of oral alpha-lipoic acid treatment in pregnant women: a retrospective observational study."" Eur Rev Med Pharmacol Sci 21.18 (2017): 4219-4227. Available here: https://pubmed.ncbi.nlm.nih.gov/29028075/ Summary Safety Review - Alpha Lipoic Acid - Assessing the Potential Risk of Low Blood Sugar (Hypoglycemic Episodes). 2016. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-alpha-lipoic-acid-assessing-potential-risk-low-blood-sugar-hypoglycemic.html Health Product Info Watch – June 2016 https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/health-product-infowatch-june-2016.html Fogacci F, Rizzo M, Krogager C, Kennedy C, Georges CMG, Knežević T, Liberopoulos E, Vallée A, Pérez-Martínez P, Wenstedt EFE, Šatrauskienė A, Vrablík M, Cicero AFG. Safety Evaluation of α-Lipoic Acid Supplementation: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Clinical Studies. Antioxidants (Basel). 2020 Oct 19;9(10):1011. doi: 10.3390/antiox9101011. PMID: 33086555; PMCID: PMC7603186. Available at https://pubmed.ncbi.nlm.nih.gov/33086555/

Chapter name	Organisation	Comment
Supporting documents attached to comments	Uriach Consumer Healthcare S.L.	see SUPPORTING INFORMATION **Uriach_CHC_Position_Statement_Lipoic_Acid_AIS**