Micronutrient bioavailability: Dietary Reference Intakes and a future perspective[1–4]

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ABSTRACT

This article provides a review of how the challenge of bioavailability was approached in establishing the Dietary Reference Intakes, with a special focus on folic acid, vitamin B-12, β-carotene, iron, selenium, and zinc, the targeted micronutrients for this workshop. In a future perspective, the necessity of having a clear working definition of bioavailability is emphasized. The bioavailability of micronutrients should be considered, with advantage, under subheadings determined by the broad factors that affect bioavailability. Special emphasis is given to giving greater and specific attention to factors involved in the maintenance of homeostasis. These factors, it is argued, are best considered separately from even a broad definition of bioavailability and have the potential to provide new insights into some micronutrient requirements. *Am J Clin Nutr* 2010; 91(suppl):1430S–2S.

INTRODUCTION

In this article I review how the challenges of bioavailability were addressed by the Food and Nutrition Board of the Institute of Medicine in developing the Dietary Reference Intakes (DRIs) and, against this background, will offer a personal perspective on how bioavailability may, with advantage, be addressed in future considerations of nutrient requirements.

BIOAVAILABILITY AND THE DRIs

The issue of bioavailability presents a major challenge with respect to multiple micronutrients in estimating DRIs. Perhaps, surprisingly, therefore, this topic was not included in the introductory chapters of the DRI books and barely in the subsequent overview book (1). The only exception to this exclusion is the chapter by the subcommittee on Upper Reference Levels of Nutrients, which provides the following definition: "The bioavailability of a nutrient can be defined as its accessibility to normal metabolic and physiologic processes." The definition continues: "Bioavailability influences a nutrient's beneficial effects at physiologic levels of intake and also may affect the nature and severity of toxicity due to excessive intakes." The inclusion of the latter statement reflects the specific role of this standing subcommittee, but, in so doing, provides an important message that bioavailability can or should be taken into account in establishing upper limits as well as in estimating requirements. The subcommittee went on to list the following factors that it perceived might affect bioavailability: concentration of nutrient, dietary factors, chemical form, supplements taken separately from meals, nutrition and health of the individual, excretory losses, and nutrient–nutrient interactions.

Apart from this contribution from the Upper Limits Subcommittee, it devolved to the individual panels to tackle the conundrum of bioavailability. The micronutrients that are the focus of this workshop were covered by the Micronutrient Panel (2) and in part by the Oxidant/Anti-oxidant Panel, ie, β-carotene and selenium (3). The other micronutrients to be considered are folic acid, vitamin B-12, calcium, iron, and zinc. Each of these micronutrients is the focus of individual attention in subsequent articles in this supplement to the Journal. A brief overview of the effects of bioavailability on DRIs for these nutrients as reported in the above publications is given in **Table 1**. As indicated in the Table 1, each of the factors listed by the Upper Limits Subcommittee was included in at least one individual chapter for the micronutrients targeted in this workshop. The list covers a broad range of factors that may affect bioavailability most frequently as inhibitors but in some instances as enhancers. The next section will address how these factors may, with advantage, be subgrouped.

A PERSPECTIVE FOR THE FUTURE

There has been little evidence of a global consensus on how to define and, more importantly, to think about bioavailability in all of its contexts. Although a very broad definition is used by many, this may detract from its value in applying to estimates of DRIs. Certainly, the list of factors given above lacks the form and substance necessary to assist in the optimal evaluation of the role of these factors in affecting bioavailability. In starting to group these and other possible contributory factors, the most essential initial separation is factors that may appear to affect bioavailability but are, in reality, triggering or the result of regulatory

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TABLE 1
Factors affecting bioavailability of selected micronutrients that were noted in the Dietary Reference Intake (DRI) publications

Factors	Examples
Chemical form	
Selenium	Selenomethionine and selenocysteine compared with selenite and selenate
Iron	Ferrous compared with ferric iron
	Nonheme compared with heme
	Fortification compounds readily or poorly soluble in the gastric juice[1]
	Fortification compounds with a built-in enhancer, ie, Na Fe EDTA[1]
Dietary factors	
Calcium	Phytate (inhibitor)
	Oxalate (inhibitor)
Iron	Polyphenols (inhibitor)
	Phytate (inhibitor)
	Muscle tissue[1] (enhancer)
	Ca, legume proteins, casein[1] (inhibitor)
	Ascorbate (enhancer)
Carotenoids	Emulsifiers (enhancer)
	Fats (enhancer)
	Antioxidants (enhancer)
	Gentle cooking (enhancer)
Zinc	Phytate (inhibitor)
Concentration (quantity ingested)	
Calcium	
Zinc	
Iron	
Vitamin B-12	
Supplements better absorbed than dietary sources	
Carotenoids	
Folic acid	
Zinc? (4)	
Host status	
Iron	
Host pathophysiology	
Vitamin B-12	Lack of intrinsic factor
Excretion	
Vitamin B-12	Defective enterohepatic circulation
Interactions	
β-Carotene	Other carotenoids
Zinc	Iron
	Copper
	Iron/vitamin A

[1] Not included in DRI publications.

responses designed to maintain optimal homeostasis. Although these responses may occur in an individual cell, tissue, or organ, they are most clearly identified in relation to the maintenance of whole-body homeostasis, which is achieved by modulating the efficiency of absorption or/and by regulating the quantity of endogenous micronutrient excreted.

An excellent example is provided by zinc as addressed in more detail in an accompanying article in this supplement to the Journal (4). As the concentration of zinc in the diet—or rather the quantity of bioavailable zinc ingested—increases, the efficiency of zinc absorption decreases. As discussed in ref. 4, this decrease in efficiency of absorption is a major factor in maintaining whole-body zinc homeostasis. Increases in ingested zinc do not decrease bioavailability and are not considered a deleterious effect. To take this concept of whole-body zinc homeostasis a step further, regulation of the excretion of endogenous zinc via the intestine will also come into play in response to the increase in ingestion of bioavailable zinc with an increase in the intestinal excretion of endogenous zinc. Again, it is confusing and potentially misleading to consider this increase in excretion as impairing bioavailability.

With respect to absorption, similar considerations apply to vitamin B-12, and possibly to high intakes of calcium, specifically, those intakes likely to result from ingestion of calcium supplements (5). Application of saturation response kinetics, as has been undertaken for zinc (4), to existing data or/and to prospectively acquired data may provide very useful new insights into homeostasis of these micronutrients, especially vitamin B-12, the absorption of which is regulated in response to the quantity of bioavailable vitamin ingested.

Host nutritional status for specific micronutrients, notably iron, has a major effect on absorption. Vitamin A status can decrease iron bioavailability by preventing hemoglobin formation. Infection will decrease erythropoeisis. Formerly considered to have a major role in the regulation of zinc absorption, zinc status is now regarded as having at most only a minor role (4). Zinc status does, however, affect the intestinal excretion of endogenous zinc, with "higher" status resulting in greater excretion of zinc in the feces. These changes in absorption and excretion in response to changes in status reflect physiologic adjustments in regulation to maintain optimal iron or zinc status.

In contrast to physiologic responses to increases in the ingestion of bioavailable zinc—or, rather, in the quantities of bioavailable zinc that present to the apical surface of enterocytes primarily in the upper small intestine—the effect of increasing quantities of dietary phytate is to progressively decrease the quantity of bioavailable zinc that is actually available for absorption. The effect of phytate on zinc bioavailability was specifically avoided in estimating the DRIs for zinc (2) because of lack of quantitative total diet data on the inhibitory effect of phytate. This situation has changed in the intervening years, and it is now possible to predict the phytate effect on zinc absorption with considerable confidence (4).To various extents, depending on dissociation constants, phytate has similar negative effects on bioavailability of other cations, especially divalent cations, which include iron and calcium but not copper (6, 7). Phytate is present in all plants, especially in unrefined cereal grains and legumes. Globally, its effect on micromineral bioavailability and therefore on nutritional status is huge. Dietary polyphenols also chelate iron in the lumen of the intestine and impair bioavailability of this micronutrient. The chemical form can also be very important, which is the case for selenium and iron. Ascorbate enhances iron bioavailability by reducing ferric to ferrous iron, the latter being the oxidation state required for absorption of inorganic iron and which is less reactive with phytate or polyphenols. Absorption of heme iron is not subject to the same regulation or to the same inhibitory factors as inorganic iron.

Host pathophysiologic changes can affect bioavailability. A classic example is impairment of vitamin B-12 absorption

attributable to a diminished or absent intrinsic factor. In elderly populations this impairment is sufficiently common that it requires attention in assessing population requirements for this micronutrient. Achlorhydria or hypochlorhydria, whether iatrogenic in origin or secondary to *Helicobacter pylori* infection or other causes, is another example of a common pathophysiologic circumstance that can, in this case, impair the bioavailability of ingested inorganic iron and likely zinc. Another example of host pathophysiology adversely affecting the bioavailability of micronutrients is defective enterohepatic circulation of vitamin B-12 in which the impaired reabsorption is attributable to lack of intrinsic factor.

Finally, micronutrient supplements had a quite prominent role when considering bioavailability in teh development of the DRIs. For example, the upper limits for zinc were established on the basis of the reported adverse effects of zinc supplements on copper status (2). This provides an example of the effect of nutrient–nutrient interactions, which, as in the case of iron–zinc interactions also, have elicited attention as a result of observations of the effects of supplements rather than food-based sources of micronutrients. DRI panels took note of the favorable absorption of β-carotene and folic acid from supplements compared with that from food-based sources. Favorable absorption has also been thought to apply to zinc, but this view now appears to be attributable at least in part to inadequate design of studies to measure zinc absorption from supplements (4).

In conclusion, $\approx$5000 publications are listed in PubMed (http://www.pubmed.gov) for micronutrient bioavailability. The intent of this article is not to provide a scholarly review of all that has been published on this subject but rather to provide a brief introductory overview that includes a synopsis of how bioavailability was considered in developing the DRIs along with a personal perspective of how best to approach this topic when estimating micronutrient requirements. Bioavailability is a challenging factor of indisputable importance in estimating dietary requirements, including upper limits, for micronutrients. Emphasis has been given to 2 issues. The first issue is the importance of having a clear working definition of bioavailability that can be subdivided into the major factors included under this definition. This is likely to become progressively more important as we learn more about genetic variations in the metabolism of the micronutrients and about both genetic and acquired differences in the availability of micronutrients at an individual cellular and subcellular level. The second issue is to decide if the definition of bioavailability should be sufficiently broad to cover changes in absorption or/and excretion attributable to physiologic regulatory mechanisms that maintain and restore optimal homeostasis. Whether or not these issues are included as a major subdivision under bioavailability, they demand specific and high priority attention in any estimates of micronutrient requirements.

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REFERENCES

1. Institute of Medicine. Dietary Reference Intakes: the essential guide to nutrient requirements. Washington, DC: National Academies Press, 2006.
2. Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington, DC: National Academies Press, 2001.
3. Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academies Press, 2000.
4. Hambidge KM, Miller LV, Westcott JE, Sheng XY, Krebs NF. Zinc bioavailability and homeostasis. Am J Clin Nutr 2010;91(suppl): 1478S–83S.
5. Food and Nutrition Board, National Research Council. Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Washington, DC: National Academy Press, 1997.
6. Egli I, Davidsson L, Zeder C, Walczyk T, Hurrell R. Dephytinization of a complementary food based on wheat and soy increases zinc, but not copper, apparent absorption in adults. J Nutr 2004;134:1077–80.
7. Lonnerdal B. Bioavailability of copper. Am J Clin Nutr 1996;63: 821S–9S.