The 6th Workshop on the Assessment of Adequate Intake of Dietary Amino Acids: Summary of General Discussion1–3

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With respect to setting safe upper levels of intake for nutrients for human consumption, participants with toxicological and regulatory backgrounds commented on the paucity of systematic data regarding the adverse effects of many of the micronutrients and noted that hazard identification and dose response data were necessary to undertake risk assessment for amino acids. As a framework for nutrient risk assessment, aspects of “A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances,” the report of a joint FAO/WHO Technical Workshop on Nutrient Risk Assessment held in May 2005, was introduced by participants of the FAO/WHO workshop. It was reported that there is a need to identify any adverse health effect and to obtain a quantitative measure relating the presence of any adverse health effect to the intake of the substance; quantitative measures normally used in risk assessment are the no observed adverse effect level, the lowest observed adverse effect level, or the benchmark intake. Uncertainties are then evaluated and an uncertainty factor is applied to the above quantitative measures to give the final upper level. Further adjustments can then be made for setting upper levels for relevant age, sex, and life stage subpopulations.

Few data indicate adverse effects caused by lysine ingestion. The use of lysine in clinical practice is very limited. On the other hand, supplemental lysine has been used for several decades to suppress chronic cold sores caused by Herpes simplex. However, it was noted that the doses used are marginal when compared with daily intakes from the diet. The scientific literature indicated a few studies of lysine as an antiherpetic remedy with doses of under 3 g lysine/d for up to 6 mo showing some benefit but without reports of significant adverse effects. In rats, a 90-d toxicological study reported no adverse effects at lysine doses as high as 3–4 g/kg body weight. It was also reported that excess lysine, 10 or 12 times the requirement, had no adverse effect at all in carnivores, whereas in omnivores, as much as 3 to 8 times the requirement had no adverse effects. In chickens, adverse effects are known to occur through lysine-arginine antagonism where large intakes of lysine can cause increased arginine requirements. The issue of whether lysine-arginine antagonism occurs in humans was discussed. In one of the talks, it was pointed out that lysine-arginine antagonism could be seen in chickens, rats, and dogs, but not in cats or pigs. It was also noted that effects of antagonisms could be observed in vitro systems but that there was no reproducible evidence that high levels of plasma lysine, for example in patients with inborn errors of metabolism such as hyperlysinemia, resulted in abnormal levels of plasma arginine or ornithine. However, it was pointed out that although plasma levels of the antagonized amino acid may not change, intracellular levels may be affected, because the transporter shared by lysine and arginine is an antiporter. It was also noted that antagonism would become an issue only if there was a limiting intake of the antagonized amino acid, which does not seem to be the case in the general population that obtains sufficient intakes of both amino acids from dietary sources.

Some discussion was devoted to the potential toxicity of chloride from lysine hydrochloride, which is the dominant form of lysine used in foods and supplements. High chloride intake may induce a hyperchloremic acidosis, especially deleterious in patients with renal failure who cannot handle high loads of acids. The same problem may theoretically apply to professional athletes taking arginine hydrochloride chronically. The mean intake of lysine for the U.S. general population from infants to the aged was 5.27 g/d, whereas the 90th percentile intake for males aged between 19 and 30 y was 10 g/d. The 90th percentile intake of arginine for the U.S. population is almost 8.0 g/d for males and almost 5.0 g/d for females, which in lactating females can increase to 6.25 g/d. The participants recognized the potential contributions of intestinal microflora to lysine requirements and speculated that this contribution might be extended to other amino acids.
Presently, the most likely intentional intake of supplemental free arginine in healthy human populations can be documented in athletes (i.e., bodybuilders) who are taking additional free arginine to enhance the circulating levels of growth hormone. This is based on the fact that, during the 1960s children with retarded growth had been given high doses of arginine (~30 g per person) to stimulate growth without major side effects being reported. In hospitalized patients with inborn errors of arginine metabolism, the hyper-argininemia was typically manifested by spastic diplegia and the severity of the biochemical symptoms was related to the level of arginine in the plasma. The critical level of arginine for such effects appeared to be at ~300 μmol/L and higher. In extreme cases, blood ammonia was increased and brain toxicity was observed. The clinical practice of using arginine in adult patients (up to 30 g i.v. or orally), which has almost 2 decades of history of use, may offer valuable insights into the safety of arginine. An indication for supplemental arginine in clinical practice is a well-documented decrease in circulating arginine following a major operation or trauma. The decreased arginine concentration can reduce the production of nitric oxide within the heart and, because nitric oxide is an important mediator of vascular tone, this can increase the risk of infarction. A recently discovered natural inhibitor of nitric oxide is asymmetric dimethylarginine (ADMA), which inhibits nitric oxide synthase. ADMA is generated from protein breakdown and is pumped into the endothelium by the same transporter as arginine. From there it can be degraded by the enzyme dimethylarginine dimethylaminohydrolase. There are 2 organs that are important in clearing ADMA: the liver and the kidney. Elevated levels of ADMA are correlated to an increased risk of heart infarction but also multiple organ failure in the Intensive Care Unit, because ADMA (by inhibiting nitric oxide) may disturb the microcirculation in vital organs such as the heart, liver, intestine, and kidney.

In addition to the cardiovascular effects, nitric oxide is a mediator of host defenses within the intestines. When the post-traumatic fall in arginine is combined with an infectious complication, the patients have a significantly disturbed arginine blood flow of the intestines, further decreasing the clinical outcomes. Recent studies suggest that arginine may effectively reduce insulin resistance and block protein degradation, due to an effect of nitric oxide to increase glucose transport by muscle cells. These effects are of high relevance in critically ill patients characterized invariably by muscle catabolism and insulin resistance as well as hyperglycemia. Additional information on subjects others than healthy adults is provided by the use of arginine in infant formulae where adverse effects have not been reported.

Some discussants emphasized that throughout the clinical practice of using supplemental arginine, based on the above rationale, there were only a very limited number of cases where side effects were reported. In particular, no cardiovascular side effects were reported at doses of up to 24 g/d given continuously for 8–12 wk. Mild gastrointestinal effects, possibly related to nitric oxide production in the gastrointestinal tract, were the most frequently reported side effects, especially in the elderly. This was recognized as possibly the most common adverse effect associated with arginine ingestion. However, it was also noted that the expression of nitric oxide synthase differs among populations and it was suggested that there might exist a sub-population that may exhibit diarrhea after ingesting arginine at doses of ~12 g/d.

Part of the general discussion was dedicated to the identification of metabolic limits for arginine or lysine excess, as it was recognized that for amino acids without clear hazard identification, such as lysine and arginine, a metabolic limit approach may offer the only adequate guidance. The first limit of excessive dietary intake of amino acids was seen as the reduction of food intake, due to a physiological response to the excess. The discussion then progressed to identifying a primary biomarker of homeostasis, including the ability to adapt to increased intakes; the endogenous production of amino acids was mentioned as a possible candidate. However, the participants recognized that the capacity to metabolize arginine was large and that in studies conducted in healthy humans, the intakes of arginine were not sufficiently high to achieve a kinetic inflection point that was shown for leucine in the previous workshop. It was noted that for citrulline there may be an inflection point at ~15 g/d intake, because there was an accumulation of citrulline, but this was not associated with any adverse effect.

More work is needed to correlate the toxicity data with the metabolic data. In the meantime, it was proposed that for the general population there might be an interim solution, as recommended by the FAO/WHO Nutrient Risk Assessment Workshop, which proposed the use of the highest observed intake concept for nutrients with no known adverse health effects. For lysine, it appeared that there were no significant adverse effects reported at the highest current levels, either dietary or supplementary, and a highest observed intake type of approach may be possible in setting upper limits. With respect to arginine, although some discussants felt that there was no evidence of adverse effects at current use levels, others felt that gastrointestinal effects could be employed as the starting point of a process to determine an upper level.

Acknowledgment
We thank Mr. Kobayashi, Ms. Masuzawa, and Dr. Smriga for their contributions in editing the transcripts.