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## **Risk Assessment of "Other Substances" – L-Glutamine and L-glutamic Acid**

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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.*

### **Article Information**

DOI: 10.9734/EJNFS/2020/v12i830261

**Grey Literature**

**Received 28 April 2020**  
**Accepted 02 July 2020**  
**Published 05 August 2020**

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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 the NFSA. These risk assessments will provide the NFSA with the scientific basis for regulating the addition of "other substances" to food supplements and other foods.

"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. They 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.

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The present report is limited to the use of L-glutamine and L-glutamic acid in food supplements. Risks related to glutamine and glutamic acid added to food and drinks, protein hydrolysates or high dietary protein intake are outside the scope of the opinion. The report is based on previous risk assessments of glutamine and glutamic acid and scientific papers retrieved from a comprehensive literature search.

L-glutamine is considered a non-essential amino acid in humans. In addition to its role in protein synthesis and the handling by the body of ammonia (via urea cycle), L-glutamine participates in other complex metabolic pathways e.g. in the central nervous system, immune system, and insulin secretion. L-glutamine is deaminated by glutaminase to form glutamic acid. L-glutamine is available from all protein-containing foods. High-protein foods contain the most (e.g. meat, fish, eggs and dairy products).

L-glutamic acid is a non-essential amino acid. At physiological conditions its side chain is fully ionised, i.e. it exists in the form of glutamate. In addition to its role as substrate in protein synthesis, glutamic acid has important metabolic roles as a source of  $\alpha$ -ketoglutarate in the citric acid cycle and in the handling by the body of ammonia (via urea cycle). Glutamic acid is also a major neurotransmitter. In the unbound form only, glutamic acid is responsible for umami, one of the five basic tastes sensed by humans. Glutamic acid is used as a flavour enhancer in the form of its salt monosodium glutamate. All meats, poultry, fish, eggs, and dairy products are excellent sources of glutamic acid. Some protein-rich plant foods also serve as sources, e.g. wheat protein contains 30% to 35% glutamic acid.

According to information from the NFSA, L-glutamine and glutamic acid are ingredients in food supplements sold in Norway. The NFSA has requested a risk assessment of the following doses of L-glutamine in food supplements: 3500 mg/day, 5000 mg/day, 8000 mg/day, 10000 mg/day, 12000 mg/day, 15000 mg/day, and 16500 mg/day, and the following doses of glutamic acid: 1000 mg/day, 2000 mg/day, 3000 mg/day, 4000 mg/day, 5000 mg/day, and 5500 mg/day. Dietary intake in Norway is not known, but data from the third National Health and Nutrition Examination Survey (NHANES III) 1988-1994 in the USA suggest a mean dietary intake of about 15 g glutamic acid per day.

In phase 1 of the present evaluation of "other substances", previous reports that assessed the safety of L-glutamine or L-glutamic acid supplementation in humans were identified. For the present report, a systematic literature search was performed to retrieve human studies published in the period 2011-2015, and in addition separate literature searches were performed for animal studies and studies in children and adolescents. The main search retrieved no publications reporting results from trials with L-glutamine or L-glutamic acid in healthy humans, nor did the search for studies in children and adolescents identify any relevant publications. Three human studies on glutamates were included as part of the risk assessment of glutamic acid. The search for animal studies retrieved four relevant reports.

No major specific issues related to safety of L-glutamine and L-glutamic acid used as food supplements were identified in previous reports. However, a lack of studies in healthy adult individuals as well as in children was pointed out, and in particular the absence of long-term studies in healthy individuals.

According to previous reports, short-term intake of doses of L-glutamine up to 0.5 g/kg bw per day has not been found to cause significant adverse effects. Up to 1.5 g per day of Lglutamic acid has been reported not to be associated with adverse effects. Conclusions in previous reports have indicated maximum supplemental levels of 3.5 and 5 g per day of Lglutamine and 1 g per day of L-glutamic acid.

For the risk characterisation of L-glutamine, in the absence of long-term human studies in healthy individuals, VKM will base the value of comparison on the highest dose tested (no observed adverse effect level; NOAEL) in two 90-day studies in rodents, 3832 mg/kg bw per day. Employing an uncertainty factor of 10 for the extrapolation between species, the value of comparison is set to 383 mg/kg bw per day, corresponding to 26.8 g per day in a 70 kg adult. Data from studies in

various patient groups support the data from the two animal studies indicating the absence of significant adverse effects with this dose.

In the risk characterisation of L-glutamic acid, in the absence of any unequivocally demonstrated reproducible adverse effect in short-term human studies and an absence of long-term studies in healthy individuals, VKM will base the value of comparison on the highest dose tested (NOAEL) in a 28-day study in rodents, 953 mg/kg bw per day. Employing an uncertainty factor of 10 for the extrapolation between species, the value of comparison is set to 95 mg/kg bw, corresponding to 6.7 g per day in a 70 kg adult. Data from early long-term studies in humans (doses up to 45 g per day) and in animals as well as short-term studies on glutamates support the data from the animal study indicating the absence of significant adverse effects with this dose.

Based on these data, the Norwegian Scientific Committee for Food Safety (VKM) concludes that:

**L-glutamine:**

- In adults (≥18 years), the specified doses of 3500, 5000, 8000, 10000, 12000, 15000 and 16500 mg/day L-glutamine in food supplements are considered unlikely to cause adverse health effects.
- In adolescents (14 to <18 years), the specified doses of 3500, 5000, 8000, 10000, 12000, 15000 and 16500 mg/day mg/day L-glutamine in food supplements are considered unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses of 3500, 5000, 8000, 10000, 12000, 15000 and 16500 mg/day mg/day L-glutamine in food supplements are considered unlikely to cause adverse health effects.

**L-glutamic acid:**

- In adults (≥18 years), the specified doses of 1000, 2000, 3000, 4000, 5000 and 5500 mg/day L-glutamic acid in food supplements are considered unlikely to cause adverse health effects.
- In adolescents (14 to <18 years), the specified doses of 1000, 2000, 3000, 4000, 5000 and 5500 mg/day L-glutamic acid in food supplements are considered unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses 1000, 2000, 3000, and 4000 mg/day Lglutamic acid in food supplements are considered unlikely to cause adverse health effects. The specified doses of 5000 and 5500 mg/day may represent a risk of adverse health effects.
- Children below 10 years were not included in the terms of reference.
- Short summary:
- The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of specified doses of L-glutamine and Lglutamic acid in food supplements. VKM concludes that:
- L-glutamine
- In adults (≥18 years), the specified doses of 3500, 5000, 8000, 10000, 12000, 15000 and 16500 mg/day L-glutamine in food supplements are considered unlikely to cause adverse health effects.
- In adolescents (14 to <18 years), the specified doses of 3500, 5000, 8000, 10000, 12000, 15000 and 16500 mg/day L-glutamine in food supplements are considered unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses of 3500, 5000, 8000, 10000, 12000, 15000 and 16500 mg/day L-glutamine in food supplements are considered unlikely to cause adverse health effects.

**L-glutamic acid:**

- In adults (≥18 years), the specified doses of 1000, 2000, 3000, 4000, 5000 and 5500 mg/day L-glutamic acid in food supplements are considered unlikely to cause adverse health effects.

- In adolescents (14 to <18 years), the specified doses of 1000, 2000, 3000, 4000, 5000 and 5500 mg/day L-glutamic acid in food supplements are considered unlikely to cause adverse health effects.
- In children (10 to <14 years), the specified doses 1000, 2000, 3000, and 4000 mg/day L-glutamic acid in food supplements are considered unlikely to cause adverse health effects. The specified doses of 5000 and 5500 mg/day may represent a risk of adverse health effects.

Children below 10 years were not included in the terms of reference.

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

Available: <https://vkm.no/download/18.645b840415d03a2fe8f26029/1502799994850/Risk%20assessment%20of%20%22other%20substances%22%20%E2%80%93%20L-glutamine%20and%20L-glutamic%20acid.pdf>

**ISBN:** 978-82-8259-215-4

#### **NOTE:**

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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**Suggested citation:** VKM. (2016) Risk assessment of "other substances" – L-glutamine and L-glutamic acid. Opinion of the Panel on Nutrition, dietetic products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety, ISBN: 978-82-8259-215-4, Oslo, Norway.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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