The role of diet- and host-related factors in nutrient bioavailability and thus in nutrient-based dietary requirement estimates

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Abstract

To convert physiological requirements into dietary requirements, adjustments are needed for some nutrients that take into account certain diet- and host-related factors specific to a country or region. Nutrients whose requirements should be adjusted in this way include calcium, magnesium, iron, zinc, protein, folate, vitamin A, and carotenoids. The diet-related factors that must be considered depend on the nature of the habitual diet and may include the chemical form of the nutrient and the nature of the dietary matrix, interactions between nutrients and/or organic components, and food preparation and processing practices within the country or region. The host-related factors can be further subdivided into intestinal and systemic factors. Reductions in the secretion of hydrochloric acid, gastric acid, and/or intrinsic factor, together with alterations in the permeability of the intestinal mucosa, are all examples of intestinal factors that can markedly influence the absorption of certain nutrients, but that are often ignored when setting dietary requirements. Systemic factors that should also be considered include nutrient status of the host, age, sex, ethnicity, genotype, and physiological state (e.g., pregnancy or lactation), and chronic and acute infectious disease states. Algorithms can estimate the bioavailability of iron, zinc, protein, folate, vitamin A, and carotenoids, although their accuracy is limited by the complex interactions among the absorption modifiers in the whole diet. For calcium and magnesium, the amount available for absorption is still estimated from their major food sources in the habitual diet. Currently, there are often large differences in the adjustments employed to convert physiological requirements to dietary requirements, even among countries consuming diets of similar patterns.

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Introduction

Variations exist among countries in estimates of nutrient requirements, even for a specified class of individuals. There are several reasons for the differences observed. This paper focuses on the factors that must be taken into account when the *physiological requirements* of a nutrient for an individual are translated into *dietary requirement* estimates. It is at this stage that adjustments are made to the dietary requirement to take into account particular types of diets consumed by individuals and certain host-related factors. The magnitude of these adjustments and their relative importance varies with the nutrient, life-stage group, and setting (e.g., environment). In this paper the following operational definitions will be used:

Physiological requirement is the requirement of absorbable and utilizable nutrient. In environments where the nature of the diet ingested and/or the intestinal or systemic conditions of the host affect either the absorption or the utilization of an ingested nutrient, the dietary requirements will be higher than the physiological requirements.

Dietary requirement is the requirement of the nutrient *as ingested* in a specified type of dietary pattern and under specified conditions of the host. Hence, this requirement takes into account both dietary and host-related factors that affect the absorption or utilization of the nutrient or both. The host-related factors include systemic factors (e.g., nutrient status, age, and physiological status) and the possible coexistence of intestinal factors (e.g., atrophic gastritis) known to influence the efficiency of intestinal digestion and absorption. Because these factors vary markedly according to the nature of the habitual dietary pattern and the conditions of the host, it follows that the dietary requirement may differ among countries, even if there is approxi-

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mate agreement on the physiological requirements.

Bioavailability is the proportion of the ingested nutrient that is absorbed and utilized through normal metabolic pathways [1]. It is influenced by diet- and host-related factors.

Bioefficacy is the efficiency with which ingested nutrients are absorbed and converted to the active form of the nutrient [2].

The objective of this paper is to examine the diet- and host-related factors that may influence the bioavailability of certain nutrients and hence the adjustments required to translate physiological requirements of these nutrients to dietary requirement estimates. For this review, the diet-related factors have been classified into the chemical form of the nutrient and the nature of the dietary matrix; interactions occurring among nutrients themselves or with other components of the diet; and pretreatment of food as a result of processing and/or preparation practices. The host-related factors considered in this paper include intestinal factors that influence the efficiency of luminal and mucosal digestion and absorption, and systemic factors such as nutrient status of the host, age, physiological status, and illness due to chronic or acute infections. The final step in setting dietary requirement estimates takes into account the variations in requirements among individuals, according to life stage and sex.

Most of the literature cited in this review encompasses results of *in vivo* human isotope studies, where possible and relevant, although some results based on *in vitro* methods and epidemiologic studies have also been included.

Dietary factors affecting the bioavailability of nutrients

Several factors in the diet can influence the bioavailability of nutrients. The magnitude depends on inhibitors and promoters in any one meal, and hence the composite diet. Increasingly, the influence on bioavailability of fortificants or supplements as well as intrinsic components of the diet must be considered.

There are some concerns about the predictive value of certain methods (e.g., *in vitro* assays) used to investigate the dietary factors affecting the bioavailability of inorganic nutrients in foods, and inconsistent results have been reported. Moreover, most of the *in vivo* isotope studies have been based on single meals. However, there is some evidence that the effects of dietary modifiers on the absorption of iron, and possibly other trace elements, from single-meal studies differ from those based on a total diet of similar composition as the single test meal [3, 4]. Therefore, caution must be used when interpreting the results in the literature on diet-related factors affecting nutrient bioavailability. In general, diet-related factors have less influence on the bioavailability of macronutrients than micronutrients. Of the latter, the bioavailability of iron and zinc is especially affected. For some micronutrients (e.g., iodine, vitamin C, thiamin), the effect of dietary factors on bioavailability appears to be very limited, and for micronutrients such as riboflavin [5], vitamin B_{12} [6], magnesium [7], and chromium [8] bioavailability data in humans are sparse. In some cases (e.g., vitamin B_6), existing bioavailability data are difficult to interpret because of methodological difficulties [9]. The three groups of dietary factors known to influence nutrient bioavailability are discussed in turn below.

Chemical form of the nutrient and nature of the dietary matrix

The absorption and/or utilization of several micronutrients are affected by the chemical form of the nutrient (i.e., speciation); some examples are given in **table 1**. Of these, the bioavailability of intrinsic iron in indigenous diets as well as the form in supplements and fortificants

TABLE 1. Examples of nutrients for which bioavailability is affected by chemical form

Nutrient	Forms
Iron	Heme iron (bound in a porphyrin ring) in hemoglobin and myoglobin from meat, poultry, and fish is more readily absorbed than nonheme iron found in foods of plant and animal origin. Bioavailability of iron from fortificants or supplements depends on their chemical form
Selenium	Main food sources of selenium are the organic forms, selenocysteine and selenomethionine. These tend to be better absorbed than the inorganic form of selenium, selenite
Zinc	Organic zinc complexes (e.g., from oysters) are more readily absorbed than inorganic zinc salts
Folate	Polyglutamates (mainly 5-methyl tetrahydrofolate [5MeTHF] in fresh food) are less well absorbed than synthetic monoglutamate form (i.e., folic acid used as fortificant and supplements)
Vitamin B_6	Free pyridoxine, pyridoxamine (plus phosphorylated forms) in plants and pyridoxal (plus phosphorylated forms in animal foods) are better absorbed than pyridoxine β-D-glucoside in heat-processed milk products
Niacin	Niacin in mature maize is present as niacytin (nicotinic acid esterified to polysaccharides), which is unavailable for absorption

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has been most extensively studied. Two forms of iron exist in foods: heme iron and nonheme iron. They are absorbed by separate pathways, but once inside the mucosal cells of the small intestine all iron enters a common pool. Heme iron, bound in a porphyrin ring, is derived mainly from hemoglobin and myoglobin in meat, poultry, and fish, whereas nonheme iron is found primarily as iron salts in a wide variety of foods of both plant and animal origin, and possibly as contaminant iron introduced during processing, preparation, and storage and by contamination from the soil [10]. Heme iron is absorbed as the intact moiety and nonheme iron from the common pool within the gastrointestinal tract [11]. Of the two forms, heme iron is much more readily absorbed than nonheme iron. Absorption of heme iron depends on the iron status of the individual, whereas absorption of nonheme iron depends not only on the individual's iron status, but also on the content of absorption modifiers consumed during the same meal. In general, for any given individual, the higher the nonheme iron content of the diet, the lower the absorption efficiency [12].

Hurrell [13] reviewed the bioavailability of the forms of iron used as fortificants. Their bioavailability is usually expressed as relative bioavailability value (RBV), i.e., bioavailability relative to that of ferrous sulfate, the latter being assigned a standard RBV of 100%. Absorption is highest for those iron compounds that are soluble in water or dilute acids (e.g., ferrous sulfate, ferrous fumurate, ferric saccharate). However, such compounds often cause oxidative reactions when added as fortificants to food unless they are manufactured in encapsulated forms. Consequently, compounds that are less likely to interact with food components (e.g., ferric pyrophosphate, ferric orthophosphate, and elemental iron) are often used, despite their lower RBV. Note that the composition of the native diet can be a more important determinant of iron absorption than the type of fortificant itself, especially in plant-based diets.

Absorption of zinc and selenium is also influenced by chemical form. In both cases, the organic forms tend to be more readily absorbed than the inorganic forms. For zinc, the organic form (in oysters) appears to be less affected by absorption modifiers than the inorganic forms [14]. Selenomethionine, the organic form of selenium found in most plant tissues (and selenized yeast) is absorbed more efficiently than the inorganic form (e.g., selenite) used in supplements [15], although absorption rates for all forms of selenium are high (70% to 95%).

Chemical form also affects the bioavailability of some vitamins. For example, the bioavailability of carotenoids varies depending on their isomeric form [16]. In contrast, there is some evidence that the bioavailability of polyglutamyl and monoglutamyl forms of native folate in foods is probably similar [17]. Nevertheless, some inconsistencies have been reported among studies that have been associated with differences in the study design and protocols used, variation among individuals in folate digestion, absorption, and metabolism, and analytic difficulties [18]. In contrast, the native polyglutamyl forms of food folate have a much lower bioavailability than does the synthetic form, folic acid, a monoglutamate used as a supplement or fortificant [6, 19, 20]. To take into account some of these differences, the Institute of Medicine [6] has introduced a new term: dietary folate equivalent (DFE). Certain forms of vitamin B_6 found in heat-processed milk products (e.g., pyridoxine β-D-glucoside) are also less available than those normally found in foods [9]. Likewise, niacin in cereals such as maize is present as niacytin, an unavailable form of which only a small amount is hydrolyzed by gastric acid in the gastrointestinal tract. Coffee beans also contain an unavailable form of nicotinic acid (trigonellin, 1-methyl nicotinic acid) that becomes available after roasting [21]. In contrast, for thiamin, chemical form has little effect on its bioavailability [22].

The food matrix probably has the greatest effect on the absorption of provitamin A carotenoids [23] and folates [17, 24]. Both of these micronutrients may be entrapped in the insoluble matrix or cellular structure of certain plant foods, reducing their bioavailability. For example, β-carotene is bound to proteins in the chloroplasts in dark-green leafy vegetables, whereas in orange and yellow fruits (mango, papaya, etc.) and pumpkin and sweet potato, carotenoids are dissolved in oil droplets in chromoplasts and are more readily extracted during digestion, so that their bioefficacy is fourfold higher than that from dark-green leafy vegetables [23]. In spinach, bioavailability of folate is higher after the leaves have been chopped, minced, or enzymatically liquefied than for the same amount of whole spinach leaves [25]. Vitamin B_{12} is also bound to enzymes or other carrier proteins in food and must be released prior to absorption.

Interactions among nutrients themselves and with other components in the whole diet

The mechanisms whereby components in the diet influence the bioavailability of nutrients may involve noncompetitive interactions between nutrients and organic components in diets whereby insoluble or soluble complexes are formed in the acid pH of the stomach and proximal duodenum, and direct competitive interactions between two (or more) inorganic nutrients with chemical similarities that share the same absorptive pathways.

Note that the bioavailability of nutrients from supplements or fortificants when taken together with a meal is affected by the same factors as those present in a food [26]. Their net effect depends on the balance between those factors inhibiting and those factors

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enhancing nutrient absorption and/or utilization in the diet. In addition, some of the isotope studies are based on single meals, which tend to exaggerate the results of nutrient interactions involving iron absorption compared with studies based on whole diets [3, 4]. Hence, caution must be used when interpreting some of the bioavailability results reported in the literature based on single-meal studies.

Noncompetitive interactions

Several organic dietary components have the capacity to form insoluble or soluble complexes with certain nutrients in the gut, thus inhibiting or facilitating absorption. In some cases, reabsorption of certain inorganic nutrients that are excreted endogenously in the gastrointestinal tract (e.g., calcium, zinc, copper) may also be affected [27, 28]. **Table 2** lists these naturally occurring organic substances, their major food sources, and summarizes their nutritional consequences. Some occur in large amounts in many of the plant-based diets in developing countries; they are discussed briefly below. Note that the effects of these organic components on bioavailability can often be modulated by pretreatment of the food with commercial and/or traditional food processing and preparation methods.

Phytate refers to phytic acid (*myo*-inositol hexaphosphate) as well as the salts: magnesium, calcium, or potassium phytate. Phytate is the major storage form of phosphorus in cereals, legumes, and oleaginous seeds, so that diets based on unrefined, unfermented cereals are especially high in phytate, whereas those based on starchy roots and tubers are low [29]. Phytate chelates metal ions, especially zinc, iron, and calcium, but not copper [30], in the gastrointestinal tract, making them unavailable for absorption. It also complexes endogenously secreted minerals such as zinc [26, 28] and calcium [31], making them unavailable for reabsorption into the body.

Myo-inositol hexaphosphate can be hydrolyzed by certain food processing and preparation methods to lower *myo*-inositol phosphates, which do not form insoluble complexes with iron and zinc. For example, *myo*-inositol phosphates with fewer than five phosphate groups (i.e., IP-1 to IP-4) do not have a negative effect on zinc absorption [32], whereas those with fewer than three phosphate groups do not inhibit nonheme iron absorption [33]. There appears to be no adaptation to the inhibitory effect of a high-phytate diet on iron absorption in long-term vegetarians [34]; whether the same is true for zinc is uncertain.

High amounts of calcium may exacerbate the inhibitory effect of phytate on zinc absorption by forming a calcium-zinc-phytate complex in the intestine that is even less soluble than phytate complexes formed by either ion alone [35]. In general, because the calcium content of most plant-based diets is low, such an effect is probably rare. Indeed, calcium did not add significant predictive power in a model developed by the International Zinc Nutrition Consultative Group (IZiNCG) [36] to predict zinc absorption. Nevertheless, some diets may be exceptions, notably diets in Latin America based on lime-soaked maize, diets of some lacto-ovo vegetarians, diets in regions where betel nut is chewed with lime [31], and cases of geophagia involving calcareous soils [37].

Soybean protein inhibits absorption of zinc as a result of its phytate content, although the magnitude of its effect may depend on the processing method. The effect of soybean protein on iron absorption depends on the processing method and food source. Some fractions of soybean protein inhibit iron absorption even when completely dephytinized (e.g., conglycinin) [38], whereas ferritin present in nodulating soybeans may be a bioavailable source of iron for persons with low iron stores [39].

Polyphenols are almost ubiquitous in plant foods. Some examples of foods and beverages that contain high levels are shown in **table 2**. Genetic and environmental factors, as well as germination, processing and storage, and degree of ripeness, influence the polyphenol content of plant foods; polyphenols are not denatured by heat [40].

Polyphenols, like phytate, form insoluble complexes with metal cations that inhibit intestinal absorption of nonheme iron [41], perhaps copper [42] and zinc [43], but not calcium [44] or manganese [45]. The active compounds are the galloyl group found in tannin and gallic acid [41]. The effect of polyphenols is independent of that of phytate [46]. Foods and beverages containing these compounds are shown in **table 2**. Several *in vivo* intervention studies based on radioiron isotopes have confirmed the inhibitory effect of tea on iron absorption [47]. The effect can be partly counteracted by simultaneous consumption of ascorbic acid [48]. Some epidemiologic studies of adults have shown that a high consumption of tea [49] or coffee [50] is associated with low iron stores. The inhibitory effect of polyphenol-containing beverages can be significant even during infancy in countries where tea (e.g., Egypt and Israel) or coffee (e.g., Guatemala) is fed to infants [51, 52].

Certain polyphenols, such as caffeic acid, chlorogenic acid, and tannins, also exhibit thiamin-inactivating properties by oxidizing the thiazole ring to the disulfide, which in turn reduces thiamin absorption [53]. Some polyphenols can also influence the digestibility of macronutrients by binding endogenous proteins such as salivary enzymes and digestive enzymes in the intestinal tract. Hence, they can reduce the digestibility of starch, protein, and lipids [54–56]. Tannins can also interfere with protein digestibility by enhancing excretion of endogenous protein, and they increase fecal fat excretion [40, 57].

Dietary fiber is composed of nonstarch polysaccha-

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TABLE 2. Effects of noncompetitive interactions involving organic substances on nutrient bioavailability: inhibiting and enhancing factors

Dietary component	Food sources	Main technical influences	Nutritional consequences
Phytate (*myo*-inositol hexaphosphate) plus magnesium, calcium, or potassium phytate[a]	Unrefined cereals, legumes, nuts, oil seeds	Binds certain cations to form insoluble complexes in gut	Zinc, iron, calcium, and probably magnesium are poorly absorbed
Soybean protein	Soybeans and unfermented soy products (e.g., textured vegetable protein)	Contain phytate In nodulating soybeans, ferritin is main source of iron	Inhibits zinc absorption Nodulating soybeans may be a bioavailable iron source when iron stores are low
Polyphenols	Certain cereals (red sorghum), legumes (red kidney beans, black beans, black grams), spinach, betel leaves, oregano Beverages: tea, coffee, cocoa, red wine	Form insoluble complexes with iron Some polyphenols inactivate thiamin Bind certain salivary and digestive enzymes Enhance excretion of endogenous protein	Inhibit nonheme iron absorption Reduce thiamin absorption Reduce digestibility of starch, protein, and lipids Interfere with protein digestibility
Dietary fiber	Unrefined cereals, legumes, nuts, oilseeds, fruits, and vegetables	Lignin and pectin bind bile acids Pectins/psyllium/gums retain water and form viscous solutions in the gut Dietary fiber is fermented in large intestine by microflora	Reduces absorption of fats, fat-soluble vitamins, and carotenoids Slows gastric emptying and digestion and absorption of nutrients Short-chain fatty acids that are produced enhance calcium solubility
Oxalic acid	Amaranth, spinach, rhubarb, yam, taro, sweet potato, sorrel, sesame seeds, black tea	Oxalates form insoluble complexes with calcium and possibly iron	Reduce absorption of calcium and possibly iron Increase urinary calcium
Organic acids (citric, lactic, acetic, butyric, propionic, formic acids)	Fermented milk products (e.g., yogurt), vegetables (e.g., sauerkraut), soy sauce, cereals (e.g., tobwa)	May form soluble ligands with some trace minerals in the gut	May enhance absorption of zinc and iron
Ascorbic acid	Citrus fruits and juices, other fruits (e.g., guava, mango, papaya, kiwi, strawberry), vegetables (e.g., tomato, asparagus, Brussels sprouts)	Reduces ferric iron to more soluble ferrous iron; forms iron–ascorbate chelate	Enhances nonheme iron absorption; may counteract inhibitory effect of phytate May enhance selenium and chromium absorption
Protein		Amount and type (e.g., animal protein) enhance bioavailability of zinc, iron, and copper, but not calcium	Enhance absorption, possibly by formation of soluble ligands Increase urinary calcium excretion
Fat	Fats and oils, animal adipose tissue, milk and milk products, vegetables, seeds, nuts	Products of fat digestion (fatty acids, monoglycerides, cholesterol, and phospholipids) plus bile salts solubilize fat-soluble vitamins and carotenoids in intestinal milieu	Enhance absorption of fat-soluble vitamins and provitamin A carotenoids

a. *Myo*-inositol phosphates with fewer than five phosphate groups (i.e., IP-1 to IP-4) do not inhibit zinc absorption [32], and those with fewer than three phosphate groups do not inhibit nonheme iron absorption [33].

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rides, which include cellulose, mixed-linkage β-glucans, hemicelluloses, pectins, and gums. These constituents are found especially in unrefined cereals, legumes, nuts, and fruits and vegetables. The effect of dietary fiber on nutrient bioavailability is linked to some of its physical properties in the gastrointestinal tract, such as cation exchange capacity, bile acid binding, water-holding capacity, viscosity, and its ability to act as a substrate for fermentative microorganisms [58].

In general, dietary fiber alone does not have a major effect on the absorption of minerals (e.g., calcium or magnesium) [59] or trace elements [26, 60], assessed *in vivo* using isotope techniques, although α-cellulose may affect the utilization or endogenous losses of copper [61]. Note that these findings are in contrast to earlier *in vivo* results in which pure fiber fractions were not used [62].

The effect of dietary fiber on the absorption of most water-soluble vitamins appears to be minimal [63]. Possible exceptions may be an interference with the bioavailability of naturally occurring vitamin B_6 in wheat, rice, and corn bran in humans, although *in vitro* studies with isolated forms of fiber have not confirmed this [9].

Absorption of fat-soluble vitamins (e.g., vitamin E) and carotenoids [23] may also be impaired by diets high in pectin and ligin through their capacity to bind bile acids *in vivo* [64] at an acidic pH and affect micelle formation in the small intestine. A high-fiber diet may also lead to enhanced elimination of vitamin D [65], probably as a result of a reduction in transit time.

Absorption of nutrients such as fatty acids is also affected by the water-holding capacity of dietary fibers such as pectins, psyllium, and various gums, which retain water within their matrix, forming highly viscous solutions in the small intestine. These can in turn alter gastric emptying time and slow the rate of nutrient digestion and absorption, although the total amount absorbed will be unaffected [58].

Fermentation of dietary fibers by the microflora in the large intestine may lead to an increase in short-chain fatty acids (SCFA) (acetate, propionate, and butyrate), depending on the type of fiber. These SCFAs are absorbed across the colonic mucosa and can serve as a source of energy (150 to 200 kcal/day) that would otherwise be lost in the stool. In addition, the acidic pH in the colon created by these SCFAs enhances the solubility of calcium and in turn calcium absorption [66].

Oxalic acid is present in many plants, the level varying with the cultivar, growing conditions, and distribution within the plant [67]; examples of food plants that contain high levels are shown in **table 2**. Some animal species (e.g., snails and certain other mollusks) also contain high levels of oxalate [68]. Oxalates form insoluble complexes with calcium, thus reducing absorption [69, 70]. Their inhibitory effect can be reduced by soaking and boiling, both of which reduce the oxalate content of foods. Whether oxalic acid inhibits the bioavailability of trace minerals such as iron and zinc is less clear. Some early human studies reported that the addition of 1 g of oxalic acid to a cabbage meal significantly reduced iron absorption [71], and foods rich in both fiber and oxalic acid, such as spinach, were reported to decrease zinc balance [72].

Vitamin C has a strong enhancing effect on absorption of nonheme iron when it is consumed in the same meal. This effect is now attributed largely to the formation of an iron–ascorbate chelate in the acid milieu of the stomach, which prevents it from forming a complex with phytate or tannin; Teucher et al. have presented a detailed review [73]. The magnitude of the enhancing effect depends on the level of ascorbic acid and the composition and properties of the meal; the effect is greater for meals that contain inhibitors of iron absorption. Vitamin C appears to enhance chromium absorption [74] and may influence the bioavailability of selenium [75]. Whether vitamin C affects copper absorption is still uncertain [76]. Note that the bioavailability of ascorbic acid from food sources is similar to its bioavailability from supplements and is not affected by the type of food consumed [77].

Organic acids (citric, lactic, acetic, butyric, propionic, and formic acids) produced during fermentation of cereals (e.g., tobwa) [78], vegetables (e.g., sauerkraut) [79], and some soy sauces [80], have the potential to form soluble ligands with trace minerals in the gastrointestinal tract [73] and thus may facilitate absorption of nonheme iron [71] and zinc [26]. Their effect on iron absorption appears to depend on the type of organic acid, the molar ratio of organic acid to iron, and the iron source, based on the results of a study in human Caco-2 cells [81]. The effect is not as consistent as that of ascorbic acid [82].

Protein, both the type and the amount, influences the bioavailability of nonheme iron, zinc, and copper. The enhancing effect of cellular animal protein on nonheme iron absorption is well documented [83]. The mechanism is not clear, but some "meat factor" may be implicated, perhaps through the release of certain amino acids, oligosaccharides, or possibly cysteine-containing peptides, during the digestion of cellular animal protein. Other proteins from eggs and from milk and dairy products (especially casein) impair iron absorption [84]. Hence, it is not surprising that some epidemiologic studies have shown positive correlations of serum ferritin with meat and fish intake but negative correlations with dairy products in adults [85, 86].

In contrast, increasing the amount of total protein enhances zinc absorption, and if the protein is from cellular animal sources, the enhancing effect is even greater [87]. Animal protein may also enhance copper absorption [88]. In contrast, diets high in protein increase the urinary excretion of calcium (i.e., hypercalciurea), which is not compensated by increased calcium absorption. However, this negative effect of

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protein is probably significant only when calcium intakes are low. It also depends on other constituents, such as potassium and phosphorus, both of which blunt the hypercalciuric response [89]. Weaver et al. [70] provide data on calcium intakes required to offset urinary losses in adults consuming various amounts of dietary protein.

The presence of protein in the small intestine also helps to stabilize fat emulsions and enhances micelle formation and thus uptake of carotenoids [23] and vitamin A [90].

Flesh foods (meat, poultry, fish, and seafood) enhance the absorption of nonheme iron and zinc from plant-based foods. In meals containing meat, fish, or chicken, nonheme iron absorption is about four times greater than that from a meal containing equivalent portions of milk, cheese, or eggs [12]. The relative enhancing effect of animal muscle proteins on nonheme iron absorption varies: beef apparently has the highest effect, followed by lamb, pork, liver, chicken, and fish [91]. No comparable data exist for zinc. The precise mechanism is unclear, as noted earlier. The enhancing effect of flesh foods on nonheme iron absorption is evident even in the presence of phytic acid [91], but its magnitude appears less when a meal is already high in ascorbic acid [82].

Carbohydrates can stimulate bacterial fermentation in the intestine and enhance absorption of certain minerals by increasing their solubility in the ileum. Examples include lactose, known to enhance both calcium and magnesium absorption [7].

Fat, both the type and the amount, influences the absorption of fat-soluble vitamins (e.g., retinol) and provitamin A carotenoids. Hence, in the low-fat, plant-based diets characteristic of developing countries, absorption of fat-soluble vitamins and carotenoids may be impaired. The minimum amount of fat required for optimal absorption of provitamin A carotenoids ranges from 5 to 10 g per day [92]. Further, there is no dose–response relationship above the threshold value. Such low levels of fat have been reported in diets of children living in rural Malawi [93]. The type of dietary fat may also be important for absorption of β-carotene: absorption may be higher with dietary fats rich in polyunsaturated fatty acids than with dietary fats rich in monounsaturated fatty acids [23].

Competitive interactions between two or more inorganic nutrients

Inorganic nutrients with similar physicochemical properties that share the same absorptive pathways are known to interact with one another by several mechanisms, only some of which are understood. They may compete for carrier sites on transport proteins. In most indigenous diets, such competitive interactions are unlikely to modify bioavailability, because the intrinsic levels of inorganic nutrients are not high enough to induce antagonistic interactions. Even if plant foods or diets are fortified with micronutrients, the risk of antagonistic interactions appears to be low, because the micronutrients become chelated to dietary ligands resulting from the digestion of food and thus are absorbed by different pathways [94]. However, these interactions could become important if high doses of micronutrient supplements are consumed without food, as may occur among certain population groups with high micronutrient requirements, such as infants, adolescents, and pregnant and lactating women. Excess zinc (25 or 50 mg/day) has been shown to decrease biochemical indices of copper status [95, 96] and in some cases also of iron status [96] in adults. In a stable isotope study of fasting pregnant Peruvian women, zinc absorption in the third trimester of pregnancy was significantly less in women receiving daily supplementation with a combination of iron (60 mg) and folate (250 μg) than in their unsupplemented counterparts [97]. Among adult ileostomy subjects, iron supplements inhibited zinc (but not copper) absorption [98]. An adverse effect of supplemental iron on biochemical zinc status [99, 100] has also been observed among infants. The mechanism for this adverse effect of supplemental iron on zinc absorption is not clear, but studies suggest that iron may inhibit both the uptake and the transfer of zinc through the intestinal cell [101].

Calcium has an acute inhibitory effect on iron absorption [102], although the mechanism for this effect is uncertain and its impact is controversial. The adverse effects have been noted in single-meal [102] and short-term [103] intervention studies; long-term studies have failed to demonstrate any significant inhibitory effect [104–106]. For example, a recent year-long study of calcium supplementation (500 mg calcium/day) in adolescent girls failed to show any adverse effect on biochemical iron indices [106]. Nevertheless, a cross-sectional study in six European countries has demonstrated a weak but inverse association between calcium and serum ferritin, but the effect was not dependent on simultaneous ingestion of calcium and iron, and no dose–response relationship was noted [107].

In some emerging countries, where pollution is a problem and where controls for landfills in mining operations are inadequate, antagonistic interactions between zinc and cadmium, iron and lead, chromium and zinc, copper and cadmium, and selenium and mercury may be of concern [27].

Influence of food processing and/or preparation practices on nutrient bioavailability

Increasingly, research has emphasized that prior treatment of food before consumption may have a marked effect on the bioavailability of nutrients and hence must be taken into account when formulating nutrient-based

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dietary requirements. Such treatments may involve commercial and/or traditional household food preparation and processing practices. The treatments may involve thermal processing (including canning, extrusion, baking, and boiling), milling or home pounding, malting, fermentation, and soaking at the commercial

TABLE 3. Examples of the influence of food processing and preparation practices on nutrient bioavailability

Processing method	Main technical influences	Nutritional consequences
Thermal processing	Destroys heat-labile vitamins such as thiamin, vitamin C, and riboflavin	Reduces amount in final product
	Releases some vitamins from poorly digested complexes	Enhances bioavailability of vitamin B_6, niacin, folate, certain carotenoids
	Inactivates heat-labile antinutritional factors	May enhance bioavailability of vitamin B_1, iodine, biotin, etc., depending on food item
	May degrade phytate, depending on temperature, but losses are modest	Possibly small improvements in bioavailability of zinc, iron, calcium
	Gelatinizes starch	Enhances starch digestibility
Baking	Induces Maillard browning in foods containing reducing sugars	Destroys basic essential amino acids: lysine, arginine, methionine; reduces protein quality and protein digestibility (specific to baking)
Boiling	Reduces oxalate content	Enhances calcium and possibly iron bioavailability
	Some leaching of water-soluble components	Some loss of water-soluble vitamins and inorganic nutrients (specific to boiling)
Extrusion	May degrade phytic acid, causing modest losses	Possibly small improvements in bioavailability of zinc, iron, calcium
	Induces starch gelatinization	Enhances starch digestibility
	Induces Maillard browning	Destroys basic essential amino acids; reduces protein quality (specific to extrusion)
Milling or home pounding	Reduces phytate content of those cereals with phytate localized in outer aleurone layer: (rice, wheat, sorghum) or in germ (maize)	May enhance bioavailability of zinc, iron, and calcium, although mineral content simultaneously reduced
	Reduces B-vitamin content	
Malting, also known as germination	Increases phytase activity via *de novo* synthesis or activation of endogenous phytases	Induces hydrolysis of phytate to lower inositol phosphates and hence may increase zinc, iron, and calcium bioavailability
	Reduces polyphenol content of some legumes *(Vicia faba)*	May enhance nonheme iron absorption
	Increases α-amylase content of cereals: sorghum and millet	Facilitates starch digestion; may increase nonheme iron absorption through a change in consistency
Microbial fermentation	Induces hydrolysis of phytate by microbial phytase	May enhance bioavailability of zinc, iron, calcium
	Increases content of organic acids	May form soluble ligands with iron and zinc and enhance bioavailability
	Microbial enzymes may destroy protein inhibitors that interfere with nitrogen digestibility	May improve protein quality in maize, legumes, groundnuts, pumpkin, millet seeds
Soaking in water and decanting	Passive diffusion of water-soluble sodium and potassium phytates in cereal and legume flours	May enhance bioavailability of zinc, iron, calcium, but some loss of water-soluble vitamins
	May activate some endogenous phytases in cereals and legumes	Some phytate hydrolysis and thus enhanced bioavailability of zinc, iron, and calcium
	Soaking maize with lime releases niacin from niacytin	Enhances bioavailability of niacin

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or household levels; they are summarized in **table 3** and discussed in turn below. When a combination of strategies is used, such as soaking, germination, and fermentation, phytate can be almost completely removed. This is important, because phytic acid is a potent inhibitor of iron absorption at low concentrations [38]. During commercial food processing, the use of certain food additives, as well as some inadvertent or intentional contaminants, may also influence the bioavailability of some nutrients.

Thermal processing

Thermal processing generally enhances the digestibility of proteins and carbohydrates and may improve the bioavailability of iodine and certain vitamins (e.g., niacin, thiamin, vitamin B_6, and some carotenoids) (**table 3**). In some cases, these improvements in nutrient bioavailability arise because of the destruction of some heat-labile antinutrients summarized in **table 4**. The digestibility of protein, for example, is enhanced by the destruction of protease inhibitors found in many legumes, grains, and other foods. Protease inhibitors block the activity of pancreatic enzymes such as trypsin and chymotrypsin but are destroyed during roasting and toasting, although boiling may not fully deactivate them. Similarly, the harmful effects of lectins (agglutinins) found in certain legumes, including soybeans and peanuts, can also be removed by heat treatment. Lectins can agglutinate red blood cells, and they also have the capacity to adhere to glycoproteins of the intestinal mucosal membrane surface, leading to a decrease in digestive and absorptive capacity as well as symptoms of nausea and diarrhea [108].

Goitrogens can also be inactivated by thermal processing. The major goitrogens in plant foods are sulfur-containing glucosides (glucosinolates) which can block the absorption or utilization of iodine, and thus its uptake into the thyroid gland. More details are given by Gaitan [109]. Their action is especially important when iodine intake is low [110]. Neonates, and to a lesser extent pregnant women, are more sensitive to the antithyroid action of dietary goitrogens than are infants and children.

Reports on the effects of thermal processing on phytate degradation are inconsistent and depend on the plant species, temperature, and/or pH. Thermal processing involving high temperatures, such as those used in canning, has been reported to reduce the phytate content of beans by 70% to 91% [111]. An *in vivo* study by Hurrell and co-workers [112], however, concluded that the extent of phytate degradation in industrially thermally processed cereal porridges or home-prepared pancakes or chappattis made from the same cereal flours (i.e., unrefined and refined wheat flour) was not sufficient to improve iron absorption.

Thermal processing can also enhance the bioavailability of some vitamins. Heat-labile thiaminases in brussels sprouts and red cabbage are destroyed (**table 4**), whereas any thiamin, vitamin B_6, niacin, or folate entrapped in the cellular structure or insoluble matrix of certain foods may be released. For example, significantly greater increases in serum β-carotene levels after consumption of cooked carrots and spinach [113] and in serum lycopene levels after consumption of cooked tomatoes [114] have been reported than after consumption of the same amounts raw. This effect is attributed to softening or disruption of plant cell walls and disruption of carotenoid–protein complexes.

In contrast, as noted in **table 3**, thermal processing, especially when it involves baking or extrusion cooking, can reduce the biological value of some proteins. This is caused by the induction of Maillard browning, which results in the destruction of certain essential amino acids, especially lysine, and to a lesser extent arginine and methionine. Oxidation of sulfur-containing amino acids can also occur. Losses of heat-labile (thiamin, vitamin C, and riboflavin) and water-soluble vitamins also occur, the extent of the losses depending on the temperature, pH, oxygen, light, and amount of water used [108]. Extrusion may also inhibit degradation of phytic acid through inactivation of phytase, resulting in less efficient apparent absorption of zinc compared

TABLE 4. Heat-labile antinutritional factors that have the potential to influence nutrient bioavailability

Antinutritional factor	Common food sources	Effects of antinutritional factor
Avidin	Egg whites	Binds biotin, making it biologically unavailable
Protease inhibitors	Legumes, grains, egg white, potatoes, sweet potatoes, soy products	Inhibit activity of digestive enzymes trypsin and chymotrypsin
Lectins (agglutinins)	Legumes: red kidney beans, black beans, yellow wax beans, soybeans, peanuts	Can agglutinate red blood cells and may also decrease digestive and absorptive capacity of GI tract
Goitrogens	Sweet potato, cassava, millet, beans, cabbage, Brussels sprouts, turnip	Cause goiter by interfering with absorption or utilization of iodine
α-Amylase inhibitors	Cereals (wheat, barley, maize, rice), peas, beans	Slow starch digestion
Thiaminases	Fish, shellfish, Brussels sprouts, red cabbage	Destroy thiamin

Source: modified from Erdman and Poneros-Schneier [108].

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with that from similar but nonextruded cereal products [79, 115], although not all studies have confirmed these findings [116]. At the same time, extrusion induces starch gelatinization, rendering it more accessible to enzymatic digestion.

Milling or household pounding

Milling or household pounding is used to remove the bran and/or germ from cereal grains such as rice, maize, sorghum, and wheat. These processes reduce the phytate content of those cereals in which the phytate is localized in the outer aleurone layer (e.g., rice, sorghum, and wheat) or in the germ (i.e., maize) [117] and thus may enhance mineral bioavailability, although the content of minerals and certain B vitamins in the milled cereals is simultaneously reduced. As a result, in some countries, milled cereal flours are sometimes enriched to compensate for the nutrients lost. Sieving unrefined maize grits, as practiced in the Philippines, can potentially enhance the bioavailability of iron and zinc in the sieved maize by removing the germ, which contains as much as 90% of the phytic acid [117].

Malting or germination

Malting, also called germination, involves soaking cereal grains or legumes in water until sprouting occurs. This leads to an increase in phytase activity through *de novo* synthesis, activation of endogenous phytase, or both, and as a result some reduction in the IP-5 and IP-6 content of the germinated whole cereal grains, most legume seeds, and most oil seeds [38, 118]. The rate of hydrolysis via phytases (*myo*-inositol hexakisphosphate 3-phosphohyrolase) (EC 3.1.3.8) varies with the species and variety, as well as stage of germination, pH, moisture content, temperature (optimal range, 45° to 57°C), solubility of phytate, and presence of certain inhibitors [119, 120]. Egli et al. [118] observed that during germination, rice, millet, and mung beans had the largest reductions in phytate content. Some loss of water-soluble sodium and potassium phytates may also occur during germination.

Germination may also reduce the content of tannins and other polyphenols in some legumes (e.g., *Vicia faba)* and red sorghum by complexing with proteins [121].

α-Amylase activity is also increased during germination of cereals, especially sorghum and millet. Because these enzymes hydrolyze amylase and amylopectin to dextrins and maltose, the viscosity of thick cereal porridges is reduced to an easy-to-swallow, semiliquid consistency, which may facilitate iron absorption. A threefold increase in iron absorption has been reported in amylase-treated, roller-dried rice cereal compared with untreated roller-dried cereal, which Hurrell et al. [112] attributed to the viscosity changes induced by α-amylase.

Microbial fermentation

Microbial fermentation also results in some hydrolysis of IP-5 and IP-6 to lower inositol phosphates through the action of microbial phytase enzymes [79]. The extent of the reduction depends on the type of fermentation; sometimes as much as 90% or more of phytate can be reduced by fermentation of maize, soybeans, sorghum, cassava, cocoyam, cowpeas, and lima beans [79, 122, 123]. The action of microbial phytase is important, because there is no phytase activity in the human intestine [124]. Such reductions in phytate can have a major impact on enhancing calcium, iron, and zinc bioavailability, as shown by *in vivo* isotope studies in which adults have been fed tortillas or polenta made from low-phytate maize hybrids compared with wild-type unmodified maize [125–127]. This effect is important, since fermented maize, sorghum, and soybean products are widely consumed in Africa and Asia. Fermentation of bread dough with yeast also induces phytate hydrolysis, although if calcium is added as a fortificant, phytase activity in yeast is inhibited.

Organic acids produced during fermentation also have the potential to enhance iron and zinc absorption via the formation of soluble ligands with iron and zinc, as noted earlier [73], and also create the low pH that is optimal for the native phytases. Improvements in protein quality have also been documented after fermenting blends of maize and legume flours [128] and groundnuts, pumpkin, and millet seeds [129], possibly associated with the destruction of protein inhibitors by microbial enzymes that interfere with nitrogen digestibility [128].

Soaking

Soaking can also reduce the IP-5 and IP-6 content of unrefined cereal (and most legume) flours by passive diffusion of water-soluble sodium and potassium phytate [130–132]. Reported reductions in IP-5 and IP-6 after soaking white rice, maize, and legume flours (e.g., mung bean flour) range from 57% for maize flour [133, 134] to more than 90% for white rice flour [135]. Note that only modest losses occur after soaking whole legume seeds and cereal grains, with the exception of rice [135]. This has important implications for diets in Southeast Asia based on glutinous rice, which is often soaked overnight and then steamed, because these practices result in a substantial loss of water soluble phytate (the author, personal communication). The extent of the losses depends on the species, pH, moisture content, temperature, and solubility of phytate, the presence of certain inhibitors, and the length and conditions of soaking. Soaking under optimal conditions may also activate endogenous phytases and result in some phytate hydrolysis, as well as some reduction in the content of other antinutrients, such as saponins and polyphenols [79]. Note that some losses of water-soluble B vitamins, such as thiamin, riboflavin, and niacin,

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may occur during soaking, so that alternative dietary sources of these vitamins must be considered.

The polyphenol content of some legumes (e.g., *Vicia faba)* and red sorghum may also be reduced by germination as a result of the complexation with proteins and gradual degradation of oligosaccharides [121]. Naturally occurring polyphenol oxidase extracted from banana or avocado can also been used to reduce the polyphenol content of red sorghum [136].

Food additives and contaminants

Some food additives used in processed foods can also influence nutrient bioavailability. An example is the practice of nixtamalization or liming used in Central America for processing maize. This increases the calcium content of tortilla-based diets to a level that may potentiate the inhibitory effect of phytate on zinc absorption [137]. This practice, however, also releases niacin from niacytin in maize [138].

In industrialized countries, erythorbic acid (also termed isoascorbic acid, D-arabo-ascorbic acid) is widely used as a preservative in processed foods. Erythorbic acid is a steroisomer of ascorbic acid that does not have any antiscorbutic activity but is a potent enhancer of nonheme iron absorption [139]. US diets can provide as much as 200 mg of erythorbic acid per day, which could enhance nonheme iron bioavailability.

Contaminants in the food supply arising, for example, from plant-based foods grown in soils contaminated with sewage sludge, phosphate fertilizers, or pesticides may influence nutrient bioavailability. Heavy metal contaminants (e.g., cadmium, lead) can cause antagonistic interactions between cadmium and zinc, cadmium and iron, lead and zinc, lead and iron, and lead and calcium, resulting in reduced bioavailability of zinc, iron, and calcium. Environmental contaminants can also accumulate in aquatic food chains, the most well-known example being methyl mercury in fish [140], which is known to bind selenium in foods and reduce its bioavailability.

Inadvertent or intentional ingestion of soil (geophagia) may also have an impact on mineral bioavailability. Indeed, geophagia was implicated in the etiology of the first cases of human zinc and iron deficiency reported in the Middle East [141, 142]. Although soils are a rich source of minerals, their ingestion does not necessarily provide a source of absorbable minerals. Absorption of minerals depends on the soil type and the timing of the consumption of soil in relation to the consumption of foods. Calcareous soils may provide a source of absorbable calcium [37], but others, such as clay, contain inhibiting constituents (e.g., silicates) that may prevent the absorption both of inorganic nutrients derived from the soil and of those intrinsic to food [143]. A detailed review of the possible impact of nonfood sources of iron on iron status is available [10].

In contrast to contaminants from the soil, trace element contaminants in food from cooking equipment, cooking pots, or storage conditions, acquired either during commercial food processing or in the household, may be readily absorbed [10]. Examples include sources of iron or zinc in foods cooked in iron or galvanized pots. A study in Ethiopia reported lower rates of anemia and higher serum ferritin concentrations among children whose food was cooked in iron pots than among those whose food was cooked in aluminum pots [144], suggesting that contaminant iron from cast-iron cookware may be sufficiently bioavailable to influence iron status under certain conditions. Note that the bioavailability of trace elements from the cooking utensils will be subject to the same interactions with components in the whole diet as the trace elements intrinsic to the food. Thus bioavailability of iron and zinc will be low in high-phytate foods.

Influence of host-related factors on bioavailability of nutrients

Several host-related factors are known to influence the bioavailability of nutrients. They can be classified as intestinal or systemic factors. Because information on these host-related factors is often limited, their effects on nutrient bioavailability are often ignored when dietary requirement estimates are set. This is unfortunate, because in some developing countries they might have a further modifying influence on nutrient bioavailability over and above that of the dietary factors discussed earlier. The extent to which they influence absorption and/or utilization varies with the nutrient, life-stage group, and environment.

Intestinal factors

Both luminal and mucosal factors can influence intestinal digestion and absorption of nutrients; some examples are summarized briefly below.

Atrophic gastritis is probably one of the most significant luminal factors influencing nutrient bioavailability, predominantly through its association with hypochlorhydria. The latter is a condition in which there is a progressive decrease in the capacity of the parietal cells of the stomach to secrete hydrochloric acid [145]. Hypochlorhydria is linked to infection with the bacterium *Helicobacter pylori,* an infection that is especially prevalent among children in developing countries, where it is typically acquired in childhood and persists throughout life. Even in Western countries, infection with *H. pylor*i has been linked to the hypochlorhydria that may affect as many as 10% to 30% of persons over 60 years of age.

Absorption of several vitamins and minerals that are

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dependent on pH for absorption can be impaired as a result of the pH changes that accompany hypochlorhydria. For example, low acid conditions of the stomach can impair the release of protein-bound vitamin B_{12} contained in food [146] and the absorption of β-carotene [147] and folate [148]. Alterations in the pH of the jejunum may also impair deconjugation of folate and thus folate absorption [24].

Absorption of iron, calcium, and possibly zinc may also be affected by reduced gastric acid secretion, because gastric acid affects the solubilization of these inorganic nutrients [149–151]. Hence, reduced gastric output arising from infection with *H. pylori* could limit the absorption of iron, calcium, and possibly zinc and may be an important factor in the etiology of iron deficiency and iron-deficiency anemia, especially among children in developing countries. However, in a recent study of *H. pylori*-infected Bangladeshi children, no increase in iron absorption was observed, despite an improvement in gastric acid output and hemoglobin concentration after treatment with antibiotics [152].

Other physiological consequences of atrophic gastritis include decreased acid-pepsin digestion in the stomach and decreased secretion of intrinsic factor, both of which result in malabsorption of vitamin B_{12}. Bacterial overgrowth in the stomach and proximal small intestine is also often associated with atrophic gastritis and may exacerbate vitamin B_{12} deficiency because the bacteria take up any freed vitamin B_{12} from food [153].

Bacterial overgrowth and infection with *Giardia lamblia*, *Ascaris lumbricoides*, rotavirus, and salmonella, as well as malaria and iron deficiency [154], can alter the integrity of the intestinal mucosal, causing increases in intestinal permeability and reductions in nutrient absorption. Such perturbations in the morphology and function of the intestine may even arise in normal healthy persons residing in tropical areas [155] and are known to reduce the absorption of vitamin A [156], folate [157], and probably those nutrients for which secretion and absorption of endogenous sources in the intestine are key homeostatic mechanisms (e.g., zinc, copper, calcium). For example, the large endogenous fecal losses of zinc that perturbed zinc homeostasis in young, apparently healthy Malawian children aged 2 to 5 years [28] may have resulted from abnormal intestinal permeability [158]. Alternatively, the high phytate content of the maize-based diets of the children may have bound endogenously secreted zinc, making it unavailable for reabsorption [26]. Alterations in the structure of the intestinal mucosa will also compromise iron homeostasis, because iron is regulated by uptake and transfer by the intestinal mucosa. The proportion of bioavailable carotene converted to retinol (bioconversion) is probably also affected, because the enzyme (15-15'-carotenoid dioxygenase) responsible for this cleavage is present in the intestinal mucosal brush border [23]. In addition, reductions in transit time are often associated with many of these infections, which will in turn decrease the time required for extensive solubilization of nutrients in the intestinal tract and again further compromise intestinal nutrient absorption.

Systemic factors

Systemic factors that can influence absorption and utilization of nutrients include age, sex, possibly ethnicity, genotype, physiological state (e.g., pregnancy, lactation), and the nutrient status of the host, together with the presence of coexisting gastrointestinal disorders or disease such as chronic and acute infections [159]. For example, during the first 6 months of infancy, maturation of both the gastrointestinal tract and the digestive and absorptive processes are known to affect bioavailability of macronutrients and probably of micronutrients as well, although no data are available at the present time [160].

Potential reductions in nutrient absorption with advancing age are especially important in those countries with an aging population. Alterations in the secretory and absorptive capacity of the intestine occur with advancing age, which in turn affect the bioavailability of certain micronutrients; macronutrients are unaffected. The micronutrients most affected are vitamin B_{12}, as noted earlier, as well as calcium, vitamin D, and possibly vitamin B_6 [153]. Decreased absorption of calcium is linked to age-related changes in vitamin D metabolism involving a reduction in the number of vitamin D receptors in the intestinal mucosa, and thus diminished capacity to absorb vitamin D [161]. Additional problems with vitamin D metabolism in the elderly include decreased ability of the kidneys to dihydroxylate 25-hydroxyvitamin D to the active 1,25-dihydroxy form and decreased ability of the skin to synthesize vitamin D after exposure to ultraviolet light [162]. Such disturbances may lead to malabsorption of both vitamin D and calcium; decreases in dietary intakes of vitamin D and sun exposure among the elderly may be exacerbating factors. Whether changes also occur during aging in the bioconversion of provitamin A carotenoids to vitamin A is unknown.

Increases in vitamin B_6 requirements with age have also been reported, although they have not been related to malabsorption, but instead to problems with cellular uptake or metabolism of the vitamin [151, 163]. Similar disturbances may also occur with thiamin during aging, but this question requires more investigation [22]. In contrast, body stores of vitamin A in the elderly do not decline, despite lower intakes. Initially, an increase in the efficiency of absorption with advancing age was said to be responsible [164], but later research confirmed that such well-maintained vitamin A stores were due to decreased clearance of the vitamin from the circulation into peripheral tissues [165]. Whether

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decreased clearance from the circulation occurs with other fat-soluble substances with advancing age is not clear. Renal function is also known to decline with advancing age [166], which could influence the bioavailability of those nutrients (or nutrient metabolites) which are excreted mainly via the kidney (e.g., selenium, iodine, chromium) and for which renal conservation plays a key role in homeostasis.

Certain physiological adaptations may occur that alter nutrient bioavailability in circumstances when nutrient needs are high (e.g., during periods of rapid growth, pregnancy, and lactation) or habitual dietary intakes are low. These adaptations may include increased gastrointestinal absorption of nutrients from the diet, enhanced renal conservation of nutrients, enhanced utilization of absorbed nutrients by tissues, and/or bone resorption [160, 167]. Conversely, when nutrient needs are low, intestinal absorption may be reduced and/or the mechanisms for renal clearance increased. Note that the extent to which these physiological adaptations compensate for the increased or decreased needs for these inorganic nutrients is not always known. Likewise, the time scale over which such homeostatic mechanisms occur is uncertain.

Table 5 summarizes the homeostatic adaptations that may occur for certain inorganic nutrients to meet these increased nutrient needs during pregnancy and lactation and in response to changes in dietary intake [27, 160, 167–169]. There is also some evidence that absorption of certain nutrients (e.g., calcium) may vary with ethnicity [170, 171]. Whether the absorption of vitamins is modified by the nutrient status of the host is uncertain; limited data are available. Some data for vitamins A and D suggest there is little or no evidence that vitamin A deficiency up-regulates conversion of β-carotene in humans [172], or that absorption of vitamin A [90] or vitamin D [173] is influenced by the nutrient status of the host. In contrast, data based on animal studies have led others to postulate that absorption of β-carotene and canthaxanthin [23, 174] and bioconversion of β-carotene to retinol [175] may be dependent on the vitamin A status of the individual. More studies are needed to confirm these suggestions.

Other highly significant determinants of nutrient requirements are chronic and acute infections. Chronic and acute infections are of marked concern when endemic and highly prevalent or when acute infectious illnesses occur frequently, especially when affected populations are poorly nourished. The latter is of particular concern because of the adverse synergy between poor nutrition and infectious illness [176]. These considerations are especially relevant to coun-

TABLE 5. Examples of homeostatic adaptations for selected inorganic nutrients in response to increased needs and changes in dietary intakes based on results from *in vivo* human studies

Nutrient	Homeostatic adaptations during pregnancy and lactation	Homeostatic adaptations in response to changes in dietary intake
Calcium	Pregnancy: increased absorption Lactation: increased renal conservation and bone resorption	Increase in fractional absorption from the diet when intake or status is low, and decrease in fractional absorption when intake or status is high. This adaptive response is reduced among the elderly
Magnesium	No data	Increase in fractional absorption from the diet when intake or status is low, and decrease in fractional absorption when intake or status is high.
Zinc	Pregnancy and lactation: » increase in zinc absorption but not in renal conservation » no release of maternal tissue zinc in pregnancy	Decrease in endogenous zinc excretion provides "fine control" to maintain zinc balance when intake or status is low; increase or decrease in fractional absorption from the diet may provide "coarse control" of body zinc when intake or status is low or high, respectively; renal conservation when intake is very low.
Iron	Pregnancy: increased absorption, especially in 3rd trimester	Increase in fractional absorption from the diet when intake or status is low, and decrease in fractional absorption when intake or status is high.
Chromium	Pregnancy: unknown Lactation: do not appear to reduce urinary chromium excretion	Possibly a reduction in urinary excretion when intake or status is low
Copper	Pregnancy: increased absorption likely Lactation: no data on copper absorption available	Increase in fractional absorption from the diet when intake or status is low, and decrease in fractional absorption when intake or status is high; reduction in urinary excretion when intake is very low

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tries with developing economies. Such countries generally have relatively high proportions of infants and children and other high-risk populations, poor disease prevention infrastructures, and inadequate availability and accessibility of health care systems able to provide prompt and efficacious treatment. These conditions are not uncommon and exacerbate the adverse synergy between poor nutrition and infection, thus it is surprising that data assessing the impact of infectious illness on energy and macro-, micro-, and trace nutrient needs remain inadequate [177–182]. Despite the inadequacy of available data, what is available often is sufficient to calculate semi-quantitative estimates of the impact of illness on nutrient needs. Impacts of illness are not uniform, however. Among the factors that should be considered in assessments of specific nutrient needs are the offending agents, illness severity, age of hosts, stage of illness (e.g., acute or convalescent phase), hosts' nutritional status, and other underlying health conditions. In assessing the impact of infections on populations, it is essential to know relatively well the prevalence of conditions of interest.

Infectious illness impacts nutrient needs by one or a combination of various mechanisms. These include decreased absorption through direct and indirect effects on gastrointestinal function, increased losses through the gastrointestinal tract or other routes (e.g. renal system), heightened metabolic activity, or the sequestration of nutrients in the liver and other sites. These mechanisms have been investigated for bacterial, parasitic, and viral infections [e.g., 183–185]. Nutrient status also influences tissue repair mechanisms and the susceptibility to disease [186]. Relationships between nutritional status and the progression of illness have been investigated most recently and intensively for HIV [187].

In the future, several other factors may also be taken into account when setting dietary requirement estimates. These may include race or ethnicity, lifestyle (e.g., smokers, oral contraceptive users), the existence of chronic disease (e.g., asthma, diabetes), environment (e.g., lead pollution), family history, and genetic predisposition to disease [188].

Implications for adjusting physiological requirements to dietary requirements

At present, the diet- and host-related factors influencing the bioavailability of many nutrients are not well established, limiting the development of algorithms to predict nutrient bioavailability. Notable exceptions are the algorithms available for iron, zinc, protein, folate, vitamin A, and carotenoids. These mathematical models attempt to predict bioavailability, taking into account the amount and form of the nutrient (where applicable), the presence of dietary enhancers and inhibitors, and, when necessary, the nutrient status of the individual. The models then apply certain general principles to the complex whole-diet matrix. However, the accuracy of the algorithms is limited by interactions known to occur between the enhancing and inhibiting factors in the whole diet, as discussed earlier. For example, when the absorption modifiers are contained in the same meal, their effects are probably not additive [189]. Furthermore, because most of the effects of the dietary modifiers on micronutrient absorption have been calculated from the results of single test meals, their effects may be exaggerated in comparison with the extent of the enhancement or inhibition measured over several days [3]. Furthermore, the magnitude of the effect of the absorption modifiers depends on the background dietary matrix [82]. These findings emphasize that as new research findings emerge, algorithms must be modified on an ongoing basis.

Algorithms for available iron

The first algorithm for estimating available iron intakes was developed by Monsen et al. [190] and can be used when intakes of flesh foods, vitamin C, and total iron at each meal are known. In this model, 40% of the total iron found in meat, poultry, and fish is assumed to be heme iron. Nonheme iron is calculated as the difference between total iron and heme iron intakes.

Absorption of heme iron was assumed to be 25% in the initial model but 23% in a later model [191]. The absorption of nonheme iron was assumed to be lower and to vary according to the amounts of meat, poultry, and fish and of ascorbic acid in each meal, as well as the level of iron stores of the individual. Total available iron intakes per day can be derived from the sum of available iron from each meal and snack. Note that this model does not take into account the amounts of any absorption inhibitors in a meal or any possible synergistic effects of absorption enhancers that are present together in the same meal.

FAO/WHO [192] has also developed a semiquantitative classification system for estimating iron bioavailability based on measures of iron absorption from typical meals in Asia, India, Latin America, and Western countries. In this model, diets are classified into three broad categories of low (iron absorption approximately 5%), intermediate (iron absorption approximately 10%), and high (iron absorption approximately 15%) bioavailability depending on their content of flesh- versus plant-based foods together with their content of ascorbic acid–rich foods. The estimates of absorption are for nonanemic persons (i.e., those with normal hemoglobin levels) with normal iron transport but no iron stores. In cases of iron-deficiency anemia (i.e., low hemoglobin levels), each absorption value is assumed to be increased by 50% [192]. Currently, it is difficult to clearly distinguish between a low- and

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intermediate-bioavailability diet with this classification system.

FAO/WHO [182] still recommends this classification system but has proposed the use of two categories of bioavailability for diets in developing countries (5% and 10%) and another two categories for more Western-type diets (12% and 15%), depending on the meat content of the diet. As more comprehensive data become available on the absorption of iron from meals of differing composition, this classification system should be refined.

Murphy et al. [193] adapted the algorithms of Monsen et al. [190] and FAO/WHO [192] to estimate iron bioavailability in diets from developing countries. To use this algorithm, quantitative data on the intake of iron and of two enhancers—ascorbic acid and protein from meat, fish, and poultry—are required. The cutoffs applied to these two enhancers are expressed per 4.18 MJ (1000 kcal), so that the same algorithm can be used for males and females across all age groups. A tea or coffee factor can also be applied, depending on the average number of cups of tea or coffee per day, to account for the inhibitory effects of usual tea or coffee consumption on nonheme iron absorption. The effect of phytate on iron absorption is not considered.

Murphy's model [193], like that of Monsen [190], also assumes that heme iron constitutes 40% of the iron in meat, poultry, and fish and assumes 25% absorption. The computer program supplied with the WorldFood Dietary Assessment System calculates intake of available iron by using Murphy's model [193]. This program is available from http://www.fao.org/infoods/.

Several alternative algorithms have been developed for calculating available iron, each of which takes into account differing numbers of absorption modifiers. For example, Tseng et al. [194] have refined Murphy's model so that nonheme iron absorption can be adjusted for the enhancing effect of meat, poultry, fish, and vitamin C. Separate adjustments can be made for the inhibitory effects of tea and phytates in the diet. However, this model does not account for the combined effect of enhancers and inhibitors on iron absorption and has not had extensive use.

Du et al. [195] compared the use of the algorithm developed by Tseng et al. [194] with the algorithms of Monsen et al. [190] and FAO/WHO [192] for estimating iron bioavailability in the diets of Chinese adults, based on 24-h recalls collected over 3 consecutive days. Hemoglobin as an indicator of iron status was also measured. None of the algorithms appeared to be appropriate for estimating iron bioavailability in these Chinese diets. These investigators emphasized that for vegetarian diets it is important to consider the combined effect of multiple dietary factors on iron bioavailability.

Two additional algorithms are available for estimating dietary iron absorption. Reddy et al. [189] studied iron status (serum ferritin) and iron absorption (via extrinsic radioiron labeling) from 25 different single meals eaten by 86 subjects. An algorithm was then developed, using multiple regression analysis, to predict iron absorption after adjustment for each individual's iron status and including dietary modifiers as independent variables. It is of interest that only 16.4% of the total variance in iron absorption was accounted for by the amount of animal tissue, phytic acid, and ascorbic acid in the typical Western diets studied, with the major portion being explained by the animal tissue and phytic acid contents of the meals. Nonheme iron, calcium, and polyphenols were not significant predictors of iron absorption. These results emphasize the relatively small influence of diet on the amount of iron absorbed in comparison with the more important but unknown physiological factors.

Of all the algorithms available to date, the model of Hallberg and Hulthén [196] is the most detailed, taking into account the affects of all the known enhancing and inhibiting factors on nonheme iron absorption, as well as interactions among the different factors. Application of this more detailed model is limited at the present time by the paucity of food-composition data for the content of both phytate and iron-binding polyphenols in foods. However, this situation is changing.

Algorithms for available zinc

The bioavailability of dietary zinc, like that of iron, is affected by the presence of several absorption enhancers and inhibitors in the whole diet, as well as the total zinc content.

Three algorithms have been developed for calculating available zinc. The first algorithm was developed by WHO [37] and takes into account the impact of one absorption enhancer (protein from meat, fish, and poultry) and two absorption inhibitors (the proportion of phytic acid to zinc, and high levels of calcium). In this algorithm, diets are classified as having low (15% absorption), moderate (30% or 35% absorption), or high (50% or 55% absorption) zinc bioavailability. Of the two inhibitors considered in this algorithm, phytate is the major determinant of zinc absorption, especially for diets in developing countries with a low content of flesh foods. Calcium is unlikely to have any adverse effect because its levels are low in plant-based diets. The inhibitory effect of phytate on zinc absorption follows a dose-dependent response [197], and the molar ratio of phytate to zinc in the diet can be used to estimate the proportion of absorbable zinc [198]. Because *myo*-inositol phosphates with fewer than five phosphate groups do not inhibit zinc absorption, any food processing or preparation method (e.g., fermentation or germination) that might hydrolyze phytate must also be considered; details are given by WHO [37]. This algorithm has been adopted by FAO/WHO [182],

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although only the absorption estimates for the normative zinc requirements (i.e., level of intake that maintains a reserve adaptive capacity) are now included.

The second algorithm for available zinc was developed by Murphy et al. [193] and is based on that of WHO [37]. It again takes into account the content of animal protein and the content of the same two inhibitory factors, phytate and calcium, in the whole diet. For this algorithm, the phytate:zinc molar ratio of the whole diet is calculated; details are given by Hotz and Brown [36]. The bioavailability of diets with phytate: zinc molar ratios of 0 to 5, 5 to 15, 15 to 30, and > 30 is 55%, 35%, 15%, and 10%, respectively. These bioavailability estimates are then further modified, depending on the animal protein and calcium content of the diet; details are given by Murphy et al. [193]. In most plant-based diets in developing countries, however, intakes of animal protein and calcium are generally too low to influence zinc absorption. Even in Latin American countries where calcium intakes are often above 1 g/day, phytate intakes are so high that any further reduction in zinc absorption is assumed to be unlikely.

The International Zinc Nutrition Consultative Group (IZiNCG) has also developed an algorithm for the bioavailability of zinc based on measurements of zinc absorption in adults using only total diet studies; studies using a semipurified diet or exogenous sources of zinc in the form of zinc salts were excluded. Details are given in Hotz and Brown [36]. A logit regression model was used to describe the relationship between four dietary factors (zinc, phytate, protein, and calcium) and the percentage of the zinc intake absorbed. However, in the final model only zinc and the phytate:zinc molar ratio were shown to be significant predictors of the percentage of zinc absorption in adults. Neither calcium nor protein added significant predictive power.

The bioavailability figures for zinc calculated by IZiNCG are 26% for men and 34% for women consuming mixed or refined vegetarian diets with phytate: zinc molar ratios of 4 to 18, and 18% for men and 25% for women consuming unrefined, cereal-based diets with phytate:zinc molar ratios >18. Whether these bioavailability factors are appropriate for children, pregnant or lactating women, or the elderly has not been established [36].

Algorithms for other nutrients

So far, steps have been taken to quantify the bioavailability of protein, folate, carotenoids, and vitamin A in human diets.

Protein intakes can be adjusted for both protein quality and digestibility by using the FAO/WHO/UNU guidelines [199]. Such adjustments are especially necessary in countries where habitual diets are plant-based, because the safe levels of protein intake were calculated from studies based on animal protein [199]. Further, large intakes of dietary fiber, especially insoluble fiber, are known to increase fecal nitrogen excretion, resulting in a reduction in apparent protein digestibility of approximately 10%. Note that the World Dietary Assessment program computes utilizable protein by adjusting intakes to account for both digestibility and amino acid score, using these FAO/WHO/UNU procedures.

In 1990, FAO/WHO recommended the use of a protein digestibility–corrected amino acid score (PDCAAS) [200]. This is based on comparison of the concentration of the first limiting amino acid in the habitual mixed diet (calculated from food-composition values) with the concentration of that amino acid in a reference pattern of essential amino acids; details are given by Schaafsma [201]. Once the amino acid score has been derived in this way, it is then corrected for true fecal digestibility, preferably by weighted summation of the individual protein sources, as specified by FAO/WHO/UNU [199].

Folate is a naturally occurring vitamin found in foods. However, the term is also used to embrace synthetic folic acid found in fortified foods and supplements. In recognition of the known differences in bioavailability between naturally occurring polyglutamate forms in foods and synthetic folic acid found in fortified foods and supplements, the Institute of Medicine [6] has introduced a new term, dietary folate equivalent (DFE), to take into account the differences in the bioavailability of all sources of ingested folate. The dietary folate equivalent content of a food is defined as

$$\mu g \text{ food folate} + (1.7 \times \mu g \text{ synthetic folic acid}).$$

This equation is based on the assumption that the bioavailability of food folate is about 50%, whereas that of folic acid taken with food is 85% (i.e., folic acid is 85/50 = 1.7 times more available) [19, 20].

Many countries are now fortifying foods such as breads and grains with the synthetic monoglutamate form, but most current food-composition tables do not distinguish folate found naturally in foods from folic acid added to foods. Work is under way in some countries to provide this information [202].

Vitamin A in the diets of most industrialized countries occurs mainly as preformed vitamin A derived from animal products. In contrast, in most tropical countries, the main sources of vitamin A are the provitamin A carotenoids from dark-green leafy vegetables and certain yellow- and orange-colored fruits and vegetables [203]. Provitamin A carotenoids include β-carotene, α-carotene, and α- and β-cryptoxanthins.

Currently there is debate about the bioefficacy of ingested provitamin A carotenoids [181, 203, 204]. For example, dietary vitamin A levels may be expressed in terms of micrograms of retinol equivalents (RE), calculated using either the FAO/WHO [192] or the West [203] conversion factors for the bioefficacy of

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ingested provitamin A carotenoids to that of retinol. An alternative term developed by the Institute of Medicine [204] and adopted by the International Vitamin A Consultative Group [205] is retinol activity equivalent (RAE). The latter is based on different conversion factors, which are discussed in detail in Institute of Medicine [204].

FAO/WHO [181] still recommends use of the 1988 FAO/WHO [192] conversion factors to calculate RE until more definitive data are available. These conversion factors do not distinguish between synthetic sources of provitamin A compounds and natural sources in plants. Increasingly, synthetic sources of retinol and provitamin A compounds (mainly β-carotene) are being added to foods or used as dietary supplements in both industrialized and developing countries.

For other nutrients, such as calcium and magnesium, the amount available for absorption is generally estimated from the major food sources of these minerals in the diet.

Alternative methods for estimating bioavailability of iron and zinc from regional or national diets

Application of the algorithms described above requires detailed food-consumption data, preferably at the national level. Unfortunately, such data are often not available, especially in developing countries. Instead, alternative approaches are needed, possibly using food-balance sheet data. Food-balance sheets, published by FAO, provide data on the annual supply of 95 individual food commodities and 15 major food groups per capita that are available for human consumption in 176 countries. The major food groups are cereals, roots and tubers, sugars and honey, pulses, nuts and oilseeds, vegetables, fruits, meat and offal, eggs, fish and seafood, milk, oils and fats, spices, stimulants, and alcoholic beverages; details are given in FAO/WHO [206].

The FAO food-balance sheets also provide data on the daily per capita availability of energy (kilocalories per day), fat (grams per day), and protein (grams per day) for each commodity and each food group, calculated from regional food-composition tables. Hence, the mean daily per capita availability of the proportion of energy from each food commodity and food group can be calculated. This may provide a useful approach for estimating the bioavailability of selected nutrients at the national level. For example, to estimate the bioavailability of iron at the national level, the mean daily availability per capita of the percentage of energy from cellular animal protein (meat, fish, poultry) may be useful, whereas for calcium, the percentage of energy from dairy products is probably more appropriate. Alternatively, if data on the mean daily per capita availability of additional nutrients such as iron, zinc, and calcium become available, then the percentage of iron or zinc from cellular animal protein, or the percentage of calcium from dairy products, could be calculated. Caution must be used, however, in the interpretation of these data if staple foods are fortified with iron, zinc, and/or calcium at the national level.

Calculation of mean daily per capita availability of phytate:zinc molar ratios from food-balance sheet data could provide a useful assessment of the bioavailability of zinc at the national level. As an example, **table 6** shows the per capita phytate:zinc molar ratios and proportion of energy from animal-source foods for selected countries calculated from FAO food-balance sheet data; further details are given by Hotz and Brown [36]. Depending on the phytate:zinc molar ratios, countries could be classified into those with diets of moderate (phytate:zinc molar ratios of 4 to 18) or low (phytate:zinc molar ratios > 18) zinc bioavailability by using the corresponding absorption estimates [36].

At present, national food-balance sheet data cannot be used to estimate the bioefficacy of provitamin A carotenoids. The food commodities itemized in the vegetable and fruit group are not comprehensive enough to compile a separate food group for green leafy vegetables, orange/yellow vegetables, or orange/yellow fruits.

Comparison of adjustments for diet- and host-related factors influencing iron and zinc bioavailability across countries

In view of the uncertainty about the bioavailability of iron and zinc in diets of differing compositions, it is not surprising that there are large differences in the adjustments employed to convert the physiological requirements for iron and zinc to yield dietary require-

TABLE 6. Phytate:zinc molar ratios and proportion of energy from animal-source foods for selected countries, based on FAO food-balance sheet data

Country	Phytate:zinc molar ratio	Energy from animal-source foods (%)
Mongolia	3.5	45.3
Egypt	27.5	7.0
United Kingdom	8.6	31.6
United States	10.6	27.8
Armenia	12.8	16.3
Cambodia	24.0	8.0
Kenya	26.7	12.6
Mexico	27.7	16.9
Bangladesh	27.7	3.1
Guatemala	36.3	8.6
Malawi	37.3	2.7

Source: data compiled from Hotz and Brown [36].

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ments, even among countries where omnivorous diets are habitually consumed. For example, in UK mixed diets, iron is assumed to have a fixed bioavailability of 15%, irrespective of age and life-stage group [207], whereas in the United States and Canada, a factor of 18% is used for the bioavailability of iron in the mixed diets of both children and nonpregnant adults, but 25% is used for women in the second and third trimesters of pregnancy and 10% for those consuming vegetarian diets [204]. Similarly, the United Kingdom uses a fixed factor of 30% for zinc, irrespective of age and life-stage group [207], but the United States and Canada apply a factor of 41% and 48% for the bioavailability of zinc from diets of adult (over 19 years) males and females, respectively, and 30% for preadolescent children [204]. Australia and New Zealand have adopted the US and Canadian bioavailability adjustments for iron for children 4 years of age or older, nonpregnant adults, and vegetarians, but the IZiNCG adjustments for zinc [36, 208]. Other expert groups, such as FAO/WHO [181] and IZiNCG [36], employ several factors to adjust for the bioavailability of iron and zinc, depending on the composition of the habitual diet, as noted earlier.

Conclusions

Adjustments are needed to translate physiological requirements into dietary requirements for certain nutrients, notably calcium, magnesium, iron, zinc, protein, folate, and vitamin A. The magnitude of the adjustments depends on the nutrient and will vary according to the nature of the habitual diet and a variety of host-related factors. However, information on some of the host-related factors, especially those that influence the efficiency of luminal and mucosal digestion and absorption, is often limited, so that their effects on nutrient bioavailability are often ignored when setting dietary requirement estimates. At present, several algorithms have been developed to predict the bioavailability of iron, zinc, protein, folate, vitamin A, and carotenoids, but there is still no consensus among countries about which are the best algorithms to use. In some countries, fixed bioavailability factors are still used for certain nutrients, even though their efficiency of absorption may vary with the dietary level of the nutrient or the life-stage group.

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