DTU Food
National Food Institute

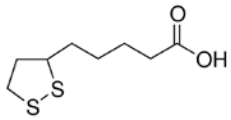
DTU Doc nr. 17/14450

Date 10.10.2017

Safety of alpha-lipoic acid use in food supplements

The Danish Veterinary and Food Administration has asked DTU FOOD to assess the safety of alpha-lipoic acid use in food supplements in a recommended daily dose of 150-200 mg per day.

Specification for alpha-lipoic acid

SYNONYMS	Thioctic acid 1,2-dithiolane-3-pentanoic acid; 1,2-dithiolane-3-valeric acid
DEFINITION	
Chemical name	1,2-Dithiolan-3-pentanic acid
CAS Number	1077-28-7
Chemical formula	
Molecular formula	$C_8H_{14}O_2S_2$
Molecular weight	206.32 g/mol
Content	Not less than 99.0% and no more than 101.0% alpha-lipoic acid determined by gas chromatography
IDENTIFICATION	
Identification test	IR absorption. The spectrum should be in accordance with an equivalent reference spectrum
A. Melting point	60-62° C
B. Specific rotation	$[\alpha]_D^{22}$: +/- 1.0° (50 mg/ml in ethanol)
PURITY	
Loss on drying	No more than 0,2%
Ashes	No more than 0.1%
Heavy metals	No more than 10 mg/kg (by method II, Ph. US 39., 673. Mercury is not identified by this test)
Lead	Not more than 1 mg/kg

Specification in accordance with the United States Pharmacopeia (USP)

Studies in humans

No studies on alpha-lipoic acid conducted in healthy subjects were identified in the literature. Healthy subjects are the target group for food supplements. Several studies conducted in different patient groups including patients with diabetic neuropathy, infertile men, overweight or obese hypertensive, diabetic or hypercholesterolemic subjects were identified (Han et al., 2012; Koh et al., 2011 ; Hahm et al., 2004;

Porasuphatana et al., 2012; Haghighian et al., 2015; Ziegler et al., 2006). Intakes of alpha-lipoic acid in these studies ranged from 300 to 1800 mg per day and the studies focused on improvement of symptoms related to the diseases. They are thus not designed to investigate possible adverse effects of alpha-lipoic acid. A number of adverse effects such as allergic skin reactions (including hives and itchiness), gastrointestinal symptoms (such as stomach ache, nausea, vomiting and diarrhea) and dizziness have been reported in these studies (Han et al., 2012; Hahm et al., 2004 Koh et al., 2011; Porasuphatana et al., 2012; Ziegler et al., 2006). In addition, case reports of intoxication after ingestion of an unknown amount alpha-lipoic acid food supplements have been described (Tolunay et al., 2015; Hadzik et al., 2014).

Studies in animals

The risk assessment of alpha-lipoic acid use in food supplements and the proposal of an upper safe intake level are based on two published articles, both by Cremer et al. (Cremer et al., 2006a; Cremer et al., 2006b). The articles assess the safety of alpha-lipoic acid in acute (a single dose) and 28-day subacute toxicity studies (Cremer et al. 2006a) and a chronic (a daily dose over a two-year period) toxicity study (Cremer et al., 2006b).

The single-dose study found no acute toxicity of alpha-lipoic acid in rats (i.e. no reported deaths) at oral dosing up to 2000 mg alpha-lipoic acid per kg body weight. However, during the 2- to 6-h post-dosing the rats administered the 2000 mg dose showed signs of reduced well-being, including sedation, apathy, piloerection, hunched posture and/or eye closure (Cremer et al, 2006a). In the subacute 28-day toxicity study, no signs of adverse effects, clinical symptoms or pathological changes were reported in rats dosed with 31.6 or 61.9 mg alpha-lipoic acid per kg body weight per day (Cremer et al. 2006a). At the highest dose level (121 mg per kg body weight per day), slight hypokinesia was displayed in one male rat at the end of the study. Several female rats in the same dose group exhibited coordination disturbances beginning 30-180 minutes post-dosing and a single animal showed slight clonic convulsions on a single occasion. In the highest dosed males, decreased cholesterol, total protein and triglyceride concentrations, as well as small but statistically significant increases in the liver enzyme alanine aminotransferase (ALT) were reported. An increase in ALT is an indicator of liver injury. Both absolute and relative kidney weights were statistically significantly increased in male and female rats at the highest dose level (121 mg per kg body weight per day). In female rats, relative kidney weight was also statistically significantly increased in animals administered the middle dose (61.9 mg alpha-lipoic acid per kg body weight per day). Absolute liver weight was statistically significantly increased in the highest dosed female rats while relative liver weight was statistically significantly increased in the lowest, middle and highest dosage groups. In males, relative liver weight was statistically significantly increased in the highest dosage group. In all groups, slightly increased incidence of microgranulomas was observed in the liver. The microgranulomas predominantly consisted of macrophages and were frequently associated with single cell necrosis of hepatocytes (i.e. cell death). The incidence was comparable between the groups, but in the highest dosed male and female rats, the changes were more severe, and the microgranulomas were larger and occurred more frequently than in the control group.

In a 2-year chronic toxicity study, female and male rats (a total of 180 rats of each sex divided into four groups) were daily administered 0, 20, 60 or 180 mg of alpha-lipoic acid per kg body weight through the diet (Cremer et al., 2006b). It should be noted that this study was performed in the 1970s by the standards of that time but not published until 2006. There was no effect of alpha-lipoic acid on body weight or body weight gain in male or female rats given the two lowest doses. The highest dose resulted in statistically significantly reduced body weight gain in both males and females (after 12 and 8 weeks of dosing for males and females, respectively),

resulting in reduced body weight for males and females of 12.8 and 22.5%, respectively, compared to the control group at sacrifice. A reduction in body weight gain of above 10% is perceived as a toxic effect (OECD 2009). Therefore, the observed decrease in body weight gain in both male and female rats observed in the highest dosage group is considered to be a toxic effect. During the same period, reduced feed intakes were seen in both sexes at the highest dose. No effects on either absolute or relative organ weights were reported after 12 months. However, absolute liver and lung weights of female rats in the highest dosage group were lower compared to controls, whereas absolute heart and thymus weights were lower in highest dosed male rats compared to controls. The relative organ weights were comparable between groups.

Kuhla et al. (2016) describe a study in male mice using only 1 dosage group (20 mg alpha-lipoic acid per kg body weight per day). The mice were dosed daily for 4 and 74 weeks, respectively. After 74 weeks of alpha-lipoic acid dosing, a statistically significant increase in the activity of the liver enzyme aspartate aminotransferase was observed. Likewise, increased leukocyte infiltration, inflammation and necrosis in the liver tissue were seen, all indicating liver damage. Although the study has experimental weaknesses and is not a standard toxicological study, it shows that a dose, corresponding to 1/3 of the dose that did not produce adverse effect in the rat studies by Cremer et al., has detrimental effect on the mouse liver. This could indicate that mice are more sensitive than rats and in line with studies showing that the LD_{50} for mice (acute oral toxicity, the dose killing half of the tested animals) is 44% lower than the corresponding LD_{50} in rats (502 and 1130 mg alfa-lipoic acid per kg body weight per day for mice and rats, respectively) (Cremer et al., 2006a).

Based on the two rat studies by Cremer et al., a dose of 60 mg alpha-lipoic acid per kg body weight per day is considered a "no observed adverse effect" (NOAEL). To reach an upper limit for a safe intake in humans, an uncertainty factor (UF) of 100 is used, which takes into account inter- and intra-species variations. With a NOAEL of 60 mg alpha-lipoic acid per kg body weight per day and an UF of 100, the upper limit of safe intake of alpha-lipoic acid is 0.6 mg per kg body weight per day. This corresponds to a maximum daily dose of 42 mg alpha-lipoic acid for a person weighing 70 kg.

Autoimmune disease

It is known that alpha-lipoic acid can cause insulin autoimmune syndrome (IAS) (DTU memo dated June 7th, 2016; EMA 2015). It is believed that the disease is caused by alpha-lipoic acid being able to cleave the body's own insulin and thereby provoke an allergic reaction. 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. IAS is characterised by the combination of hypoglycaemia and high concentrations of immunoreactive insulin and high titres of antibodies to endogenous insulin without prior exposure to exogenous administered insulin (EMA 2015). This manifests itself in neurological symptoms such as tremor, palpitation, anxiety, sweating, hunger and numbness/tingling. Extreme hypoglycaemia can cause coma. Treatment and discontinuation of ingestion of alpha-lipoic acid will over time cause IAS to disappear.

There is a strong genetic element in the development of IAS, which is associated with two specific genotypes in the blood type marker Human Leucocyte Antigen (HLA). The genotype HLA-DRB1*04:06 is predominantly found in Japanese (3.1% of the population) and in Korean individuals, while the genotype HLA-DRB1*04:03 is predominantly found in ethnic Europeans (1.1% of the population in Italy are carriers). Despite the fact that the disorder is rarely described among ethnic Europeans, Gullo et al. (2014) speculate that the disorder is likely to be under-reported and misdiagnosed as insulinoma. They further speculate that the increase in use of alpha-lipoic acid in food supplements in Italy likely is associated with the increase the frequency of IAS. Thus, they have

diagnosed six cases of IAS caused by alpha-lipoic acid in 22 months, of which one of the diagnosed had diabetes. In addition, it is not common to know one's HLA blood type and thus know if a person is at risk of developing AIS.

Conclusion

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 conclude 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.

References

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