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Risk Assessment of "Other Substances" – L-Citrulline

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Authors' contributions

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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Grey Literature

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 in food supplements and concentrations in energy drinks given by NFSA. These risk assessments will provide NFSA with the scientific basis while 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 and/or physiological effect. It is 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-citrulline, and it is based on a previous risk assessment and articles retrieved from a literature search.

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According to information from NFSA, L-citrulline is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of 1000, 1500 and 2000 mg/day of L-citrulline in food supplements. The intake of L-citrulline was estimated for the age groups children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Other sources of L-citrulline, such as foods and cosmetics, have not been included in the present risk assessment.

The natural isoform of citrulline is the L-form. In mammals, it is found in all organisms and tissues. L-Citrulline is not part of the amino acids that are incorporated into proteins by the standard genetic code; therefore it is classified as a non-protein amino acid. Thus, its presence in a protein always results from a post-translational modification of the protein.

L-citrulline is found in high levels in certain Cucurbitacea, including watermelon, cucumber, pumpkin and courgette, and in certain algae such as Grateloupia vulgaris. It is also present in fish, meat, pulses and milk, and in vegetables such as onions and garlic.

Following oral intake of L-citrulline, plasma L-citrulline concentration increases rapidly but returns to baseline values within 5-8 hours post-exposure. There are three interconnected metabolic pathways for L-citrulline: 1) arginine biosynthesis, 2) nitric oxide (NO) cycle, and 3) the complete urea cycle. Renal L-citrulline reabsorption appears very efficient because urinary loss is very low even at high (up to 15 g) L-citrulline intake.

No adverse health effects of L-citrulline were observed in six human studies covering the ages 12 months to 56 years, with L-citrulline exposure lengths varying from less than one day (acute doses) to 2 years. The doses varied from 2.1-179 mg/kg bw per day for children.

(<14 years), 1.5-175 mg/kg bw per day for adolescents (14 to <18 years) and 21-214 mg/kg bw per day in adults. The human studies available had low number of participants and, with exception of one study, included non-healthy populations. In a 2-year study by Rajantie et al. (1980), 19 patients with lysinuric protein intolerance, ages 1.9-32.7 years, were included. No adverse effects were reported from daily intakes of 65 mg/kg bw in children (10 to <14 years), 46 mg/kg bw in adolescents (14 to <18 years) and 40 mg/kg bw in adults (highest doses applied). These age-specific reference points were used for comparisons with the estimated exposures in the risk characterization.

For children, from a daily intake of 1000, 1500 and 2000 mg the estimated exposures are 23.0, 34.6 and 46.1 mg/kg bw per day, respectively. These intake values are below 65 mg/kg bw per day. VKM therefore considers it unlikely that a daily intake of 1000, 1500 or 2000 mg L-citrullline from food supplements causes adverse health effects in children (10 to <14 years).

For adolescents, from a daily intake of 1000, 1500 and 2000 mg the estimated exposures are 16.3, 24.5 and 32.6 mg/kg bw per day, respectively. These intake values are below 46 mg/kg bw per day. VKM therefore considers it unlikely that a daily intake of 1000, 1500 or 2000 mg L-citrullline from food supplements causes adverse health effects adolescents (14 to <18 years).

For adults, from a daily intake of 1000, 1500 and 2000 mg the estimated exposures are 14.3, 21.4 and 28.6 mg/kg bw per day, respectively. These intake values are below 40 mg/kg bw per day. VKM therefore considers it unlikely that a daily intake of 1000, 1500 or 2000 mg L-citrullline from food supplements causes adverse health effects in adults (≥18 years).

Since LPI patients have a different intestinal absorption, renal reabsorption and reduced intracellular efflux of cationic amino acids compared to healthy individuals, it is uncertain whether doses given to LPI patients can be directly extrapolated to healthy individuals.

Persons with citrullinemia caused by mutations in enzymes involved in citrulline metabolism are potentially vulnerable to intake of additional L-citrulline from supplements. In addition, humans with

chronic renal failure and/or mutations in renal citrulline transporters are potentially vulnerable to supplementation of L-citrulline.

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

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COMPETING INTERESTS

Authors have declared that no competing interests exist.