Adaptation to high and low copper intakes: its relevance to estimated safe and adequate daily dietary intakes\textsuperscript{1,2}

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ABSTRACT Different approaches are used to determine ideal ranges of intakes and threshold levels of safe intakes for nutrients. A consequence of this is that, for inorganic nutrients particularly, a safe level set by traditional toxicologic procedures might be compromised because it is inconsistent with physiologic observations and customary intakes and because the levels set may allow an inordinately narrow range of safe intakes above the upper limit of recommended intakes. This article used data from studies in animal models and in human volunteers to construct a provisional continuum of adaptive processes and pathophysiologic phenomena associated with a range of copper intakes extending from toxic to deficient to suggest an approach to establishing an acceptable range of intakes for copper that would address simultaneously the advisory and regulatory needs of nutritionists and toxicologists. Am J Clin Nutr 1998(suppl);67:1061S–3S.

INTRODUCTION

The physiologic basis of adaptation to high and low intakes of copper is presented by several authors in this supplement and need not be reiterated in detail. This compilation provides an integrated overview of the physiologic and pathologic responses to excess and deficient intakes of copper with the aim of stimulating critical discussion and experimentation to enable the establishment of more confident limits for adequate intakes of copper.

SAFE UPPER LIMITS

The need for such an approach for determining safe upper limits of copper intake and the associated risk of toxic effects of short-term and long-term excessive intakes has been appreciated increasingly (1, 2). Intakes at or below such a reference dose (RID) are unlikely to have any risk of toxicity, but, whereas occasional intakes above this level would also be safe, sustained intakes above the RID do carry a risk of toxicity. For both organic and inorganic micronutrients, the traditional approach of toxicology in setting RDIs has its limitations. Such methods, when applied to nonessential elements, depend on defining an intake or exposure level at which no observed adverse effects of biological significance are observed or, alternatively, the lowest level at which adverse effects are detected. The adjustment of these levels by using uncertainty factors, modifying factors, or both, to determine the RID for the upper limits of intakes that are thought to have no significant effect for humans, is subject to judgment.

Whereas this approach is reassuring in the context of nonessential compounds and public health, when it is applied to essential nutrients it can lead to paradoxical situations in which the RID might well be inconsistent with observed customary, and presumably safe, intakes. This approach may also lead to situations in which there is a very narrow range of acceptable or safe intakes between the recommended dietary allowances (RDAs) or reference nutrient intakes (2) and the RID. In some circumstances the RID for a micronutrient could be lower than the RDA for a micronutrient (2).

ACCEPTABLE RANGE OF ORAL INTAKES

When the Food and Nutrition Board of the National Research Council calculated the RDAs for some nutrients, data for copper were inadequate to determine an RDA; thus, an estimated safe and adequate daily dietary intake (ESADDI) was proposed instead (3). Recently, at a World Health Organization International Programme on Chemical Safety meeting on risk assessment for essential elements, it was felt that there was a need to develop comparable procedures to define the health risks from deficient intakes as well as from excessive intakes. The concept and term of an acceptable range of oral intakes (AROI) was foreseen (4), which is conceptually similar to the ESADDI.

The definition and determination of the AROI for copper were considered to depend on the known phenomena associated with deficiency and toxicity, ie, by using the classic outline of phenomena seen with excessive and deficient intakes (5) to understand these limits (Figure 1). This spectrum of effects ranges from the clearly defined but nonspecific endpoint of death for both toxicity and inadequate intake. In the midst of this spectrum are the safe and adequate intakes at which the systemic copper burden is regulated by adaptations in gastrointestinal uptake, hepatic turnover, and biliary excretion. Estimation of the lower level of the ESADDI is that which appears to avoid evidence of impaired activities of cuproenzymes (12). It is proposed that the lower limit of the AROI is determined similarly; a means of assessing the upper level is less evident.

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Approximate daily intakes

**TOXICITY**

Gross dysfunction and disturbance of metabolism of other nutrients; hepatic detoxification and homeostasis overwhelmed; gastrointestinal metallothionein induced (possible differing effects of acute and chronic exposure); plateau of absorption maintained; homeostatic mechanisms regulate absorption; hepatic uptake (9), sequestration, and excretion; glutathione-dependent uptake of copper; binding to metallothionein; and lysosomal excretion. Hepatic turnover and homeostasis; biliary excretion and gastrointestinal uptake normal. Hepatic deposits reduced; conservation of endogenous copper; gastrointestinal absorption increased. Negative copper balance; functional defects, eg, lysyl oxidase and superoxide dismutase. Activities reduced. Peripheral pools disrupted. Gross dysfunction and disturbance of metabolism of other nutrients.

**ADEQUACY**

11 μg/kg (7, 8)

9 μg/kg (8)

8.5 μg/kg (10) oxidase and superoxide dismutase

5.2 μg/kg (8) activities reduced. Peripheral pools disrupted. Gross dysfunction and disturbance of metabolism of other nutrients.

2.2 μg/kg (11)

**DEATH**

The main route of copper loss is via the gastrointestinal tract. Although there is appreciable gastrointestinal excretion of copper, much of this is reabsorbed and that in the bile is the principal form of excreted copper. Studies in animal models indicate that with increasing supraphysiologic intakes of copper there is hepatic sequestration and excretion of the metal involving at least one pathway, which is possibly dependent on glutathione and a mechanism involving lysosomal exocytosis (9, 17). On the basis of studies in which copper loads were administered intra-

venously, both processes seem to be saturable, and the vesicular pathway seems able to operate at higher copper burdens. It is probable that the up-regulation of these mechanisms interacts with the induction of hepatic metallothionein (9, 18) and might precede the mucosal block imposed by the increased metallothionein synthesis in the gastrointestinal mucosa, which appears to depend on relatively large intakes of copper (6). However, in this context, there might well be differences between the outcomes of acute and chronic exposure to large doses of the metal.

Wilson disease exemplifies what happens when hepatic detoxification systems are overwhelmed: tissue and functional effects of chronic excessive systemic copper accumulation manifest in the liver, basal ganglia, eye lens, renal tubules, and joints, etc. The similar systemic accumulation of copper after chronic exposure to excessive copper has long been appreciated in workers in the copper industry, who have been reported to have developed green teeth and hair, skin discoloration, and even green bones (19) and other systemic features of copper overload.

With inadequate intake there is increased conservation of endogenous copper followed, possibly, by increased gastrointestinal absorption. It is only after these adaptive changes have failed that one would expect functional defects—such as reduced activities of lysyl oxidase, superoxide dismutase, and cytochrome-c oxidase—to develop (10, 20) and then disturbances in the metabolism of other nutrients to ensue as the metabolic pools of copper become disrupted.

**COPPER HOMEOSTASIS**

The availability of large repositories of copper to use either as stores during inadequate intake or as buffers against excessive intake makes a systematic investigation in humans of safe upper and lower limits of dietary copper intake a difficult and prolonged undertaking. The serial balance studies by Turnlund et al (7, 8), using stable isotopic labels, illustrate the care and effort that are required in this type of study. Data from their studies of human males show a plateau phenomenon of absolute copper absorption (0.8–1.0 mg/24 h) at intakes of 1.68–7.53 mg/24 h (7, 8). As yet, the homeostatic mechanisms involved and the response to higher intakes have not been characterized.

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CONCLUSIONS

The approach described herein involves many approximations. In particular, it was not possible to use most of the reports on animal models, not because of an understandable caution about extrapolating between species, but because few of these reports provide enough information to enable approximations of the daily intakes and body burdens of copper. Thus, although such reports contribute to knowledge about adaptive mechanisms in copper metabolism, they do not as yet enable further assessment of safe limits of intakes; perhaps not even for rats. Nonetheless, this spectrum provides a basis for interpreting the current data on the metabolism of copper and assessing ways in which it might be possible to extend the data to enable the establishment of an AROI or an ESADDI.

**REFERENCES**

8. Turnlund JR, Keyes WR, Anderson HL, Acord LL. Copper absorp-


