Draft scientific opinion on the relationship between intake of alpha-lipoic acid (thioctic acid) and the risk of insulin autoimmune syndrome

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Abstract

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 relationship between intake of alpha-lipoic acid (ALA, or thioctic acid) and the risk of insulin autoimmune syndrome (IAS). The Panel was also asked to provide advice on the dose 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. There is no pre-established rule for the evaluation of the safety of foods/substances when classical toxicity tests cannot be used for the assessment, such as for autoimmune diseases. The scientific opinion is based on published scientific evidence retrieved through comprehensive literature searches, in particular 49 case reports on the consumption of ALA and the development of IAS. The Panel concludes 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. The plausible mechanism by which ALA may increase this risk has not yet been fully elucidated. EFSA has not identified any evidence of a link between ALA naturally occurring in foods and IAS. The individuals carrying the relevant polymorphisms cannot be readily identified without genetic testing. Based on the limited data available and the low prevalence of IAS in Europe the risk associated with the development of IAS following consumption of ALA cannot be quantified precisely neither for the general population overall nor for sub-groups or individuals with genetic susceptibility. An 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.

Keywords

Alpha-lipoic acid, insulin autoimmune syndrome, comprehensive literature search, genetic determinants, case report, food supplement

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1 Introduction

1.1 Background

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[1] 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[2], and in an expert opinion on the safety of placing dietary supplements with alpha-lipoic acid on the market for the general population[3] 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.

1.2 Terms of Reference as provided by the requestor

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.

1.3 Interpretation of the Terms of Reference

The Panel understands that it is expected to provide information on the relationship between oral consumption of alpha-lipoic acid (ALA) that is added to food, including food supplements, and insulin autoimmune syndrome (IAS).

The Panel is also expected to provide advice on the dose below which ALA added to foods is not expected to cause IAS in the general population or in vulnerable subgroups thereof.

In line with the mandate, it is out of the scope to review possible adverse effects other than IAS associated with the oral consumption of ALA.

Also out of scope of the mandate are the assessment of metabolic/beneficial effect(s) of oral consumption of ALA, a risk-benefit analysis of ALA supplementation, and an exposure assessment of ALA in the European population.

1.4 Context of the assessment

Article 8 of Regulation (EC) No 1925/2006 provides for a procedure for the regulatory management of substances other than vitamins or minerals added to foods that may present a potential risk to consumers. Upon its own initiative or on the basis of information provided by Member States, the European Commission may ask EFSA for a scientific assessment of the

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

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

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

safety of such a substance[4]. On the basis of EFSA's assessment, the European Commission together with Member States may decide either to allow the use of the substance (with or without restrictions) in food, to prohibit the use of the substance in food, or to put the substance under scrutiny.

1.5 Previous assessments

ALA is used as an active ingredient in medicinal products mainly for the treatment of diabetic neuropathy. It is also available as a food supplement.

Several scientific bodies in the area of food or medicinal product have published scientific assessments on ALA within the European Union (EU), in particular in relation to the risk of IAS, that are summarised in chronological order below.

In 2008, the **French Food Safety Agency** (AFSSA, 2008) (now called ANSES) published an opinion on a draft regulatory text from the French risk management authorities, about the use of substances with nutritional or physiological effect and plants or plant preparations in food supplements. Several substances were considered, including ALA, for which no maximal dose was proposed in the draft regulatory text. The French Food Safety Agency discussed amongst others a paper describing an acute and a sub-acute toxicity study in rats (Cremer et al., 2006b). Regarding data in humans, the French Food Safety Agency reviewed references on tolerance of ALA treatment for patients with diabetic neuropathy and three published case reports of IAS (Furukawa et al., 2007; Ishida et al., 2007; Takeuchi et al., 2007). Overall, it concluded that the risk of occurrence of this syndrome following consumption of ALA cannot be excluded, but the risk is very low in the French population. Similar considerations were repeated in another opinion of the French Food Safety Agency in 2011 on the assessment of the risks associated with substances with nutritional or physiological effects with a view to restricting or prohibiting their use in foodstuffs (ANSES, 2011).

The **Superior Health Council of Belgium** (2015) noted that ALA may be sold as a medicinal product (e.g. in Germany) used for the treatment of diabetic neuropathy, and that adverse effects of treatment with this substance have been observed without further details in the report. The Council recommended that ALA should be used as a medicinal product instead of a food supplement and consumed under medical supervision (as ALA was available as food supplement in Belgium at the time when these conclusions were drawn).

The **Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency** (EMA) published in 2015 recommendations for an update of the product information for medicinal products containing thioctic acid (a synonym for ALA) and occurrence of IAS (EMA, 2015). It was explained that the summary of product's characteristics should be updated to indicate the following:

- Under 'special warnings and precautions for use'

  *'Cases of Insulin Autoimmune Syndrome (IAS) have been reported during treatment with thioctic acid. Patients with human leukocyte antigen genotype such as HLA-DRB1*04:06 and HLA-DRB1*04:03 alleles, are more susceptible to develop IAS when treated with thioctic acid. HLA-DRB1*04:03 allele (susceptibility to IAS odds ratio: 1.6) is especially found in Caucasians, with a higher prevalence in southern than in northern*

[4] To date EFSA has delivered five scientific opinions in the context of Article 8(2) of Regulation (EU) No 1925/2006, i.e. Scientific Opinions the safety of 1) Ephedra species, 2) Yohimbe (Pausinystalia yohimbe (K. Schum.) Pierre ex Beille, 3) hydroxyanthracene derivatives, 4) green tea catechins, and 5) monacolins in red yeast rice:
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3467
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3302
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5090
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5239
https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5368

*Europe and HLA-DRB1*04:06 allele (susceptibility to IAS odds ratio: 56.6) is especially found in Japanese and Korean patients.*

IAS should be considered in the differential diagnosis of spontaneous hypoglycaemia in patients using thioctic acid […].'

- Under 'undesirable effects'

'*Immune system disorders*

Frequency unknown: insulin autoimmune syndrome'

Also, it was recommended that the package leaflet should indicate the following:

- '*Patients with a certain human leukocyte antigen genotype (which is more frequent in Japanese and Korean patients, but is also found in Caucasians) are more prone to development of insulin autoimmune syndrome (disorder of the blood glucose regulating hormones with pronounced lowering of blood sugar levels) when treated with thioctic acid.*'

In 2017, the **Danish National Food Institute (DTU)** (DTU Food, 2017) described a number of adverse effects other than IAS related to the consumption of ALA by humans, such as allergic skin reactions, stomach ache, nausea, vomiting, diarrhoea and dizziness. DTU discussed a paper describing an acute and a sub-acute toxicity study in rats (Cremer et al., 2006b) as well as another paper on a chronic toxicity study also in rats (Cremer et al., 2006a). From these studies on endpoints unrelated to IAS, DTU concluded that '*a dose of 60 mg alpha-lipoic acid per kg body weight per day is considered a no observed adverse effect (NOAEL)'*. Using an uncertainty factor of 100 to take into account inter and intra-species variability, DTU derived from the NOAEL '*an upper limit of safe intake of alpha-lipoic acid'* of *'0.6 mg/kg body weight per day'*, corresponding to '*a maximum daily dose of 42 mg alpha-lipoic acid for a person weighing 70 kg*'. This NOAEL did not apply to the risk of developing IAS. In this relation, DTU mentioned that '*it is known that alpha-lipoic acid can cause insulin autoimmune syndrome'*, and that '*since it is an immunological response (autoimmune response), it is assumed that the dose consumed does not play a crucial role in the development of the disease'*. DTU also discussed data on the '*strong genetic element in the development of IAS'*. Finally, DTU stated the following: '*Based on a calculated upper safe intake of 42 mg alpha-lipoic acid per person per day determined from two rat studies and a general risk of increased incidence of IAS (irrespective of dosage level and due to increased exposure of the population), DTU FOOD concludes that a supplement with a recommended daily intake of 150-200 mg alpha-lipoic acid (as proposed by the applicants) gives rise to safety concern'*.

2 Data and Methodologies

2.1 Data

For this scientific assessment, a protocol (Appendix B) has been developed in line with existing methodology (EFSA, 2020)[5].

This Scientific Opinion is based on data that were retrieved through comprehensive literature searches in Embase and PubMed on 04 September 2020 for relevant publications in one of the EU languages. The Panel is aware that case reports published only in non-European languages were not taken into account in the assessment. However, the Panel considers, in view of the previous assessments conducted by other bodies, and the number of published

[5] http://www.efsa.europa.eu/en/supporting/pub/en-1843

case reports identified in EU languages for this assessment, that such an exclusion did not impact the overall assessment and conclusions.

The searches were conducted without applying limits to the date of publication. The database searches were complemented by searches on websites of relevant institutions and authorities, such as the US Food and Drug Administration (FDA), Health Canada, or Food Standards Australia New Zealand (FSANZ). The hits on these websites were added to the ones obtained from the databases and used in particular for the general sections of this opinion.

Three searches were set up. Only data in humans were considered for this assessment, as no animal or *in vitro* model of IAS was identified.

1. Through search 1, EFSA retrieved case reports published in peer-reviewed journals of IAS associated with ALA consumption. In some instances, these case reports were accompanied by reviews of the evidence. The information provided in the review section of these papers were also considered.
2. The purpose of search 2 was to retrieve literature reviews on IAS.
3. Search 3 was focussed on retrieving clinical trials in which ALA was administered either alone or in combination. The original aim of search 3 was to identify clinical trials in humans in which IAS or symptoms indicative of IAS have been reported as adverse effects. Following a protocol amendment (No 1), search 3 was only used to retrieve pharmacokinetic studies in humans as well as studies specifically designed to investigate safety of ALA in humans. While relevant pharmacokinetic studies were identified, no relevant safety studies were found. The list of references of the retrieved studies were screened for additional publications. Some reviews that were found in search 3 were kept as background information and were also used in the opinion.

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.

The title and abstract screening was carried out in duplicate in Distiller SR®. Title and abstract screening was done by EFSA staff members in parallel. Full text screening was performed by a single EFSA staff member (protocol amendment No 3). Data from case reports were extracted in tabular format in Microsoft Excel® by one EFSA staff member and double-checked by another.

While all pertinent case reports have been included in the assessment, data coming from reviews and pharmacokinetic studies were only described as appropriate. Previous assessments from other scientific bodies were used for hand search in their lists of references, applying the inclusion criteria of the present assessment.

No author was contacted to collect missing information.

The PRISMA flow-charts of the three searches are included in Appendix A.

The eligibility criteria of the searches are reported in the protocol as Appendix B of this Scientific Opinion.

2.2 Methodologies

There is no pre-established rule for the evaluation of the safety of foods/substances in cases where classical toxicity tests cannot be used as a basis of the assessment, such as for autoimmune diseases. There is no guidance document available on how to perform such an assessment. In the present case, the Panel relied on published case reports that linked the consumption of ALA to the development of IAS.

In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments from the scientific community and stakeholders, this draft opinion is released for public consultation.

2.3 Protocol amendments

1. Search 3 was only used to retrieve pharmacokinetic studies in humans as well as studies specifically designed to investigate safety of ALA in humans instead of all clinical trials conducted with ALA in humans.
2. Signal data from vigilance databases were not used in the assessment.
3. Full text screening was done by a single EFSA staff member instead of performing it in duplicate.
4. ALA analogues, derivatives or metabolites were not included in the assessment, as no case report was retrieved in which an ALA analogue, derivative or metabolite was linked to the development of IAS.

3 Assessment

3.1 Identity of alpha-lipoic acid

ALA (also called thioctic acid, $C_8H_{14}O_2S_2$, CAS Number: 1077-28-7, IUPAC name: 5-[(3R)-1,2-dithiolan-3-yl]pentanoic acid, molecular weight 206.3 g/mol) is an eight-carbon fatty acid (Evans et al., 2002) that has a chiral centre in its 1,2-dithiolane ring (Ikuta et al., 2016). Therefore, ALA exists in the form of two enantiomers: R-(+) and S-(–). 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.[6]

R-(+)-ALA *S*-(–)-ALA

Figure 1 Stereochemistry of alpha-lipoic acid

[6] https://lpi.oregonstate.edu/mic/dietary-factors/lipoic-acid

3.2 Source, production process, stability and type of formulations available

In its natural form, ALA occurs in foods of animal and plant origin, with the highest content in tissues with a high metabolic activity such as the heart and lower contents in muscle tissue. For example, pig hearts contain 1.1-1.6 mg/kg and calf muscles 0.07-0.15 mg/kg ALA (Biewenga et al., 1997).

For the industrial production, several ways exist to produce ALA synthetically, as reviewed by FDA (Zhang et al., 2018). In particular, one high-yield, efficient synthetic production process is cited in which dihydrolipoic acid, containing two sulfhydryl groups (see Section 3.5.4), and finally ALA are produced from cyclohexanone, vinyl ethyl ether and thiourea. Dihydrolipoic acid can be a residue of the ALA synthesis or generated from the photolysis of ALA. FDA states that impurities from the production process likely include, apart from dihydrolipoic acid, oligomers from its polymerisation and trace amounts of solvents and reagents. The European Pharmacopoeia monograph (Ph. Eur. 10.0, 4020-4021) identifies as specified impurities 5-[(4Rs)-1,2,3-trithian-4-yl]pentoic acid and α-hydro-ω-hydroxypoly[sulfanediyl(3-sulfanyl-8-oxooctane-1,8-diyl)], the latter being a mixture of ALA polymers. Limits for these substances are set in the European Pharmacopoeia based on comparison with reference substances. No information was found in the retrieved literature on potential contamination or adulteration of ALA containing products (see Appendix B, Section 1.1).

ALA is light- and heat-sensitive. The FDA review concluded that it is likely to be stable in solid formulations when protected from light and heat, but less stable in liquid formulations. The R-(+) form is less stable than the racemic mixture (Zhang et al., 2018).

The Superior Health Council of Belgium (2015) reports that ALA as food supplement is mainly sold in tablet or capsule form with recommended intakes usually between 300 and 600 mg/day.

The Panel notes that in the retrieved evidence there was no information on whether production processes used to produce food-grade ALA substantially differ from those used to produce ALA for use in medicinal products, or whether impurities or degradation products may be different in nature or amount between food supplements and medicinal products. However, considering that IAS has been observed in conjunction with the intake of ALA as food supplement and with its intake as medicinal product, the Panel considers that, even if compositional differences in terms of impurities or degradation products may have been present, these were unlikely to play a role in the development of IAS (see Appendix B).

3.3 Biochemistry

ALA is present in all prokaryotic and eukaryotic cells. Together with its reduced form, dihydrolipoic acid, it acts as a redox couple (Biewenga et al., 1997). ALA is covalently bound to a lysine of the E2 (dihydrolipoate acyltransferase) subunit of several 2-oxo acid dehydrogenase multienzyme complexes (Teichert et al., 2003; Mignini et al., 2011) and acts as a cofactor that catalyses oxidative decarboxylation of pyruvate, α-ketoglutarate and branched-chain α-ketoacids, formed during transamination of leucine, isoleucine and valine. ALA is also an element of a mitochondrial complex involved in glycine synthesis and degradation (Bilska and Wlodek, 2005). ALA is found both in hydrophilic (cytoplasm, extracellular matrix) and hydrophobic (plasma membranes) environments (Brufani and Figliola, 2014).

3.4 Absorption, distribution, metabolism and excretion of ALA

It has been suggested that R-(+)-ALA from natural sources is absorbed as lipoyllysine[7] and is then not found unbound in humans. On the contrary, supplemental ALA is absorbed as such and then found in its free form in the circulation (Biewenga et al., 1997).

Supplemental ALA is readily absorbed. No information was found on the potential mechanisms of absorption (i.e. passive or active absorption) or on a potential interaction with other substances. In the fasting state, several studies report mean time to maximum plasma concentrations (T_{max}) in adults mostly in the range of 0.5 to 1.0 hour for both enantiomers (Gleiter et al., 1996; Hermann et al., 1996; Teichert et al., 1998; Breithaupt-Grögler et al., 1999; Evans et al., 2002; Hermann et al., 2014; Zheng et al., 2014; Rhee et al., 2018). Mignini et al. (2007) found a mean T_{max} of up to 2 hours, depending on the formulation (i.e. solid or liquid). In the fed state, absorption is delayed. Gleiter et al. (1996) observed mean T_{max} of about 2.5 hours and 1 hour in the fed state and in the fasting state in the same subjects, respectively. Liquid formulations seem to be absorbed more rapidly than solid formulations (Hermann et al., 1996; Hermann et al., 2014).

R-(+)-ALA is generally more bioavailable than the S-(-) form (Gleiter et al., 1996; Hermann et al., 1996; Breithaupt-Grögler et al., 1999; Hermann et al., 2014). Breithaupt-Grögler et al. (1999) reported 40-50% more bioavailability of R-(+)-ALA, and Hermann et al. (2014) a bioavailability of R-(+)-ALA that is twice that of the S-(-) form. It has been speculated that this difference might be attributed to different intestinal uptake mechanisms between R-(+)-ALA and S-(-)-ALA (i.e. active, transporter-mediated absorption for the R-(+)-form vs passive or less effective active absorption for the S-(-) form) (Hermann et al., 2014).

Hermann et al. (2014) observed that, after body weight normalisation of data, ALA was consistently more bioavailable in females than in males (n=12 per sex) both for R-(+)-ALA and S-(-)-ALA. Area under the curve (AUC) outcomes were on average 40% higher in females compared with males. Differences in T_{max} and C_{max}, although higher in females, did not reach statistical significance. This sex-specific effect was consistent for all formulations studied (i.e. liquid and various doses of solid formulations).

Pharmacokinetic parameters have been demonstrated to react in a linear and proportional dose-dependent manner in the dose range of oral intakes of ALA of 50-600 mg (Breithaupt-Grögler et al., 1999).

ALA is rapidly removed from circulation. The mean half-life of ALA in plasma is generally described to be about 30 minutes (Hermann et al., 1996; Biewenga et al., 1997; Teichert et al., 1998; Breithaupt-Grögler et al., 1999; Teichert et al., 2003; Zheng et al., 2014; Rhee et al., 2018), though Mignini et al. (2007) reported a mean half-life of around 6 hours. Breithaupt-Grögler et al. (1999) found that there was no difference in half-life between R-(+)-ALA and S-(-)-ALA. A significant first pass effect (Teichert et al., 2003; Zhang et al., 2018), in which total plasma clearance of ALA is in the same range as the plasma flow in the liver, is responsible for the relatively low bioavailability of around 20-40%, depending on the isomer and the formulation (i.e. liquid or solid) (Biewenga et al., 1997; Teichert et al., 2003). Following absorption, ALA is taken up into cells (Bustamante et al., 1998) and reduced to dihydrolipoic acid and both are predominantly metabolised via β-oxidation and excreted in the urine mainly in the form of metabolites, such as 4,6-bis(methylthio)hexanoic acid (Teichert et al., 2003; Zhang et al., 2018). 4,6-Bis(methylthio)hexanoic acid is also the main metabolite in plasma (Teichert et al., 1998).

[7] i.e. bound to the amino acid lysine

3.5 Insulin autoimmune syndrome (IAS)

3.5.1 Definition of IAS

IAS is a medical condition which is caused by an autoimmune reaction and characterised by high titres of insulin autoantibodies (IAA), a marked increase in total serum insulin and free insulin concentrations often within the normal range (Archambeaud-Mouveroux et al., 1989). C-peptide and proinsulin concentrations are either elevated or within the normal range (depending partly on whether IAA are also able to bind C-peptide and proinsulin and partly on the laboratory assay used) (Censi et al., 2018b). IAS was classically considered to occur in individuals that have not been exposed to exogenous insulin, even though more recently some cases of IAS in diabetic subjects having received exogenous insulin have been reported (Cappellani et al., 2020).

Antibodies are mostly polyclonal IgG with kappa light chains (Cooper, 1999) and to a minor extent with lambda light chains. However, the presence of IgA, IgM and monoclonal IgG has also been described (Archambeaud-Mouveroux et al., 1989; Censi et al., 2018b).

3.5.2 Epidemiology of IAS

IAS is relatively rare: in a survey in all hospitals with more than 300 beds in Japan (Yamada et al., 2020), conducted in the years 2017-2018, 22 cases of IAS (of all causes) were identified, out of 785 patients with endogenous hyperinsulinaemic hypoglycaemia who required treatment (i.e. 2.8%). Based on the assumption that these 22 IAS cases were all cases that had occurred in Japan in the years 2017-2018, the authors calculated an incidence of IAS in the general population in Japan of 0.017 cases per 100.000 inhabitants in these years. In an older study (Takayama-Hasumi et al., 1990), conducted from 1979 to 1981 also in Japan, IAS was identified as the third cause (11.7% of the cases) of severe hypoglycaemic attacks presenting to the hospitals other than the administration of oral hypoglycaemic agents or insulin preparations.

The incidence of IAS in Caucasians seems to be lower than in the Japanese population (Cappellani et al., 2020). However, the number of case reports regarding Caucasians has been increasing in recent years (Bresciani et al., 2011; Gullo et al., 2014; Michalopoulou Alevras et al., 2015; Lio et al., 2016; Ferreira et al., 2017; Bolayir et al., 2018; Cappellani et al., 2018; Veltroni et al., 2018; Alagüney et al., 2019; Moffa et al., 2019; Cambria et al., 2020; Okuroglu et al., 2020; Yukina et al., 2020). It is, however, difficult to estimate the actual prevalence or conclude on a true increase in the disease incidence among Caucasians, because of a possible underestimation of the occurrence of the syndrome linked to a possible unawareness of the disease and its subsequent underdiagnosis (Cappellani et al., 2020).

3.5.3 Genetic determinants of IAS

The presence of the Human Leukocyte Antigen HLA-DR4 (Uchigata et al., 2010), and in particular the alleles DRB1*04:06 (most of the Asian cases), DRB1*04:03 (most of the Caucasian cases) and DRB1*04:07 (Patel et al., 2020) and to a lesser extent DRB1*04:15 (Cappellani et al., 2018; Cambria et al., 2020) are associated with an increased risk of developing the disease.

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 (Yukina et al., 2020). DRB1*04:03 can be considered as the ancestral allele from which DRB1*04:06 and DRB1*04:07 developed independently by nucleotide substitution or by gene conversion (in case of DRB1*04:07) (Uchigata et al., 2000).

As reported in the Allele Frequency Net Database (Gonzalez-Galarza et al., 2019)[8], DRB1*04:03 was found to occur in various populations worldwide.[9] In populations living in Europe, the frequency is reported to range from 0.4-3.9% (data from Austria (1.5%), Germany (0.6-1.8%), Greece (6%), Ireland (0.4%), Italy (1.0-2.1%), the Netherlands (2.2%), Slovenia (0.7-1%), Spain (3.1-4%), UK (0.7-3.9%), Poland (1.3%) (Gonzalez-Galarza et al., 2019) and France (1.9%) (Uchigata et al., 2000). In comparison, in Japan and South Korea the prevalence is 1.6-12.3% (Uchigata et al., 2000; Gonzalez-Galarza et al., 2019).

DRB1*04:06 is mostly present in East Asian populations (e.g. prevalence in Japan between 5.3-13.2%), while in Europe it is between 0.1-1% (data from studies in Italy (1%), the Netherlands (0.2%), Spain (0.5-0.6%), Poland (0.1%) (Gonzalez-Galarza et al., 2019) and France (0.3%) (Uchigata et al., 2000).

The prevalence of DRB1*04:07 in Europe has been observed to be in the range of 0.5-3.4%; in Japan and South Korea it is 0.3-2.8% (Uchigata et al., 2000; Gonzalez-Galarza et al., 2019).

3.5.4 Pathophysiology of IAS

IAS has been described as an autoimmune disease mainly associated with intake of substances that contain a sulfhydryl group (such as methimazole or dihydrolipoic acid; see Section 3.2). IAS can also be triggered by viral infections and, in some cases, the trigger cannot be identified. It may also occur together with other autoimmune diseases (Archambeaud-Mouveroux et al., 1989).

It has been proposed that substances containing sulfhydryl groups may cleave the disulfide bonds between the insulin chains A and B which would make the endogenous insulin more immunogenic (Cappellani et al., 2020). The resulting peptides have been shown to bind to gene products of DRB1*04:06. This leads to the insulin-specific proliferation of T cells (Ito et al., 1993), and the subsequent production of IAA by B cells.

Wasada et al. (1988) performed a study in which methimazole was incubated together with biosynthetic recombinant human insulin. The insulin appeared not to be structurally changed, although the authors did not directly investigate cleavage of disulphide bonds. Even if *in vitro* antibody binding of insulin that had been incubated with methimazole was not observed, the Panel notes that this does not allow to conclude on the ability of the incubated insulin to induce the production of IAA.

Most authors hypothesise that IAA bind to endogenous insulin that is released from beta-cells in response to a glucose stimulus. Insufficient free insulin is therefore available, causing a temporary hyperglycaemia. This hyperglycaemia stimulates insulin secretion further. When the IAA-insulin complexes dissociate post-prandially, biologically active insulin is released into circulation, resulting in an excess of insulin and a subsequent hypoglycaemia (Ismail, 2016; Censi et al., 2018a; Cappellani et al., 2020). Hypoglycaemia typically occurs within 2-6 hours post-prandially with varying severity, as the half-life of insulin in IAS is increased from minutes to hours. The severity of hypoglycaemia depends on the antibody characteristics (i.e. binding capacity and affinity that determines the dissociation rate) and their titres (Ismail, 2016). High capacity/low affinity antibodies are more likely to cause hypoglycaemia (Redmon and Nuttall, 1999).

To investigate this hypothesis, Dozio et al. (1998) administered ^{125}I-labelled insulin intravenously to a patient with IAS and a healthy volunteer. In the healthy subject, radio-labelled insulin was quickly removed from plasma and taken up by the liver and the kidney. In the patient, radioactivity remained in the blood with hardly any uptake in the liver and kidney; 93.6% of the radioactivity was bound to antibodies.

[8] http://www.allelefrequencies.net/

[9] As case reports on IAS associated with ALA are mainly available for Europe as well as Japan and South Korea, allele frequencies are only reported for these two regions

It has been reported that, in some parts of the population, IAA are present in serum and are not associated with adverse effects. For example, Sodoyez et al. (1990) reported the presence (> mean + 3SD) of IAA in 1% of 2,200 healthy blood donors. Hattori et al. (2014) found IAA in 2.7% (of 263) of type 2 diabetics never having received insulin. Cooper (1999) cited a study in which 6% (of 206) of patients treated with methimazole (a substance associated with an increased risk of developing IAS) had IAA without developing symptoms of IAS. In that study, IAA insulin-binding capacity was lower than usually observed in IAS; the IAA concentrations peaked 2-3 months after methimazole administration and declined thereafter to almost undetectable levels. In addition, Cooper (1999) mentioned another report in which also 6% (of 95) patients treated with methimazole or carbimazole had IAA. The Panel notes that this indicates that IAA with different affinities exist. Another possible explanation could be that there is a threshold below which IAA do not cause adverse effects.

The Panel notes that there is a plausible mechanism by which ALA may increase this risk of developing IAS in individuals with certain genetic polymorphisms. However, this mechanism has not yet been fully elucidated.

3.5.5 Symptoms of IAS

IAS is most often associated with post-prandial hypoglycaemia (Okuroglu et al., 2020). Symptoms are of neuroglycopenic (e.g. behavioural changes, confusion, fatigue, seizures and loss of consciousness), neurogenic (e.g. palpitations, tremor, anxiety) or cholinergic (e.g. sweating, hunger, paresthesia) nature (Davi et al., 2017; Censi et al., 2018b). Symptoms usually resolve with food intake. Fasting hypoglycaemia occurred in only a few cases (Cappellani et al., 2020).

IAS usually resolves within a few months once the trigger (see Section 3.5.4) is removed (hence the symptoms disappear). However, a certain percentage of patients will require pharmacological treatment (Cappellani et al., 2020). When the trigger is re-introduced, the syndrome may reappear (Bae et al., 2013); see Table 1.

3.6 Summary of case reports linking ALA intake with IAS

From the comprehensive literature search, 49 cases of IAS linked to the consumption of ALA as medicinal product or as food supplement were retrieved that were published as case reports or part of reviews in English language (see Table 1). Case reports only published in non-European languages were not considered as part of this Opinion (see Section 2.1.). In all cases, authors confirmed that circulating IAA were present. However, in the case report series described by Gullo et al. (2014), the assay that was used to determine IAA was not specific for IAA.

Of the 49 cases identified, 20 occurred in Europe, out of which 19 were presumably Caucasians (one was a woman of Sri Lankan origin). Most Caucasian cases were reported for Italy (n=13). One case was identified in Spain and one in Portugal, three in Turkey and one in Russia. Outside Europe, the majority of cases were observed in Japan (n=22), three were reported in South Korea and four in India (supposedly all of Asian origin, i.e. 30 cases in individuals with Asian ethnicity in total (including the woman of Sri Lankan origin diagnosed in Italy).

There was a predominance of female cases (41 out of 49). Ages ranged from 28 to 82 years.

The time to onset in the investigated case reports, ranged from 1 week to 4 months and doses of ALA from 200 to 800 mg/day. There was no obvious association between dose and time to onset. However, for several cases, information on the dose or duration of consumption or both was not available (e.g. 24 cases reporting neither the dose nor the duration of consumption).

Among the cases, one South Korean 67-year-old woman underwent two accidental re-challenges with ALA. In all three instances, in which she had consumed ALA in amounts of 600 mg/day, she developed IAS, which completely resolved before each re-challenge. In

addition, in all cases reported, IAS resolved after a few weeks to months when ALA was discontinued (see Table 1).

Out of the 49 cases, data on health status, other possible concomitant medication, and HLA class DRB1* genotype were available in 26, 20 and 38 cases, respectively.

In 44 cases, no concomitant intake of other substances that are potential triggers of IAS, was reported. In four cases, omeprazole was taken and in one case gliclazide. For both substances, only one case report each exists in which the development of IAS was associated with the use of the substance (as reported in the review by Cappellani et al. (2020)). The woman who had consumed gliclazide (Bae et al., 2013) had done this prior to the ingestion of ALA and symptoms of IAS started only after the intake of ALA. In addition, she developed two additional episodes of IAS upon re-exposure to ALA (see South Korean case described above). Given the wide-spread use of these substances, the Panel considers it unlikely that gliclazide or omeprazole were involved in the development of IAS in these cases.

The Panel notes that the one case (Bae et al., 2013) in which evidence of a double re-challenge was available allows to attribute the development of IAS with a high probability to the consumption of ALA. In addition, similar signs and symptoms occurred in the 27 cases for which this information was available. The development of symptoms has always been preceded by the consumption of ALA either as food supplement or medicinal product; in 44 cases without concomitant intake of other substances that have been reported to be a potential trigger of IAS. The reported times to onset of IAS are compatible with the emergence of an autoimmune disease. IAS resolved upon withdrawal of ALA after several weeks to months. These observations are in line with the plausible mechanism that has been put forward by which ALA could increase the risk of developing IAS (see Section 3.5.4).

The Panel considers that there is an association between the consumption of ALA and an increased risk of development of IAS in individuals with certain polymorphisms in the HLA region (see Section 3.5.3 on genetic determinants).

578 **Table 1** Summary of case reports reporting on insulin autoimmune syndrome (IAS) related to consumption of alpha-lipoic acid (ALA) (published in a
579 EU language, date of search 04/09/2020, chronological order)

Reference (year of 1st publication for reviews)	Country of diagnosis	Amount mg/d Duration	Sex Age (years) Ethnicity (if reported)	Health status	Other concomitant medication	Symptoms	Time to remission	Treatment of IAS	ALA as medicinal product or food supplement	HLA class DRB1*
Bae et al. (2013) from review (2003)	JP	NR	F 55	NR	NR	NR	NR	NR	NR	04:06
Bae et al. (2013) from review (2006)	JP	NR	F 32	NR	NR	NR	NR	NR	NR	04:06
Bae et al. (2013) from review (2006)	JP	NR	F 34	NR	NR	NR	NR	NR	NR	04:06
Bae et al. (2013) from review (2006)	JP	NR	F 44	NR	NR	NR	NR	NR	NR	04:06
Bae et al. (2013) from review (2006)	JP	NR	F 49	NR	NR	NR	NR	NR	NR	04:06
Bae et al. (2013) from review (2006)	JP	NR	F 64	NR	NR	NR	NR	NR	NR	DR4
Bae et al. (2013) from review (2006)	JP	NR	M 66	NR	NR	NR	NR	NR	NR	04:06
Bae et al. (2013) from review (2006)	JP	NR	F 67	NR	NR	NR	NR	NR	NR	NR
Bae et al. (2013) from review (2007)	JP	NR	F 32	NR	NR	NR	NR	NR	NR	04:06
Bae et al. (2013) from review (2007)	JP	NR	F 34	NR	NR	NR	NR	NR	NR	04:06

Bae et al. (2013) from review (2007)	JP	NR	M 35	NR	NR	NR	NR	NR	NR	04:06
Bae et al. (2013) from review (2007)	JP	NR	F 36	NR	NR	NR	NR	NR	NR	NR
Bae et al. (2013) from review (2007)	JP	NR	F 36	NR	NR	NR	NR	NR	NR	NR
Bae et al. (2013) from review (2007)	JP	NR	F 40	NR	NR	NR	NR	NR	NR	04:03
Bae et al. (2013) from review (2007)	JP	NR	F 41	NR	NR	NR	NR	NR	NR	NR
Bae et al. (2013) from review (2007)	JP	NR	F 45	NR	NR	NR	NR	NR	NR	04:03
Bae et al. (2013) from review (2007)	JP	NR	F 48	NR	NR	NR	NR	NR	NR	0406
Bae et al. (2013) from review (2007)	JP	NR	M 55	NR	NR	NR	NR	NR	NR	04:06
Furukawa et al. (2007)	JP	200 Unclear	F 44	Oligomenorrhea	Norgesterel/Ethinylestradiol, Q10 and carnitin	Recurrent attacks of weakness and malaise	Shortly after withdrawal of ALA	None	Food supplement	04:06
Ishida et al. (2007)	JP	200 2 mo	F 32	Diabetes	None	Pre-prandial weariness	Within around 3 wk	None (only discontinuation of ALA)	Food supplement	04:06
Yamada et al. (2007)	JP	1 mo	F 45	NR	NR	Hypoglycaemic coma	NR	NR	Food supplement	04:03
Takeuchi et al. (2007)	JP	225 1 wk	M 55	History of obesity, hypertension, and hyperuricemia; slight liver dysfunction, hyperuricemia	NR	Hunger, sweating, palpitations and tremor, lost consciousness	Few wk	Fractionate meals	Food supplement	04:06
Bae et al. (2013) from review	KR	NR	F 71	NR	NR	NR	NR	NR	NR	04:06

Bresciani et al. (2011)	IT	600 17 d	F 70 Caucasian	Healthy	None	Recurrent episodes of sweating, weariness, and fainting occurring both fasting and postprandial	1 wk from first dose of diazoxide (hypoglycaemia persisted after prednisone)	Prednisone and then diazoxide	Food supplement	04:06
Vimalraj et al. (2011)	IN	NR	F 28	NR	NR	Repeated episodes of weakness, sweating, palpitations, hunger and tremor; lost consciousness	4 wk	None	Medicinal product	NR
Bae et al. (2013)	KR	600 2 wk Re-challenge	F 67	T2DM	Gliclazide	Repeated episodes of hunger, hand tremor, cold sweat, and dizziness 3 to 4 hr after a meal, but symptoms improved after eating snacks	2 mo	Prednisolone	Medicinal product (thioactacid)	04:06
Bae et al. (2013) from review (2013)	KR	NR	F 67	NR	NR	NR	NR	NR	NR	04:06
Gullo et al. (2014)	IT	600 120 d	F 40 Caucasian	Disk hernia	None	Dizziness, tachycardia, sweating, loss of consciousness	Within 3 mo	Oral sucrose and/or repeated high carbohydrate snacks for 2–5 d	NR	04:03
Gullo et al. (2014)	IT	600 45 d	M 53 Caucasian	Membrano-proliferative glomerulo-nephritis	Ramipril	Lost consciousness	Within 3 mo	Prednisone (100 d) + oral sucrose and/or repeated high carbohydrate snacks for 2–5 d	NR	04:03
Gullo et al. (2014)	IT	600 30 d	M 56 Caucasian	Disk hernia, hypertension	Losartan; omeprazole; acetylsalicylic acid	Sweating, trembling, dizziness, lost consciousness	Within 3 mo	Prednisone (20 d) + oral sucrose and/or repeated high carbohydrate snacks for 2–5 d	NR	04:03
Gullo et al. (2014)	IT	600 70 d	F 70 Caucasian	Depression, hypertension, osteoporosis, autoimmune thyroiditis	Candesartan, omeprazole; L-thyroxine; calcidiol, hydrochlorothiazide	Trembling, sweating, weakness	Within 3 mo	Prednisone (60 d) + oral sucrose and/or repeated high carbohydrate snacks for 2–5 d	Food supplement (see Gatti et al. (2020)	04:03
Gullo et al. (2014)	IT	600 30 d	M 75 Caucasian	Renal disease, hypertension, asthmatic bronchitis, rheumatoid arthritis	Furosemide; candesartan; leflunomide; celecoxib	Lost consciousness	Within 3 mo	Prednisone (60 d) + oral sucrose and/or repeated high carbohydrate snacks for 2–5 d + IV 10% dextrose	Food supplement (see Gatti et al. (2020)	04:06
Gullo et al. (2014)	IT	600 60 d	F 77 Caucasian	Hypothyroidism, hypertension, atrial fibrillation, osteoporosis, diabetes	Acenocoumarol, omeprazole; atorvastatin; bisoprolol; lisinopril; doxazosin; L-thyroxine;	Confusion, lost consciousness	Within 3 mo	Prednisone (100 d) + oral sucrose and/or repeated high carbohydrate snacks for 2–5 d	Food supplement (see Gatti et al. (2020)	04:03

Michalopoulou Alevras et al. (2015)	ES	200 15 d	F 55 Caucasian	Allergy to iodinated contrast	No habitual medication	Adrenergic and neuroglycopenic symptoms, both in fasting and postprandial states	Unclear	Fractionated diet and 200 g of iv glucose + IV Prednisone	Food supplement	NR
Lio et al. (2016)	IT	300-600 3 wk	F 68	Rheumatoid arthritis, hypertensive cardiomyopathy, one episode of atrial fibrillation with proper electrical cardioversion, cholecystectomy	Prednisone at very low doses, hydroxychloroquine, cholecalciferol, NSAIDs, paracetamol; bisoprolol, amlodipine, ASA, pantoprazole	Recurrent episodes of impaired consciousness, diaphoresis and non-diabetic spontaneous, symptomatic, both fasting and postprandial hypoglycaemia with sweating, tremors, instability	Within 3 mo	IV 10% glucose, Prednisone	Food supplement	04:03
Pavithran et al. (2016)	IN	NR	F 69	T2DM	NR	NR	6 wk	Prednisolone, short-acting insulin before breakfast and lunch	Food supplement	NR
Ferreira et al. (2017)	PT	Few wk	F 57 Caucasian (supposedly)	Behcet disease	Tapenthadol, flupirtine	Hypoglycaemic episodes 2.5 hr after breakfast, abdominal discomfort, tremors and blurred vision-symptoms resolved after sugar ingestion	NR	Hydrocortisone (the patient did not tolerate well prednisone)	Food supplement	NR
Bolayir et al. (2018)	TR	NR NR (until 3 wk before hospitalisation)	F 62	Hypertension and hyperlipidaemia	Indapamide, nebivolol and atorvastatin	Recurrent episodes of sweating, weariness, heart palpitations and anxiety occurring both fasting and postprandial	NR	Diet with low carbohydrate and frequent small meals was planned	Food supplement	NR
Cappellani et al. (2018)	IT	2 wk	F 35 Asian	Endometriosis	Estroprogestins	Asthenia, blurred vision, aphasia, loss of coordination and partial amnesia	15 mo	High frequent and low-caloric meals, rich in simple sugars + flash glucose monitoring (FGM) system FreeStyle Libre	Food supplement	04:15
Izzo et al. (2018)	IT	800 1 mo + 10 d after a suspension of 15 d	F 66 Presumably Caucasian	Negative clinical anamnesis	NR	Repeated episodes of hand tremor and hunger that appeared 3–4h after a meal. Malaise and sweating	NR	Continuous iv 5% dextrose for 10 d	Unclear (therapy for joint pain)	04:03
Prabhakar and Dass (2018)	IN	9 d NR	F 59	Recent bilateral knee-pain	NR	Episodic sudden severe fatigue, profuse sweating and palpitations	8 wk	IV Hydrocortisone initially, then Prednisolone orally, dietary modifications	Food supplement	DRB1*04, DRB1*15, DRB4, DRB5
Veltroni et al. (2018)	IT	600 2 wk	F 56 Caucasian	Healthy, obese, surgical transsphenoidal removal of a prolactin-secreting pituitary adenoma 20 y before, carpal tunnel decompression surgery 1 mo before	NR	Blurred vision, diaphoresis and confusion, mainly occurring 2–3 h after meal and resolving with food intake; lost consciousness, asthenia, dizziness	3 mo	1 wk infusion with 20% glucose, recommended small frequent meals, avoiding simple sugars and increasing complex carbohydrates. Prednisone 50mg/d for 6 mo	Food supplement	04:03

Alagüney et al. (2019)	TR	NR	M 50	Without pathology	Proton pump inhibitors (esomeprazole and rabeprazole), pregabalin	Fever, sweating and palpitations, symptoms aggravated with hunger and 2-3 h after the meal; food cravings 2 or 3 times a night	NR	NR	Food supplement	NR
Moffa et al. (2019)	IT	600 Until 1 wk before hospitalisation	F 66 Caucasian	No history of major chronic diseases; hypertension	Ramipril	Sweating, hunger, palpitations, and tremors that occurred 2 or 3 h after meals and during the night	Unclear, but Prednisone suspended after 4 mo	Prednisone	NR	04:03
Moffa et al. (2019)	IT	300 NR	F 82 Caucasian	No history of alcohol abuse or diabetes and no previous exposure to diabetes medications	Bisoprolol, irbesartan, aspirin	Lost consciousness	Unclear, but Prednisone suspended after 9 mo	Prednisone	NR	04:03
Cambria et al. (2020)	IT	Few wk	F 76	T2DM	Metformin until the first hypoglycaemic episode	Recurrent hypoglycemic episodes	Unclear but diazoxide was suspended only 4 months later	diazoxide	Food supplement	04:15
Okuroglu et al. (2020)	TR	600 1 mo	F 62	Hypertension and chronic obstructive lung disease. No previous diagnosis of diabetes	Telmisartan/hydrochlorothiazide and budesonide plus formoterol	Recurrent dizziness, malaise, and fatigue	After discharge (hospitalised for 72 hr) she did not experience any hypoglycaemia episodes	Advised to avoid ALA, eat small meals but frequently, eat low-carbohydrate foods, and avoid fasting	NR	04:03
Patel et al. (2020) from review (NR)	IN	6 wk	F 50	NR	NR	NR	NR	Prednisolone	NR	NR
Yukina et al. (2020)	RU	NR 1 mo	F 46	Grade II obesity, dyslipidemia, hyperuricemia, cholelithiasis, hiatal hernia, mixed gastritis (superficial and erosive). In 2016, surgical removal of uterus and ovaries for bilateral contained pyosalpinx, ovarian abscess, and endomyometritis. In September 2017, surgery for discitis, followed by a 2-mo antibacterial therapy incl. Ciprofloxacin, Doxycycline, and Metronidazole.	NR	Dizziness, sense of fear, and 'creeping' sensations occurring 2–3 hr after meals	≈3 mo (from December 2017 to February 2018)	ALA avoidance, no medicinal therapy	Medicinal product	DRB1*03-DQA1*05:01-DQB1*02/DRB1*04-DQA1*03:01-DQB1*03:02

AR = Argentina; d = day(s); ES = Spain; F = female; hr = hour(s); HLA = human leukocyte antigen; IN = India; IT = Italy; JP = Japan; KR = Korea, Republic of; LK = Sri Lanka; M = male; mo = month(s); NR = not reported; PT = Portugal; RU = Russia Federation; T2DM = type 2 diabetes mellitus; TR = Turkey; wk = week(s); y = year(s).

3.7 Dose below which IAS is not expected to occur

The lowest ALA intake that was associated with the development of IAS in the case reports described in Section 3.8 was reported to be 200 mg/day. However, no data are available that would allow a judgement to be made on whether IAS also occurs at lower doses. The Panel notes that generally the susceptibility of individuals to triggers of autoimmune diseases varies. It is therefore likely that this is also the case for IAS.

With respect to the NOAEL (0.6 mg/kg body weight per day) proposed by DTU, the Panel notes that this was based on toxicological endpoints unrelated to IAS and therefore does not necessarily protect from the development of IAS. In addition, the Panel notes that standard toxicity tests are not suitable for determining a threshold below which an autoimmune disease is unlikely to occur.

The Panel considers that, based on the data available, a dose below which IAS is not expected to occur cannot be derived, neither for the general population nor for vulnerable sub-groups thereof.

4 Conclusions

The Panel concludes that the consumption of ALA added to foods, including food supplements, is likely to lead to an increased risk of development of IAS in individuals with certain genetic polymorphisms, although the plausible mechanism by which ALA may increase this risk has not yet been fully elucidated. EFSA has not identified any evidence of a link between ALA naturally occurring in foods and IAS.

The prevalence of the three main HLA alleles associated with an increased risk of development of IAS has been reported to be around 0.1-3.9% in Europe, depending on the alleles and the country (Uchigata et al., 2000; Gonzalez-Galarza et al., 2019). The Panel nhotes that the individuals carrying the relevant polymorphism cannot be readily identified without genetic testing.

The incidence of IAS (of all causes) for the years 2017-2018 in the general population in Japan has been estimated to be 0.017 per 100.000 inhabitants (i.e. a total of 22 cases in these years) (Yamada et al., 2020). The incidence in Europe is likely to be lower, considering that the prevalence of alleles associated with an increased risk of development of IAS is less frequent in populations with Caucasian than Asian ethnicity. However, based on the limited data available, the Panel concludes that the prevalence of IAS in Europe and the risk associated with the development of IAS following consumption of ALA cannot be quantified neither for the general population nor for sub-groups or individuals with genetic susceptibility.

The Panel also concludes that an ALA dose below which IAS is not expected to occur is likely to vary between individuals and can therefore not be determined based on the data that are available.

5 Uncertainties

The following sources of uncertainties have been detected:

- There is a lack of information on whether the industrial production of ALA that is used in food supplements differs from the one of ALA used in medicinal products, i.e. whether food-grade and pharmaceutical-grade ALA are interchangeable.
- Publications in non-EU languages have not been considered;
- It is unlikely that all cases of IAS following ALA consumption in Europe have been published;
- A plausible mechanism by which ALA may trigger IAS in individuals with certain genetic polymorphisms has been suggested, but it still needs to be demonstrated;
- Even though data on allele frequency is available for a number of European countries, data covering a sufficiently large representative sample of the whole EU population is missing.

The Panel acknowledges these uncertainties, but they do not diminish the scientific conclusions.

6 Recommendations

In order to reduce the uncertainties, the Panel has identified the following recommendations for research:

- Elucidation of the mechanism of action by which ALA increases the risk of developing IAS;
- Investigation of the prevalence of IAS in the EU also in conjunction with the use of ALA;
- Investigation of the prevalence of HLA alleles associated with an increased risk of development of IAS in a representative sample of the EU population.

7 Documentation as provided to EFSA

The following documentation was provided together with the mandate from the European Commission:

- DTU Food, 2017. Safety of alpha-lipoic acid use in food supplements. DTU Doc nr. 17/14450, 5 pp
- Superior Health Council of Belgium, 2015. Innocuité de l'acide alpha-lipoïque dans les compléments alimentaires. Avis du Conseil Supérieur de la Santé No 9274, 10 pp

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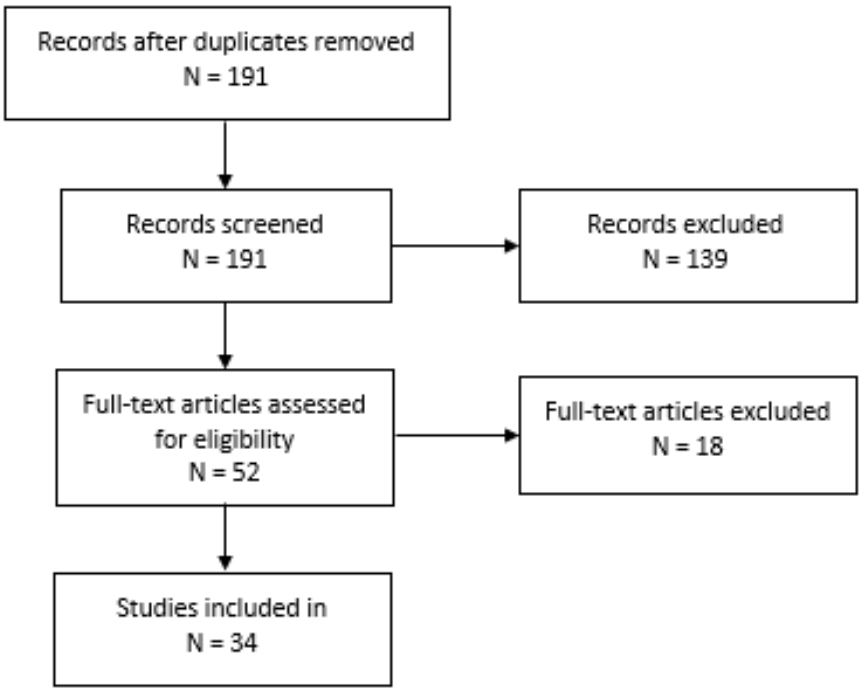
Appendix A – PRISMA flow charts for the three literature searches

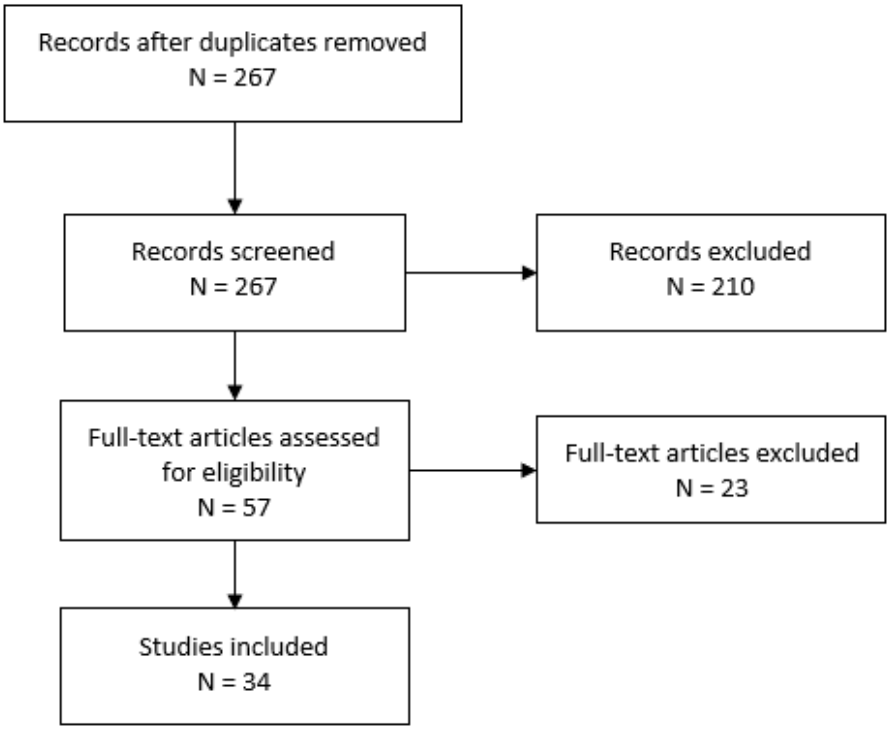
PRISMA flow chart search 1

Aimed at identifying case reports that link the development of IAS to the intake of ALA



PRISMA flow chart search 2

Aimed at identifying reviews on IAS



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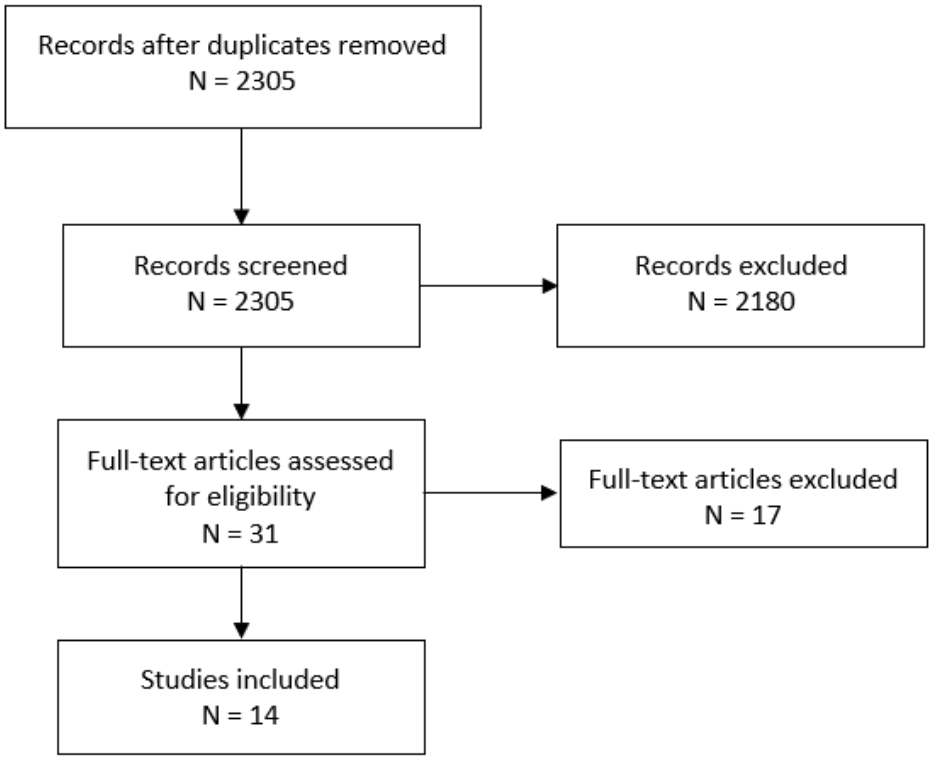
884 **PRISMA flow chart search 3**

885 Aimed at identifying pharmacokinetic studies and safety studies in humans



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Appendix B - Protocol for the assessment of the relationship between intake of alpha-lipoic acid (thioctic acid) and the risk of insulin autoimmune syndrome

1. Problem formulation and planned approach towards the evidence retrieval from the scientific literature

The following protocol has been developed in line with existing methodology (EFSA et al., 2020).

1.1. Assessment questions and sub-questions

In order to answer the Terms of Reference (ToR) as interpreted in Section 1.3., the Panel considers that the following questions and sub-questions need to be answered.

1. Identity of the ALA
    - What are the chemical structure, the stereochemistry, the nomenclature (e.g. IUPAC chemical name, CAS number, EINECS number)?
    - What are the synonyms that are used to refer to the same substance?
    - Analogues, derivatives, metabolites that are on the market?
    - Is the substance occurring also naturally in food or is it only produced synthetically?
    - How is ALA that is used in food supplements produced (e.g. source material, process)?
    - Is there any difference between ALA used for food supplements and the one used for medicines (structure, purity, production, source etc)?
    - How stable is ALA throughout shelf-life, are there any degradation products that are produced that need to be considered?
    - Are there impurities or contaminants in industrial ALA? If yes, are they related to the mode of production? Is there data in the literature pertaining on contamination or adulteration of ALA?
2. How is ALA absorbed, distributed, metabolised, excreted?
    - Is ALA absorbed as such or are there any modification in the gastro-intestinal tract before absorption?
    - What is its bioavailability? Are there bioavailability variations between individuals?
    - What are the mechanisms regulating ALA absorption and distribution: transporters or passive absorption, interaction with other substances/nutrients, circulating forms? What are the metabolites of ALA?
    - Which metabolic pathways are involved?
    - Are there any interindividual differences in metabolism (that could lead to a higher susceptibility of certain individuals than others)?
    - How long is the half-life of ALA and its metabolites in blood circulation?
    - Can ALA be accumulated in any form in the organism?
    - How are ALA and its metabolites excreted?
3. What is IAS?

- What are the prevalence and incidence of the disease?
- Which is the aetiology of the disease (are there any other causes than ALA that would need to be considered when evaluating the data on the link between ALA and the disease)?
- Which polymorphisms have been associated with a higher risk of developing the disease and what are the reasons?
- Are there any vulnerable sub-populations that can be readily defined? Are there subpopulations with certain recognisable characteristics (with no need for genetic testing) that have a higher susceptibility for the disease? Are children, elderly, lactating or pregnant women at a higher/lower risk?
- What is the definition and pathophysiology of the disease?
- What are symptoms of the disease and its differential diagnosis?

4. What is the association between ALA and IAS in humans?
   - Which previous assessments from official scientific bodies are available and what are the conclusions?
   - Which are documented case reports in humans available in the literature?
   - Are there any additional reports in European Nutravigilance databases of European Member States or the EMA Eudravigilance database, not yet published in the literature?
   - IAS reported in clinical trials.
   - How strong is the association (how reliable was the ascertainment of the disease, how reliable was the exposure assessment, are there data on challenge-re-challenge)?
   - Has a causal relationship between ALA and IAS been established?
   - What are the mechanisms of action involved in the detrimental effects of ALA?
5. What is the minimum eliciting dose?
   - At which doses of ALA and exposure durations was IAS observed in well documented cases?
   - Is there any health-based guidance value that could be set from the data?

1.2. Formulation of the sub-questions

For each of the questions above, the objectives of the sub-questions are as follows:

1. Identity of the ALA
   - Objective 1: Map the main characteristics of ALA (chemical structure, enantiomer, natural or synthetic occurrence)
   - Objective 2: Identify synonyms for ALA
   - Objective 3: Identify the production process of ALA for food supplements
   - Objective 4: Compare the production/source of ALA for medical or food purpose
   - Objective 5: Identify the shelf-life of ALA and whether degradation products could have effects
2. How is ALA absorbed, distributed, metabolised, excreted?

- Objective 1: Identify the mechanisms of absorption, distribution, metabolization, storage and excretion of ALA

3. What is IAS?
   - Objective 1: Map the main characteristics of IAS (symptoms, pathophysiology, causes of the disease)
   - Objective 2: Identify genetical predisposition to developing IAS
   - Objective 3: Identify vulnerable sub-populations
   - Objective 4: Prevalence and incidence of the disease
4. What is the association between ALA and IAS in humans?
   - Objective 1: Identify the link between the intake of ALA and IAS.
5. What is the minimum eliciting dose?
   - Objective 1: based on the literature mentioned before, identify, if possible, a no observed adverse effect level (NOAEL) of ALA intentionally added to foods regarding IAS for the general population and vulnerable sub-groups.

1.3. Definition of the search strategy and eligibility criteria for study selection (i.e. evidence needs)

Questions 1 and 2 (Section 1.1.) will be answered following a narrative approach (i.e. no comprehensive search, no data extraction forms), while questions 3, 4 and 5 will be answered based on a comprehensive literature search, further described afterwards, and considering also other types of data (e.g. reports from relevant scientific institutions and authorities, such as FDA, Health Canada, Australia or New Zealand authorities). Information for questions 1 and 2 will be retrieved from relevant websites, books and publications.

For question 4 (What is the association between ALA and IAS in humans?), three types of data are expected:

- Published trials that would report IAS as an adverse effect:

  PICO framework:[10] (p) general population (i) consuming ALA or other drugs/substances vs (c) placebo or another comparator (o) developing IAS.

- Published case reports of IAS that would report the occurrence of IAS in a limited number of individuals and the investigation to identify the cause (e.g. previous exposure to ALA or another drug)

  PO framework:[11] (p) the individual(s) that is/are described in the case reports, (o) that developed IAS.

- Other types of data (e.g. relevant institutions and authorities, such as FDA, Health Canada, Australia or New Zealand authorities)

In order to answer the questions 3, 4 and 5 identified above (section 1.1. of the protocol), the following dedicated comprehensive literature searches will be conducted by EFSA's information specialist, in Embase and Pubmed, with no limitation on the date of publication and limiting the search to EU languages. The search strings that will be used can be found in Appendix C.

[10] Population (p), Intervention (i), Comparator (c) and Outcome (o) in a question about an intervention effect

[11] Population (p) and Outcome (o) in a descriptive question

The following inclusion and exclusion criteria will be applied:

- Search 1 related to Q4 (What is the association between ALA and IAS in humans?): Papers (intervention or observational studies) on oral consumption of ALA in humans and IAS
    - Inclusion:
        - Trials (also single arm) on oral consumption of ALA as food, supplement, or medicinal product, also in combination with other substances, in humans that report on IAS
        - Observational studies, in particular case reports, on the occurrence of IAS in a limited number of individuals (that may report on the investigation to identify the cause, possibly ALA, only in the full text)
        - Abstracts of conferences on potential case reports
        - Statements/opinions from competent authorities e.g. US FDA, Health Canada, etc.
        - All population independently of age, healthy/disease status, ethnicity, etc.
        - ALA in different forms i.e. tablets, capsules, etc. (even with the same dose)
    - Exclusion:
        - Protocols
        - Studies on animals or cells as no animal or *in vitro* model of IAS was identified
        - Reviews/meta-analyses
        - Studies not on ALA and/or not on IAS
        - Studies not on oral consumption (e.g. injection of ALA)

- Search 2 related to Q3 (What is IAS?): Reviews (systematic or narrative) on IAS
    - Inclusion: review (narrative or systematic including also meta-analysis) on IAS (whatever aspects of this disease) or autoimmune reaction related to insulin or hypoglycaemia or autoimmune polyendocrine syndrome.
        - NB: The purpose of this question is to identify plausible mechanisms (in humans, and possibly also from data on animal or cell cultures), if reported in the reviews. This will be discussed in a dedicated section of the opinion.
    - Exclusion:
        - All types of intervention or observational studies
        - Protocols, abstracts of conference/congress/symposium
        - Reviews not on IAS or autoimmune reaction related to insulin or or hypoglycaemia or autoimmune polyendocrine syndrome

- Search 3: Clinical trials on oral consumption of ALA
        - Trials on oral consumption of ALA, alone or in combination, as food, supplement, or medicinal product that report on side effects.

- Exclusion:
  - Protocols, abstracts of conference/congress/symposium
  - Reviews/meta-analyses
  - Studies not on ALA
  - Studies not on oral consumption

Regarding the grey literature, additional searches will be performed on the websites of relevant institutions and authorities, such as FDA, Health Canada, Australia or New Zealand authorities. Websites will be browsed or searched to retrieve published reports on the relationship of ALA and IAS. Methods to retrieve the information will be reported. Vigilance databases will also be searched to retrieve case reports not published elsewhere.

1.4. Definition of the methods for selecting studies for inclusion/exclusion

For questions 3, 4 and 5 of section 1.1, the screening will be done in duplicate by EFSA staff members using DistillerSR (Evidence Partners, Ottawa, Canada), at the level of the title and abstract and then at the level of the full text. Conflicts that might arise will be discussed first amongst the two reviewers of that study and if the conflict is not solved all reviewers will be involved. The references will then be exported to EndNote®.

1.5. Definition of the methods for extracting data from studies included from the systematic literature search

Data will be extracted from case reports and clinical trials. Extraction will be done in Microsoft Excel®, where one reviewer will do the extraction, and another will validate it.

The items extracted will cover, e.g. RefID from DistillerSR® (Evidence Partners, Ottawa, Canada), extraction date, author name, year, location, ALA dose, ALA as medicinal product or food supplement, subject characteristics, duration of ALA consumption.

1.6. Definition of the methods for appraising evidence

No appraisal is foreseen.

1.7. Preliminary identification of the sources of uncertainty and definition of the methods for prioritising them

For all questions identified in Section 1.1., limited answers may be the consequence of lack of data. Uncertainty analysis of the scientific assessment, i.e. identifying possible limitations in scientific knowledge and assessing their implications for scientific conclusions, will be discussed briefly, based on the EFSA guidance document on uncertainty (EFSA Scientific Committee et al., 2018). This implies in particular identifying the sources of uncertainty affecting the assessment, prioritising these sources based on their expected influence on the outcome/results and final overall discussions and planning how the uncertainty analysis will be handled. It is expected that the following identified sources of uncertainties will be discussed qualitatively (descriptive method) and no quantitative analysis will be undertaken.

Uncertainties that might be encountered for question 1: Identity of ALA?, question 2: How is ALA absorbed, distributed, metabolised and excreted?, and question 3: what is IAS? (identified in section 1.1.):

- Lack of published data

Uncertainties that might be encountered for question 4: What is the association between ALA and IAS in humans? and question 5: What is the minimum eliciting dose? (identified in section 1.1.):

- Exposure /compliance of subjects (in case of trials), i.e.
  - uncertainty of dose inducing IAS leading to possible over/underestimation.
- Insufficient reporting on the assessment/diagnosis of the adverse effects by investigators
  - Potential misclassification of adverse effects
- Limited information on genetical susceptibility and impossibility to identify populations at risk.
- Publication bias
  - Case reports may not all be published
  - Adverse effects not adequately/extensively reported in trials
- Precision of the measurements made (if any)
- Power (for trials)
- Heterogeneity of the dataset
- Language of the SR
  - Case reports published in non-EU languages will not be considered.
- Appraisal
  - Due to time constrains it might not be feasible to conduct one.
- Representativity
  - Relevance for the EU population will be assessed by expert judgement, as the case reports are expected to be from a limited number of countries.

1.8. Definition of the methods for synthesising evidence within the sub-question

Question 4 (section 1.1.). What is the association between ALA and IAS in humans?

It will depend on the evidence that will be obtained. Possibly qualitative.

Question 5 (section 1.1.). What is the minimum eliciting dose?

It will depend on the evidence that will be obtained. Possibly semi-quantitative. Expert knowledge elicitation (EKE) might be needed, taking into account the relevant EFSA guidance (EFSA, 2014).

1.9. Definition of the methods for analysing uncertainties individually and combined

Uncertainties will be identified at each step of the assessment, but no formal uncertainty assessment is foreseen.

Appendix C – Search strings

Search 1

Embase

Date of the search 04-09-2020

Set	Query	Results
#8	#5 AND #6 AND ([basque]/lim OR [bulgarian]/lim OR [catalan]/lim OR [croatian]/lim OR [czech]/lim OR [danish]/lim OR [dutch]/lim OR [english]/lim OR [estonian]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [greek]/lim OR [hungarian]/lim OR [irish gaelic]/lim OR [italian]/lim OR [latvian]/lim OR [lithuanian]/lim OR [macedonian]/lim OR [norwegian]/lim OR [polish]/lim OR [polyglot]/lim OR [portuguese]/lim OR [romanian]/lim OR [scottish gaelic]/lim OR [serbian]/lim OR [slovak]/lim OR [slovenian]/lim OR [spanish]/lim OR [swedish]/lim)	154
#7	#5 AND #6	160
#6	'hirata disease'/exp OR 'hypoglycemia'/exp OR 'insulin autoimmune syndrome'/exp OR aih:ti,ab,kw OR ('insulin'/exp AND ('immunopathology'/de OR 'immune system'/de OR 'autoimmune disease'/de)) OR ((hirata* NEAR/3 disease*):ti,ab,kw) OR hypoglycaemia:ti,ab,kw OR hypoglycaemic:ti,ab,kw OR hypoglycemia:ti,ab,kw OR hypoglycemic:ti,ab,kw OR ias:ti,ab,kw OR ((insulin NEAR/5 autoimmune):ti,ab,kw)	134,940
#5	#3 OR #4	10,181
#4	alipure:ti,ab,kw OR 'alpha-lipogamma':ti,ab,kw OR 'alphalipogamma':ti,ab,kw OR 'alpha-lipon':ti,ab,kw OR alphalipon:ti,ab,kw OR 'alpha liponaure':ti,ab,kw OR alphaliponaure:ti,ab,kw OR alphaliponsaure:ti,ab,kw OR 'alpha liponsaure':ti,ab,kw OR 'alpha lippon':ti,ab,kw OR alphalippon:ti,ab,kw OR 'alpha vibolex':ti,ab,kw OR alphavibolex:ti,ab,kw OR azulipont:ti,ab,kw OR berlition:ti,ab,kw OR berlithione:ti,ab,kw OR biletan:ti,ab,kw OR 'biomo lipon':ti,ab,kw OR biomolipon:ti,ab,kw OR 'byodinoral r':ti,ab,kw OR 'coenzyme compositum':ti,ab,kw OR 'discus compositum':ti,ab,kw OR duralipon:ti,ab,kw OR 'espa lipon':ti,ab,kw OR espalipon:ti,ab,kw OR fenint:ti,ab,kw OR 'hepar compositium':ti,ab,kw OR heparlipon:ti,ab,kw OR juthiac:ti,ab,kw OR 'ledum compositum':ti,ab,kw OR 'lycopodium compositum':ti,ab,kw OR liposan:ti,ab,kw OR 'liponsaure-ratiopharm':ti,ab,kw OR liponsaureratiopharm:ti,ab,kw OR lipothion:ti,ab,kw OR mtwalphaliponsaure:ti,ab,kw OR neurium:ti,ab,kw OR octolipen:ti,ab,kw OR oktolipen:ti,ab,kw OR 'pleomix alpha':ti,ab,kw OR 'quamtrax ala':ti,ab,kw OR thioctacid:ti,ab,kw OR thioctacide:ti,ab,kw OR thioctan:ti,ab,kw OR thioctsan:ti,ab,kw OR	141

	thiogamma:ti,ab,kw OR thiotacid:ti,ab,kw OR tromlipon:ti,ab,kw OR tioctacid:ti,ab,kw OR tioctan:ti,ab,kw OR tioctidasi:ti,ab,kw OR 'ubichinon compositum':ti,ab,kw OR 'verla lipon':ti,ab,kw OR verlalipon:ti,ab,kw OR zeel:ti,ab	
#3	#1 OR #2	10,122
#2	(('1 2 dithiolan 3 pentanic' OR 12dithiolan3pentanic OR '1 2 dithiolane 3 pentanoic' OR '12dithiolane3pentanoic' OR '1 2 dithiolane 3 valeric' OR '12dithiolane3valeric' OR '5 dithiolan 3 yl valeric' OR '5dithiolan3ylvaleric' OR '5 1 2 dithiolan 3 yl valeric' OR 512ditiolan3ylvaleric OR 68thioctic OR '6 8thioctic acid' OR αlipoic OR alipoic OR lipoic OR liponic OR thioctic OR tioctic) NEAR/3 (acid OR acids)):ti,ab,kw	6,833
#1	'thioctic acid'/exp OR '1077 28 7':ti,ab,kw OR 1077287:ti,ab,kw	9,259

1137

1138 Pubmed

1139 Date of the search: 04-09-2020

Search	Query	Results
#6	Search: #5 AND ("bulgarian"[Language] OR "catalan"[Language] OR "croatian"[Language] OR "czech"[Language] OR "danish"[Language] OR "dutch"[Language] OR "english"[Language] OR "estonian"[Language] OR "finnish"[Language] OR "french"[Language] OR "german"[Language] OR "greek modern"[Language] OR "hungarian"[Language] OR "italian"[Language] OR "latvian"[Language] OR "lithuanian"[Language] OR "multiple languages"[Language] OR "norwegian"[Language] OR "polish"[Language] OR "portuguese"[Language] OR "romanian"[Language] OR "scottish gaelic"[Language] OR "serbian"[Language] OR "slovak"[Language] OR "slovenian"[Language] OR "spanish"[Language] OR "swedish"[Language] OR "undetermined"[Language] OR "welsh"[Language]) Sort by: Most Recent	54
#5	Search: #3 AND #4	59
#4	Search: ("Insulin"[Mesh] AND ("Immune System Diseases"[Mesh:noexp] OR "Immune System"[Mesh:noexp] OR "Autoimmune Diseases"[Mesh:noexp])) OR "Hypoglycemia"[Mesh] OR aih[tiab] OR (hirata*[tiab] AND disease*[tiab]) OR Hypoglycaemia[tiab] OR Hypoglycaemic[tiab] OR Hypoglycemia[tiab] OR Hypoglycemic[tiab] OR ias[tiab] OR (Insulin[tiab] AND autoimmune[tiab])	76,375
#3	Search: #1 OR #2 Sort by: Most Recent	6,051
#2	Search: "Thioctic Acid"[Mesh] OR "1077-28-7"[tiab] OR 1077287[tiab] OR "1,2-Dithiolan-3-pentanic acid"[tiab] OR "1,2-Dithiolan-3-pentanic acids"[tiab] OR "1 2 dithiolane 3 pentanoic acid"[tiab] OR "12dithiolane3pentanoic acid"[tiab] OR "1 2 dithiolane 3 valeric acid"[tiab] OR '"2dithiolane3valeric acid"[tiab] OR "5 dithiolan 3 yl valeric acid"[tiab] OR "5dithiolan3ylvaleric acid"[tiab] OR "5 1 2 dithiolan 3 yl valeric acid"[tiab] OR "512ditiolan3ylvaleric acid"[tiab] OR "1 2 dithiolane 3 pentanoic acids"[tiab] OR "12dithiolane3pentanoic acids"[tiab] OR "1 2 dithiolane 3 valeric acids"[tiab] OR '"2dithiolane3valeric acids"[tiab] OR "5 dithiolan 3 yl valeric acids"[tiab] OR	6.014

	"5dithiolan3ylvaleric acids"[tiab] OR "5 1 2 dithiolan 3 yl valeric acids"[tiab] OR "512ditiolan3ylvaleric acids"[tiab] OR "68thioctic acid"[tiab] OR "68thioctic acids"[tiab] OR "6 8thioctic acid"[tiab] OR "6 8thioctic acids"[tiab] OR "αlipoic acid"[tiab] OR "αlipoic acids"[tiab] OR "lipoic acid"[tiab] OR "lipoic acids"[tiab] OR "liponic acid"[tiab] OR "liponic acids"[tiab] OR "thioctic acid"[tiab] OR "thioctic acids"[tiab] OR "tioctic acid"[tiab] OR "tioctic acids"[tiab]	
#1	Search: Alipure[tiab] OR "Alpha-Lipogamma"[tiab] OR "AlphaLipogamma"[tiab] OR "Alpha-Lipon"[tiab] OR AlphaLipon[tiab] OR "alpha Liponaure"[tiab] OR alphaLiponaure[tiab] OR AlphaLiponsaure[tiab] OR "Alpha-Liponsaure"[tiab] OR "Alpha Lippon"[tiab] OR AlphaLippon[tiab] OR "Alpha Vibolex"[tiab] OR alphaVibolex[tiab] OR Azulipont[tiab] OR Berlithion[tiab] OR Berlithione[tiab] OR Biletan[tiab] OR "Biomo lipon"[tiab] OR Biomolipon[tiab] OR "Byodinoral R"[tiab] OR "coenzyme compositum"[tiab] OR "discus compositum"[tiab] OR Duralipon[tiab] OR "Espa-lipon"[tiab] OR Espalipon[tiab] OR Fenint[tiab] OR "Hepar compositum"[tiab] OR Heparlipon[tiab] OR Juthiac[tiab] OR "Lycopodium compositum"[tiab] OR "Ledum compositum"[tiab] OR Liposan[tiab] OR "Liponsaure-ratiopharm"[tiab] OR Liponsaureratiopharm[tiab] OR Lipothion [tiab] OR MTWAlphaliponsaure[tiab] OR Neurium[tiab] OR Octolipen[tiab] OR Oktolipen[tiab] OR "Pleomix Alpha"[tiab] OR "Quamtrax ALA"[tiab] OR Thioctacid[tiab] OR Thioctacide[tiab] OR Thioctan[tiab] OR Thioctsan[tiab] OR Thiogamma[tiab] OR Thiotacid[tiab] OR Tromlipon[tiab] OR Tioctacid[tiab] OR Tioctidasi[tiab] OR Tioctan[tiab] OR Tioctidasi[tiab] OR "Ubichinon compositum"[tiab] OR "Verla Lipon"[tiab] OR VerlaLipon[tiab] OR Zeel[tiab]	78

1140

1141 **Search 2**

1142 Embase

1143 Date of the search: 04-09-2020

Set	Query	Results
#6	#5 AND #4	123
#5	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'review'/exp OR 'systematic review (topic)'/exp OR 'biomedical technology assessment'/exp OR (((systematic* OR methodologic* OR quantitative OR research OR integrative OR collaborative) NEAR/3 overview*):ti,ab) OR review*:ti,ab,kw OR ((pool* NEAR/3 analy*):ti,ab)	36,427,795
#4	#3 AND ([basque]/lim OR [bulgarian]/lim OR [catalan]/lim OR [croatian]/lim OR [czech]/lim OR [danish]/lim OR [dutch]/lim OR [english]/lim OR [estonian]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [hungarian]/lim OR [norwegian]/lim OR [polish]/lim OR [polyglot]/lim OR [portuguese]/lim OR [romanian]/lim OR [scottish	699

	gaelic]/lim OR [serbian]/lim OR [slovak]/lim OR [slovenian]/lim OR [spanish]/lim OR [swedish]/lim)	
#3	#1 OR #2	775
#2	((autoimmune NEAR/3 (hypoglycaemia OR hypoglycemia)):ti,ab,kw) OR ((('insulin autoimmune' OR 'autoimmune insulin') NEAR/3 (syndrom* OR disease*)):ti,ab,kw) OR ((endogenous NEAR/3 hyperinsulinemic NEAR/3 (hypoglycaemia OR hypoglycemia)):ti,ab,kw) OR ((hirata* NEAR/3 disease*):ti,ab,kw) OR ((insulin NEAR/3 autoimmune NEAR/3 (hypoglycaemia OR hypoglycemia)):ti,ab,kw) OR 'insulin autoimmunity':ti,ab,kw OR ((spontaneous NEAR/3 (hypoglycaemia OR hypoglycemia) NEAR/3 (attack* OR insulin)):ti,ab,kw) OR ((insulinNEAR/3 ('autoimmune disease' OR 'autoimmune diseases' OR 'autoimmune syndrome' OR 'autoimmune syndromes')):ti,ab,kw)	761
#1	'hirata disease'/exp OR 'insulin autoimmune syndrome'/exp	107

PubMed

Date of the search: 04-09-2020

Search	Query	Results
#5	**Search: #4 AND #3**	187
#4	**Search: "review"[sb] OR "**systematic"[sb] OR "meta-analysis"[pt] OR "meta-analysis as topic"[Mesh] OR "meta-analysis"[Mesh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal:__jrid21711]	3,795,869
#3	**Search:** #1 AND #2 **Sort by:** Most Recent	936
#2	**Search:** ("bulgarian"[Language] OR "catalan"[Language] OR "croatian"[Language] OR "czech"[Language] OR "danish"[Language] OR "dutch"[Language] OR "english"[Language] OR "estonian"[Language] OR "finnish"[Language] OR "french"[Language] OR "german"[Language] OR "greek modern"[Language] OR "hungarian"[Language] OR	29,780,296

	"italian"[Language] OR "latvian"[Language] OR "lithuanian"[Language] OR "multiple languages"[Language] OR "norwegian"[Language] OR "polish"[Language] OR "portuguese"[Language] OR "romanian"[Language] OR "scottish gaelic"[Language] OR "serbian"[Language] OR "slovak"[Language] OR "slovenian"[Language] OR "spanish"[Language] OR "swedish"[Language] OR "undetermined"[Language] OR "welsh"[Language]) **Sort by:** Most Recent	
#1	**Search:** (autoimmune hypoglycaemia[tiab] OR autoimmune hypoglycaemia[tiab] OR (("insulin autoimmune"[tiab] OR "autoimmune insulin"[tiab]) AND syndrom*[tiab])OR "insulin autoimmune disease"[tiab] OR "insulin autoimmune diseases"[tiab] OR (endogenous[tiab] AND hyperinsulinemic[tiab] AND (hypoglycaemia[tiab] OR hypoglycemia[tiab])) OR (hirata*[tiab] AND disease*[tiab]) OR (insulin[tiab] AND autoimmune[tiab] AND (hypoglycaemia[tiab] OR hypoglycemia[tiab])) OR "insulin autoimmunity"[tiab] OR (spontaneous[tiab] AND (hypoglycaemia[tiab] OR hypoglycemia[tiab]) AND (attack*[tiab] OR insulin[tiab])) OR (insulin[tiab] AND ("autoimmune syndrome"[tiab] OR "autoimmune syndromes"[tiab])) OR ("insulin autoimmune disease"[tiab] OR "insulin autoimmune diseases"[tiab]))	981

1147

1148 **Search 3**

1149 Embase

1150 Date of the search: 04-09-2020

Set	Query	Results
#17	#16 NOT #17 AND [english]/lim	2,203
#18	#16 NOT #17	2,400
#17	(rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset*:ti) AND 'animal experiment'/de	1,077,288
#16	#14 NOT #15	2,405
#15	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,272,297
#14	#5 AND #13	3,014
#13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	5,520,026
#12	((data NEAR/1 (synthes* OR extraction* OR abstraction*)):ti,ab) OR handsearch*:ti,ab OR 'hand search':ti,ab OR 'hand searches':ti,ab OR 'hand searching':ti,ab OR 'mantel haenszel':ti,ab OR peto:ti,ab OR 'der simonian':ti,ab OR dersimonian:ti,ab OR 'fixed effect':ti,ab OR 'fixed effects':ti,ab OR 'latin square':ti,ab OR 'latin squares':ti,ab OR 'meta analysis':ti,ab OR 'meta analyses':ti,ab OR 'met analysis':ti,ab OR 'met analyses':ti,ab OR metaanaly*:ti,ab OR metanaly*:ti,ab OR 'meta regression':ti,ab OR 'meta regressions':ti,ab OR metaregression*:ti,ab OR medline:ti,ab OR cochrane:ti,ab OR pubmed:ti,ab OR medlars:ti,ab OR embase:ti,ab OR cinahl:ti,ab OR cochrane:jt OR 'evidence report':jt OR ((comparative NEAR/3 (efficacy OR effectiveness)):ti,ab) OR 'outcomes research':ti,ab OR 'relative	475,049

	effectiveness':ti,ab OR (((indirect OR 'indirect treatment' OR 'mixed treatment') NEAR/3 comparison):ti,ab)	
#11	((systematic* NEAR/3 (review* OR overview*)):ti,ab) OR ((methodologic* NEAR/3 (review* OR overview*)):ti,ab) OR ((quantitative NEAR/3 (review* OR overview* OR synthes*)):ti,ab) OR ((research NEAR/3 (integrati* OR overview*)):ti,ab) OR ((integrative NEAR/3 (review* OR overview*)):ti,ab) OR ((collaborative NEAR/3 (review* OR overview*)):ti,ab) OR ((pool* NEAR/3 analy*):ti,ab)	283,769
#10	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR 'biomedical technology assessment'/exp	415,886
#9	'crossover procedure'/exp OR (((crossover OR 'cross over') NEAR/10 (study OR studies OR design* OR method* OR procedure OR comparison)):ti,ab)	94,585
#8	((singl* OR doubl* OR trebl* OR tripl*) NEAR/10 (mask* OR blind* OR dumm*)):ti,ab	252,294
#7	'clinical trial (topic)'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'triple blind procedure'/exp	542,371
#6	'clinical trial'/exp OR 'randomization'/exp OR randomized:ti,ab OR randomised:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab	4,935,446
#5	#3 OR #4	10,181
#4	alipure:ti,ab,kw OR 'alpha-lipogamma':ti,ab,kw OR 'alphalipogamma':ti,ab,kw OR 'alpha-lipon':ti,ab,kw OR alphalipon:ti,ab,kw OR 'alpha liponaure':ti,ab,kw OR alphaliponaure:ti,ab,kw OR alphaliponsaure:ti,ab,kw OR 'alpha liponsaure':ti,ab,kw OR 'alpha lippon':ti,ab,kw OR alphalippon:ti,ab,kw OR 'alpha vibolex':ti,ab,kw OR alphavibolex:ti,ab,kw OR azulipont:ti,ab,kw OR berlition:ti,ab,kw OR berlithione:ti,ab,kw OR biletan:ti,ab,kw OR 'biomo lipon':ti,ab,kw OR biomolipon:ti,ab,kw OR 'byodinoral r':ti,ab,kw OR 'coenzyme compositum':ti,ab,kw OR 'discus compositum':ti,ab,kw OR duralipon:ti,ab,kw OR 'espa lipon':ti,ab,kw OR espalipon:ti,ab,kw OR fenint:ti,ab,kw OR 'hepar compositium':ti,ab,kw OR heparlipon:ti,ab,kw OR juthiac:ti,ab,kw OR 'ledum compositum':ti,ab,kw OR 'lycopodium compositum':ti,ab,kw OR liposan:ti,ab,kw OR 'liponsaure-ratiopharm':ti,ab,kw OR liponsaureratiopharm:ti,ab,kw OR lipothion:ti,ab,kw OR mtwalphaliponsaure:ti,ab,kw OR neurium:ti,ab,kw OR octolipen:ti,ab,kw OR oktolipen:ti,ab,kw OR 'pleomix alpha':ti,ab,kw OR 'quamtrax ala':ti,ab,kw OR thioctacid:ti,ab,kw OR thioctacide:ti,ab,kw OR thioctan:ti,ab,kw OR thioctsan:ti,ab,kw OR thiogamma:ti,ab,kw OR thiotacid:ti,ab,kw OR tromlipon:ti,ab,kw OR tioctacid:ti,ab,kw OR tioctan:ti,ab,kw OR tioctidasi:ti,ab,kw OR 'ubichinon compositum':ti,ab,kw OR 'verla lipon':ti,ab,kw OR verlalipon:ti,ab,kw OR zeel:ti,ab	141
#3	#1 OR #2	10,112
#2	(('1 2 dithiolan 3 pentanic' OR 12dithiolan3pentanic OR '1 2 dithiolane 3 pentanoic' OR '12dithiolane3pentanoic' OR '1 2 dithiolane 3 valeric' OR '12dithiolane3valeric' OR '5 dithiolan 3 yl valeric' OR '5dithiolan3ylvaleric' OR '5 1 2 dithiolan 3 yl valeric' OR 512ditiolan3ylvaleric OR 68thioctic OR '6 8thioctic	6,833

	acid' OR alipoic OR alipoic OR lipoic OR liponic OR thioctic OR tioctic) NEAR/3 (acidOR acids)):ti,ab,kw	
#1	'thioctic acid'/exp OR '1077 28 7':ti,ab,kw OR 1077287:ti,ab,kw	9,259

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1153 PubMed

1154 Date of the search: 04-09-2020

Search	Query	Results
#12	**Search:** "english"[Language] AND #11	772
#11	**Search:** #9 NOT #10	843
#10	**Search:** (rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR swine[ti] OR porcine[ti] OR murine[ti] OR sheep[ti] OR lambs[ti] OR pigs[ti] OR piglets[ti] OR rabbit[ti] OR rabbits[ti] OR cat[ti] OR cats[ti] OR dog[ti] OR dogs[ti] OR cattle[ti] OR bovine[ti] OR monkey[ti] OR monkeys[ti] OR trout[ti] OR marmoset*[ti])	2,021,263
#9	**Search:** #7 NOT #8	934
#8	**Search:** ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	4,731,720
#7	**Search:** #6 AND #3	1,511
#6	**Search:** #4 OR #5	3,788,408
#5	**Search:** "clinical trial"[pt] OR "Random Allocation"[Mesh] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Clinical Trials as Topic"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) AND (mask*[tiab] OR blind*[tiab] OR dumm*[tiab])) OR "Cross-Over Studies"[Mesh] OR ((crossover[tiab] OR "cross over"[tiab]) AND (study[tiab] OR studies[tiab] OR design*[tiab] OR method*[tiab] OR procedure[tiab] OR comparison[tiab]))	3,516,499
#4	**Search:** systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[Mesh] OR meta-analysis[Mesh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal:__jrid21711]	433,871
#3	**Search:** #1 OR #2 **Sort by:** Most Recent	6,014

#2	**Search:** "Thioctic Acid"[Mesh] OR "1077-28-7"[tiab] OR 1077287[tiab] OR "1,2-Dithiolan-3-pentanic acid"[tiab] OR "1,2-Dithiolan-3-pentanic acids"[tiab] OR "1 2 dithiolane 3 pentanoic acid"[tiab] OR "12dithiolane3pentanoic acid"[tiab] OR "1 2 dithiolane 3 valeric acid"[tiab] OR '"2dithiolane3valeric acid"[tiab] OR "5 dithiolan 3 yl valeric acid"[tiab] OR "5dithiolan3ylvaleric acid"[tiab] OR "5 1 2 dithiolan 3 yl valeric acid"[tiab] OR "512ditiolan3ylvaleric acid"[tiab] OR "1 2 dithiolane 3 pentanoic acids"[tiab] OR "12dithiolane3pentanoic acids"[tiab] OR "1 2 dithiolane 3 valeric acids"[tiab] OR '"2dithiolane3valeric acids"[tiab] OR "5 dithiolan 3 yl valeric acids"[tiab] OR "5dithiolan3ylvaleric acids"[tiab] OR "5 1 2 dithiolan 3 yl valeric acids"[tiab] OR "512ditiolan3ylvaleric acids"[tiab] OR "68thioctic acid"[tiab] OR "68thioctic acids"[tiab] OR "6 8thioctic acid"[tiab] OR "6 8thioctic acids"[tiab] OR "αlipoic acid"[tiab] OR "αlipoic acids"[tiab] OR "lipoic acid"[tiab] OR "lipoic acids"[tiab] OR "liponic acid"[tiab] OR "liponic acids"[tiab] OR "thioctic acid"[tiab] OR "thioctic acids"[tiab] OR "tioctic acid"[tiab] OR "tioctic acids"[tiab]	5,970
#1	**Search: Alipure[tiab] OR "Alpha-Lipogamma"[tiab] OR "AlphaLipogamma"[tiab] OR "Alpha-Lipon"[tiab] OR AlphaLipon[tiab] OR "alpha Liponaure"[tiab] OR alphaLiponaure[tiab] OR AlphaLiponsaure[tiab] OR "Alpha-Liponsaure"[tiab] OR "Alpha Lippon"[tiab] OR AlphaLippon[tiab] OR "Alpha Vibolex"[tiab] OR alphaVibolex[tiab] OR Azulipont[tiab] OR Berlithion[tiab] OR Berlithione[tiab] OR Biletan[tiab] OR "Biomo lipon"[tiab] OR Biomolipon[tiab] OR "Byodinoral R"[tiab] OR "coenzyme compositum"[tiab] OR "discus compositum"[tiab] OR Duralipon[tiab] OR "Espa-lipon"[tiab] OR Espalipon[tiab] OR Fenint[tiab] OR "Hepar compositum"[tiab] OR Heparlipon[tiab] OR Juthiac[tiab] OR "Lycopodium compositum"[tiab] OR "Ledum compositum"[tiab] OR Liposan[tiab] OR "Liponsaure-ratiopharm"[tiab] OR Liponsaureratiopharm[tiab] OR Lipothion [tiab] OR MTWAlphaliponsaure[tiab] OR Neurium[tiab] OR Octolipen[tiab] OR Oktolipen[tiab] OR "Pleomix Alpha"[tiab] OR "Quamtrax ALA"[tiab] OR Thioctacid[tiab] OR Thioctacide[tiab] OR Thioctan[tiab] OR Thioctsan[tiab] OR Thiogamma[tiab] OR Thiotacid[tiab] OR Tromlipon[tiab] OR Tioctacid[tiab] OR Tioctidasi[tiab] OR Tioctan[tiab] OR Tioctidasi[tiab] OR "Ubichinon compositum"[tiab]**	78

	OR "Verla Lipon"[tiab] OR VerlaLipon[tiab] OR Zeel[tiab]	

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Abbreviations

AFSSA	French Food Safety Agency
ALA	alpha-lipoic acid
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
AUC	area under the curve
CAS	Chemical Abstracts Service
DTU	Danish National Food Institute
EC	European Commission
EFSA	European Food Safety Authority
EINECS	European Inventory of Existing Chemical Substances
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FSANZ	Food Safety Australia New Zealand
HLA	human leukocyte antigen
IAA	insulin autoantibodies
IAS	insulin autoimmune syndrome
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IUPAC	International Union of Pure and Applied Chemistry
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NOAEL	no observed adverse effect level
Ph. Eur.	European Pharmacopeia
PRAC	Pharmacovigilance Risk Assessment Committee