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Risk Assessment of "Other Substances" – L- tryptophan

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Authors' contributions

This work was carried out in collaboration among all authors. The opinion has been assessed and approved by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of VKM. All authors read and approved the final manuscript.

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Grey Literature

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ABSTRACT

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the risk of "other substances" in food supplements and energy drinks sold in Norway. VKM has assessed the risk of doses given by NFSA. These risk assessments will provide NFSA with the scientific basis for regulating the addition of "other substances" to food supplements.

"Other substances" are described in the food supplement directive 2002/46/EC as *substances other than vitamins or minerals that have a nutritional or physiological effect*. "Other substances" are added mainly to food supplements, but also to energy drinks and other foods. VKM has not in this series of risk assessments of "other substances" evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of L-tryptophan and is based on previous risk assessments of L-tryptophan and scientific papers retrieved from systematic literature searches.

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L-tryptophan is an indispensable amino acid in humans, which in addition to its role in protein synthesis, also participates in complex metabolic pathways where it acts as a precursor to the potent neurotransmitter serotonin, the hormone melatonin, and the vitamin niacin (vitamin B3). L-tryptophan is available from a wide variety of protein-rich foods in the normal diet, including meat, fish, milk and dairy products, egg, beans, lentils and also bread and grains, pasta, rice, fruit and vegetables.

According to information from NFSA, L-tryptophan is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of the following doses of L-tryptophan in food supplements: 250 mg/day, 300 mg/day, and 450 mg/day for adults, adolescents and children 10 years and above. Usual dietary intake of L-tryptophan in Norway is not known, but data from the USA and the UK suggest an average dietary intake of about 900 mg/day of which the main part is bound in food protein.

In phase 1 we have identified seven previous reports that have aimed to assess the safety of L-tryptophan supplementation in humans; the most recent was published by VKM in 2013. To complement the existing reports, a literature search was performed in MEDLINE and EMBASE to retrieve studies published in the period 2012-2015. This search retrieved two recent randomised trials with L-tryptophan. In addition, we performed a literature search concerning safety of L-tryptophan in children and adolescents with no time restriction. This search retrieved no relevant results that met the inclusion criteria.

Four aspects related to safety of L-tryptophan were identified in previous reports: 1) adverse effects reported at high doses, including appetite suppression, nausea and vomiting, faintness, dizziness, drowsiness, tremor, fatigue, and headache; 2) a suggested, but not established, increased risk of cataract; 3) the eosinophilia-myalgia syndrome (EMS), which is thought to be caused by contaminants produced in the manufacturing of L-tryptophan supplements, however this is still unresolved; 4) the risk of adverse drug reactions caused by excessive serotonergic action by concomitant use of antidepressants, including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants and other drugs, known as the *serotonin syndrome.*

According to previous reports, doses of 3 to 6 g/day of L-tryptophan have been associated with adverse effects. Using an uncertainty factor of 10, conclusions in previous reports have suggested a maximum level of 220 mg/day for adults. An upper tolerable intake level (UL) of 220 mg/day was first proposed in a report by the UK Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in 2004, and was derived from the average dose of L-tryptophan consumed as a prescription drug against depression in the UK at the time (2228 mg/day). This level has been maintained in later reports by other committees, most recently VKM in 2013 as a tentative guidance level. Additional information from the publications retrieved in the literature search did not provide evidence of sufficient weight to change the previous conclusions concerning UL.

There is a lack of well-designed supplementation studies with L-tryptophan in humans designed to address adverse effects and dose-response relationship as primary outcome. There is also a lack of data about potential adverse health effects of L-tryptophan supplementation in children and adolescents.

Patients using antidepressant drugs constitute a specific vulnerable subgroup of the population with regard to possible adverse effects of L-tryptophan supplements, due to the potentially life-threatening drug interaction effects that occur from excessive serotonergic action.

The Norwegian Scientific Committee for Food Safety (VKM) concludes that:

- In adults (≥18 years), the specified doses 250, 300, and 450 mg/day L-tryptophan in food supplements may represent a risk of adverse health effects.
- In adolescents (14 to <18 years), the specified doses 250, 300, and 450 mg/day L-tryptophan in food supplements may represent a risk of adverse health effects.

- In children (10 to <14 years), the specified doses 250, 300, and 450 mg/day L-tryptophan in food supplements may represent a risk of adverse health effects.
- Children below 10 years were not included in this assessment.

Keywords: Adverse health effect; L-tryptophan; food supplement; negative health effect; Norwegian Scientific Committee for Food Safety; other substances; risk assessment; VKM.

Available:https://vkm.no/download/18.645b840415d03a2fe8f2602c/1502802082645/Risk%20assessment%20of%20%22other%20substances%22%20%E2%80%93%20L-tryptophan.pdf

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This work was carried out in collaboration between all authors. The opinion has been assessed and approved by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of VKM. All authors read and approved the final manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.