A Proposal for an Upper Limit of Leucine Safe Intake in Healthy Adults\textsuperscript{1–3}

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Abstract
Based on recent research, an upper limit of safe intake (ULSI) for leucine is proposed for healthy adults: 0.53 g/(kg d).

Summary
Leucine, with or without isoleucine and valine, is widely used as a dietary supplement by people practicing intensive exercise and sport. The aim of such supplementation is to reduce muscle soreness (1,2), increase performance (3) and/or decrease postexercise central fatigue (4). The rationale for the 2 former goals is that leucine activates the mammalian target of rapamycin signaling pathway (5). The rationale for the third is that leucine competes with tryptophan at the brain barrier level and therefore decreases serotonin formation into the brain (5). Whether or not leucine is efficient in fulfilling any of these 3 goals is beyond the scope of this paper.

The International Council for Amino Acid Sciences (ICAAS) is a not-for-profit organization aiming to study the safety of amino acid intake from foods and dietary supplements. In the 2000s, a series of 7 workshops was organized by the authors of this paper, who also act as a Scientific Committee to ICAAS. The workshops aimed at defining adequate surrogate markers and studying various groups of amino acids. One of these workshops was devoted to the issues related to the safety of BCAA (6). In addition, ICAAS sponsored a series of studies, the results of which were presented during the 8th Amino Acid Assessment Workshop held in Washington on November 10 and 11, 2011. The results of these 2 studies (7,8) form a coherent picture allowing us to propose an upper limit of safe intake (ULSI) for leucine in healthy adults.

Pencharz et al. (7) enrolled 5 young (25–35 y), healthy men who received graded stepwise increases in intake from 50 to 1250 mg/(kg-d) (7 dosages). The endpoints were leucine oxidation and other surrogate markers such as plasma glucose, alanine aminotransferase, and ammonia to monitor for adverse effects. The metabolic limit to oxidize leucine and the rise in leucine and ammonia plasma concentrations were all observed at intakes >500 mg/(kg-d).

Kato et al. (8) performed a study in male Sprague-Dawley rats for 1 wk. Rats were fed low-, moderate-, or high-protein intakes together with 4 levels of leucine supplementation (0–8%). Endpoints were food intake and transcriptomic analysis. Except when animals were fed a low-protein diet, leucine intake up to 8% had no adverse effects. This intake corresponds to 5.3 g leucine/(kg-d). Considering that protein and energy requirements in rats are ~10 times those of humans and considering that normal healthy people have moderate protein intakes and those practicing exercise or sport have generally high protein intakes,
the no observed adverse event level in humans should be set at 0.53 g/(kg·d). Although previous metabolic studies in rats indicate a 1.7-times higher upper limit (9), the above-proposed no observed adverse event level fits very well with the results found by Elango et al. (7). Taken as a whole, these data allow us to propose an ULSI for leucine at 0.53 g/(kg·d).

Limitations to this recommendation include the facts that the human study included only males (7) and only participants from the general healthy population, not from the specific subpopulation that is consuming such dietary supplements. Because it is quite possible that humans practicing intensive exercise or sport undergo metabolic adaptation, a specific study in this given subpopulation is required to adjust our recommendation. Finally, the human study (7) was acute. Even though the rat study (8) had a longer duration (1 wk, which corresponds in humans to ~3 y), we cannot exclude an adaptation to chronic leucine intake at high dosages in humans. This deserves further important studies.

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Literature Cited