Application of Key Events Dose Response Framework to Defining the Upper Intake Level of Leucine in Young Men1–4

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Abstract

Leucine is sold in large doses in health food stores and is ingested by weight-training athletes. The safety of ingestion of large doses of leucine is unknown. Before designing chronic high-dose leucine supplementation experiments, we decided to determine the effect of graded doses of leucine in healthy participants. The Key Events Dose Response Framework is an organizational and analytical framework that dissects the various biologic steps (key events) that occur between exposure to a substance and an eventual adverse effect. Each biologic event is looked at for its unique dose-response characteristics. For nutrients, there are a number of biologic homeostatic mechanisms that work to keep circulating/tissue levels in a safe, nontoxic range. If a response mechanism at a particular key event is especially vulnerable and easily overwhelmed, this is known as a determining event, because this event drives the overall slope or shape of the dose-response relationship. In this paper, the Key Events Dose Framework has been applied to the problem of leucine toxicity and leucine’s tolerable upper level. After analyzing the experimental data vis a vis key events for leucine leading to toxicity, it became evident that the rate of leucine oxidation was the determining event. A dose-response study has been conducted to graded intakes of leucine in healthy human adult male volunteers. All participants were started at the mean requirement level of leucine [50 mg/(kg · d)] and the highest leucine intake was 1250 mg/(kg · d), which is 25 times the mean requirement. No gut intolerance was seen.

Blood glucose fell progressively but remained within normal values without any changes in plasma insulin. Maximal leucine oxidation levels occurred at an intake of 550 mg leucine/(kg · d), after which plasma leucine progressively increased and plasma ammonia also increased in response to leucine intakes >500 mg/(kg · d). Thus, the “key determining event” appears to be when the participants reach their maximal leucine oxidation level, after which the risk of metabolic adverse effects progressively increased. J. Nutr. 142: 2225S–2226S, 2012.

The establishment of tolerable upper intake levels (UL) for nutrients began in the US with the most recent edition of the Dietary Reference Intakes (1). The UL is defined as the highest level of intake of a nutrient when taken on a daily basis that poses no risk of toxicity for almost all individuals in a population. The risk assessment framework under which the UL for nutrients have been established consists of the following:

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described his group acid leucine. Framework is applied to the determination of a UL for the amino published (3). In this current paper, the Key Events Dose Response technique that are already in use. For many nutrients, there will not be enough known about each key event to do a complete analysis. The Key Events Dose Framework neverthe-

Finally, it is important to note that this study was of an acute ingestion of leucine. If such high levels were ingested over a period of time, although adaptation might occur, it is also possible that adverse effects might be seen at lower levels.

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Literature Cited