SUMMARY

Zinc functions as a component of various enzymes in the maintenance of the structural integrity of proteins and in the regulation of gene expression. Overt human zinc deficiency in North America is not common, and the symptoms of a mild deficiency are diverse due to zinc’s ubiquitous involvement in metabolic processes. Factorial analysis was used to set the Estimated Average Requirement (EAR). The Recommended Dietary Allowance (RDA) for adults is 8 mg/day for women and 11 mg/day for men. Recently, the median intake from food in the United States was approximately 9 mg/day for women and 14 mg/day for men. The Tolerable Upper Intake Level (UL) for adults is 40 mg/day, a value based on reduction in erythrocyte copper-zinc superoxide dismutase activity.

BACKGROUND INFORMATION

Function

Zinc has been shown to be essential for microorganisms, plants, and animals. Deprivation of zinc arrests growth and development and produces system dysfunction in these organisms. The biological functions of zinc can be divided into three categories: catalytic, structural, and regulatory (Cousins, 1996). There is extensive evidence in support of each of these functions, and there may be some overlap.
Nearly 100 specific enzymes (e.g., EC 1.1.1.1 alcohol dehydrogenase) depend on zinc for catalytic activity. Zinc removal results in loss of activity, and reconstitution of the holoenzyme with zinc usually restores activity. Examples of zinc metalloenzymes can be found in all six enzyme classes (Vallee and Galdes, 1984). Well-studied zinc metalloenzymes include the ribonucleic acid (RNA) polymerases, alcohol dehydrogenase, carbonic anhydrase, and alkaline phosphatase. Zinc is defined as a Lewis acid, and its action as an electron acceptor contributes to its catalytic activity in many of these enzymes. Changes in activity of zinc metalloenzymes during dietary zinc restriction or excess have not been consistent in experimental studies with humans or animals.

The structural role of zinc involves proteins that form domains capable of zinc coordination, which facilitates protein folding to produce biologically active molecules. The vast majority of such proteins form a “zinc finger-like” structure created by chelation centers, including cysteine and histidine residues (Klug and Schwabe, 1995). Some of these proteins have roles in gene regulation as dioxyribo- nucleic acid binding transcription factors. Examples include nonspecific factors such as Sp1 and specific factors such as retinoic acid receptors and vitamin D receptors. These structural motifs are found throughout biology and include the zinc-containing nucleocapsid proteins of viruses such as the human immunodeficiency virus (Berg and Shi, 1996). The relationship of zinc finger protein bioactivity to zinc in the diet has not received extensive study. Zinc also provides a structural function for some enzymes; copper-zinc superoxide dismutase is the most notable example. In this instance, copper provides catalytic activity, whereas zinc’s role is structural. Also of potential relevance as a structural role is the essentiality of zinc for intracellular binding of tyrosine kinase to T-cell receptors, CD4 and CD8α, which are required for T-lymphocyte development and activation (Huse et al., 1998; Lin et al., 1998).

The role of zinc as a regulator of gene expression has received less attention than its other functions. Metallothionein expression is regulated by a mechanism that involves zinc’s binding to the transcription factor, metal response element transcription factor (MTF1), which activates gene transcription (Cousins, 1994; Dalton et al., 1997). The number of genes that are activated by this type of mechanism is not known, however, because a null mutation for MTF1 is lethal during fetal development of mice, suggesting some critical genes must be regulated by MTF1 (Günes et al., 1998). Zinc transporter proteins associated with cellular zinc accumulation and release may be among the metal response element-regulated family.
of genes (McMahon and Cousins, 1998). Zinc has been shown to influence both apoptosis and protein kinase C activity (McCabe et al., 1993; Telford and Fraker, 1995; Zalewski et al., 1994), which is within the regulatory function. The relationship of zinc to normal synaptic signaling processes also falls within the regulatory role (Cole et al., 1999). The most widely studied MTF-regulated gene is the metallothionein gene. An unequivocal function has not been established, but this metalloprotein appears to act as a zinc trafficking molecule for maintaining cellular zinc concentrations (Cousins, 1996) and perhaps as part of a cellular redox system for zinc donation to zinc finger proteins (Jacob et al., 1998; Roesijadi et al., 1998). Upregulation of metallothionein by specific cytokines and some hormones suggests a function that is critical to a stress response. Induction of metallothionein by changes in dietary zinc intake has received considerable attention in experiments with both animals and humans (reviewed in Chesters, 1997; Cousins, 1994). Erythrocyte metallothionein concentrations decreased rapidly in humans fed a phytate-containing diet of very low zinc content (Grider et al., 1990). Erythrocyte metallothionein concentration appears to be a measure of severe zinc depletion, and the extent of a change in concentration can distinguish between low and adequate levels of zinc intake under experimental conditions (Thomas et al., 1992). Erythrocyte metallothionein and monocyte metallothionein messenger RNA concentrations increase with elevated zinc intake levels such as those encountered with dietary supplements (Grider et al., 1990; Sullivan et al., 1998). Studies of metallothionein concentration in blood cells or plasma during large human dietary trials have not been undertaken. Consequently, the use of metallothionein as a static or functional indicator of zinc status needs further study.

While knowledge of the biochemical and molecular genetics of zinc function is well developed and expanding, neither the relationship of these genetics to zinc deficiency or toxicity nor the function(s) for which zinc is particularly critical have been established. For example, explanations for depressed growth, immune dysfunction, diarrhea, altered cognition, host defense properties, defects in carbohydrate utilization, reproductive teratogenesis, and numerous other clinical outcomes of mild and severe zinc deficiency (Hambidge, 1989; King and Keen, 1999) have not been conclusively established.

**Physiology of Absorption, Metabolism, and Excretion**

Zinc is widely distributed in foods. Because virtually none of it is present as the free ion, bioavailability is a function of the extent of
digestion. Digestion produces the opportunity for zinc to bind to exogenous and endogenous constituents in the intestinal lumen, including peptides, amino acids, nucleic acids, and other organic acids and inorganic anions such as phosphate. The vast majority of zinc is absorbed by the small intestine through a transcellular process with the jejunum being the site with the greatest transport rate (Cousins, 1989b; Lee et al., 1989; Lonnerdal, 1989).

Absorption kinetics appear to be saturable, and there is an increase in transport velocity with zinc depletion. Paracellular transport may occur at high zinc intakes. Transit time also influences the extent of absorption to an extent that, in malabsorption syndromes, zinc absorption is reduced. Transfer from the intestine is via the portal system with most newly absorbed zinc bound to albumin.

Considerable amounts of zinc enter the intestine from endogenous sources. Homeostatic regulation of zinc metabolism is achieved principally through a balance of absorption and secretion of endogenous reserves involving adaptive mechanisms programmed by dietary zinc intake (King and Keen, 1999). Zinc depletion in humans is accompanied by reduced endogenous zinc loss on the order of 1.3 to 4.6 mg/day, derived from both pancreatic and intestinal cell secretions. Strong evidence suggests zinc transporter proteins in the various tissues act in concert to obtain such adaptation, but evidence is lacking in humans (McMahon and Cousins, 1998).

Measurement of true absorption, which eliminates the contribution of endogenous zinc from calculations, shows that zinc depletion increases the efficiency of intestinal zinc absorption. Regulation of absorption may provide a “coarse control” of body zinc, whereas endogenous zinc release provides “fine control” to maintain balance (King and Keen, 1999). An autosomal recessive trait, acrodermatitis enteropathica, is a zinc malabsorption problem of undetermined genetic basis. The mutation causes severe skin lesions and cognitive dysfunction (Aggett, 1989). The genetic defect suggests that one gene has a major influence on zinc absorption.

Tracer studies have shown that zinc is metabolically very active with initial uptake by liver representing a rapid phase of zinc turnover. Over 85 percent of the total body zinc is found in skeletal muscle and bone (King and Keen, 1999). While plasma zinc is only 0.1 percent of this total, its concentration is tightly regulated at about 10 to 15 µmol/L. Stress, acute trauma, and infection cause changes in hormones (e.g., cortisol) and cytokines (e.g., interleukin 6) that lower plasma concentration. Small changes in tissue pools could cause the decrease. In humans, plasma zinc concentrations are maintained without notable change when zinc intake is restricted.
or increased unless these changes in intake are severe and pro-
longed (Cousins, 1989a). Preliminary kinetic data indicate that the
combined size of readily exchangeable zinc pools (i.e., those that
exchange with zinc in plasma within 72 hours) decreases with dietary
zinc restriction (Miller et al., 1994). Fasting results in increased
plasma zinc concentration, an outcome that possibly reflects cata-
bolic changes in muscle protein. Cyclic postprandial changes in
plasma zinc concentration have been documented (King et al.,
1994). In both cases, hormonally regulated events are the biochem-
ical basis for the changes. Albumin is the principal zinc-binding
protein in plasma from which most metabolic zinc flux occurs. Func-
tional aspects of zinc tightly bound to α-2-macroglobulin have not
been described. Plasma amino acids bind some zinc and could be
an important source of zinc excretion.

Zinc secretion into and excretion from the intestine provides the
major route of endogenous zinc excretion. It is derived partially
from pancreatic secretions, which are stimulated after a meal. Biliary
secretion of zinc is limited, but intestinal cell secretions also con-
tribute to fecal loss (Lonnerdal, 1989). These losses may range from
less than 1 mg/day with a zinc-poor diet to greater than 5 mg/day
with a zinc-rich diet, a difference that reflects the regulatory role
that the intestinal tract serves in zinc homeostasis. Urinary zinc
losses are only a fraction (less than 10 percent) of normal fecal
losses (King and Keen, 1999). Zinc transporter activity may account
for renal zinc reabsorption (McMahon and Cousins, 1998), and
glucagon may help regulate it. Increases in urinary losses are con-
comitant with increases in muscle protein catabolism due to starva-
tion or trauma. The increase in plasma amino acids, which constit-
tute a potentially filterable zinc pool, is at least partially responsible.
Zinc loss from the body is also attributed to epithelial cell desqua-
mation, sweat, semen, hair, and the menstrual cycle.

Clinical Effects of Inadequate Intake

Individuals with malabsorption syndromes including sprue,
Crohn’s disease, and short bowel syndrome are at risk of zinc defi-
ciency due to malabsorption of zinc and increased urinary zinc
losses (Pironi et al., 1987; Valberg et al., 1986). In mild human zinc
deficiency states, the detectable features and laboratory/functional
abnormalities of mild zinc deficiency are diverse. This diversity is
not altogether surprising in view of the biochemistry of zinc and the
ubiquity of this metal in biology with its participation in an extra-
ordinarily wide range of vital metabolic processes. Impaired growth
velocity is a primary clinical feature of mild zinc deficiency and can be corrected with zinc supplementation (Hambidge et al., 1979b; Walravens et al., 1989). Other functions that respond to zinc supplementation include pregnancy outcome (Goldenberg et al., 1995) and immune function (Bogden et al., 1987). Evidence of the efficacy of zinc lozenges in reducing the duration of common colds is still unclear (Jackson et al., 2000).

Severe zinc deficiency has been documented in patients fed intravenously without the addition of adequate zinc to the infusates (Chen et al., 1991) and in cases of the autosomal recessively inherited disease acrodermatitis enteropathica (Walling et al., 1989). Because of the ubiquity of zinc and the involvement of this micronutrient in so many core areas of metabolism, it is not surprising that the features of zinc deficiency are frequently quite basic and nonspecific, including growth retardation, alopecia, diarrhea, delayed sexual maturation and impotence, eye and skin lesions, and impaired appetite. Clinical features and laboratory criteria are not always consistent. This inconsistency poses a major difficulty in the quest to validate reliable, sensitive clinical or functional indicators of zinc status that apply to a range of otherwise potentially useful laboratory indicators such as alkaline phosphatase activity.

A further major conundrum is posed by the impressive, yet apparently imperfect, homeostatic mechanisms that maintain a narrow range of zinc concentrations within the body in spite of widely diverse dietary intakes of this metal and in spite of differences in bioavailability. This situation applies, for example, to circulating zinc in the plasma, which consequently provides only an insensitive index of zinc status (King, 1990). Therefore, it has become increasingly apparent that homeostatic mechanisms fall short of perfection and that clinically important features of zinc deficiency can occur with only modest degrees of dietary zinc restriction while circulating zinc concentrations are indistinguishable from normal.

**SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR ZINC**

**Principal Indicator**

The selection of zinc absorption (more specifically, the minimal quantity of absorbed zinc necessary to match total daily excretion of endogenous zinc) as the principal indicator for adult Estimated Average Requirements (EAR) has been based on the evaluation of a factorial approach to determining zinc requirements. Details of this
approach are discussed under “Findings by Life Stage and Gender Group—Adults Ages 19 Years and Older”. A sufficient number of metabolic studies of zinc homeostasis have been reported to permit an estimation of dietary zinc requirements in adults.

The first step in this approach is to calculate nonintestinal losses of endogenous zinc, that is, losses via the kidney and integument with smaller quantities in semen and menstrual losses. Although urinary zinc excretion decreases markedly with severe dietary zinc restriction (Baer and King, 1984), extensive data indicate that excretion by this route is unrelated to dietary zinc intake over a wide range (4 to 25 mg/day) that is certain to encompass the dietary zinc requirements for adults. Data regarding this lack of relation between intake and integumental and semen losses of zinc are more limited. Therefore, nonintestinal losses of endogenous zinc have been treated as a constant in response to varied zinc intake.

In contrast to excretion of zinc via other routes, excretion of endogenous zinc via the intestine is a major variable in the maintenance of zinc homeostasis and is strongly correlated with absorbed zinc. The second step in estimating dietary zinc requirements is to define this relationship (Figure 12-1). After it has been defined and adjusted by the constant for other endogenous losses, one can calculate the minimum quantity of absorbed zinc necessary to offset endogenous zinc losses (Figure 12-1).

The dietary zinc intake corresponding to this average minimum quantity of absorbed zinc is the EAR. This value has been determined from the plot of the asymptotic regression analysis of absorbed zinc versus ingested zinc (Figure 12-2).

Theoretically, given the results described in detail for adults below, balance could also be used as an indicator. However, review of all published data on zinc balance (and net [apparent] absorption) studies in young adult men (excluding those studies that have included tracer data and are being utilized for the current factorial calculations) collectively revealed no correlation with dietary zinc. Presumably this lack of correlation reflects the vagaries of balance studies. The factorial calculations for adults are based on tracer/metabolic studies in which participants were fed diets from which the bioavailability of zinc was likely to be representative of typical diets in North America or, in some instances, possibly greater than average.
FIGURE 12-1 The relationship between endogenous zinc excretion and absorbed zinc. Heavy line represents the linear regression of intestinal excretion of endogenous zinc (mg/day) versus absorbed zinc (mg/day) from means of ten data sets for healthy men ages 19 through 50 years. The bold dashed lines above and parallel to the regression line represent the total endogenous zinc losses for men and women in relation to zinc absorption. The faint dashed line is the line of perfect agreement or equality of endogenous zinc and absorbed zinc. The intersect of this line with that of total endogenous zinc excretion indicates the average minimum quantity of absorbed zinc necessary to match endogenous losses for men and women. SOURCE: Hunt JR et al. (1992), Jackson et al. (1984), Lee et al. (1993), Taylor et al. (1991), Turnlund et al. (1984, 1986), Wada et al. (1985).

Secondary Indicators

Physical Growth Response to Zinc Supplementation

In contrast to studies on the effects of low-dose zinc supplements on clinical features (e.g., pneumonia, diarrhea [Bhutta et al., 1999]) and on nonspecific laboratory functional tests of zinc status (e.g., tests of neuro-cognitive function [Sandstead et al., 1998]) or immune status (Shankar and Prasad, 1998), studies of the effects of zinc supplementation on physical growth velocity in children are useful in evaluating dietary zinc requirements for several reasons.
FIGURE 12-2 Asymptotic regression of absorbed zinc and ingested zinc. Individual points are means for the same data sets in Figure 12-1. SOURCE: Hunt JR et al. (1992), Jackson et al. (1984), Lee et al. (1993), Taylor et al. (1991), Turnlund et al. (1984, 1986), Wada et al. (1985).

First, confirmation of the effect of zinc supplements on growth velocity (linear growth and weight) in children with varying degrees of growth retardation has been shown in a number of studies from many countries (Brown et al., 1998; Umeta et al., 2000). Second, because a sufficient number of these studies have been undertaken in North America, growth is applicable as a functional/clinical indicator of zinc requirement in North American children (Gibson et al., 1989; Walravens and Hambidge, 1976; Walravens et al., 1983, 1989). Third, baseline dietary data typically included in these studies are adequate to use for group analyses.

Size and Turnover Rates of Zinc Pools

Strong positive correlations have been observed between dietary zinc content, especially the amount of absorbed zinc, and estimates of the size of the combined pools of zinc that exchange with zinc in
Once links to clinical, biochemical, or molecular effects of zinc deficiency have been achieved and appropriate cut-off levels for different age groups and gender have been defined, pool size and turnover measurements may be of value in future refinements of EARs. Even simpler models involving the measurement of plasma zinc clearance may be useful in assessing zinc deficiency, but dietary data derived by such a method are not available at this time (Kaji et al., 1998; Nakamura et al., 1993; Yokoi et al., 1994). More detailed model-based compartmental analyses, when specifically applied to the evaluation of dietary requirements, also have the potential to contribute to a more precise understanding of zinc requirements (Miller et al., 1998; Wastney et al., 1986).

**Plasma and Serum Zinc Concentration**

While both plasma zinc concentration and serum zinc concentration are used as indicators of zinc status, plasma zinc concentration is preferable because of the lack of contamination of zinc from the erythrocyte. Homeostatic mechanisms are effective in maintaining plasma zinc concentrations for many weeks of even severe dietary zinc restriction (Johnson et al., 1993; Wada et al., 1985). A number of studies have reported no association between dietary zinc intake and plasma or serum zinc concentration (Artacho et al., 1997; Kant et al., 1989; Neggers et al., 1997; Thomas et al., 1988). Payette and Gray-Donald (1991) did observe a significant correlation between dietary zinc intake and serum zinc concentration in noninstitutionalized elderly; however, the correlation was positive for men and negative for women. Discernible relationships have been reported between plasma zinc concentration and habitual dietary zinc intake, even within the range typically occurring in North America. These relationships are of some utility in providing a supportive indicator of zinc requirements. For example, serum zinc concentrations of Canadian adolescent girls aged 14 to 19 years vary inversely with phytate:zinc molar ratios, and a greater percentage of lacto-ovo-vegetarians have serum zinc values below 70 µg/dL than do omnivores (Donovan and Gibson, 1995). Cut-off concentrations for lower limits have been established and depend on the time of day at which collections are made because of the substantial and cumulative effects of meals in lowering concentrations (King et al., 1994). The cut-off concentrations for prebreakfast samples is 70 µg/dL. Different cut-off concentrations are not considered necessary for different age groups or genders.
Insufficient and inconsistent data exist for plasma or serum zinc concentrations in apparently normal subjects whose habitual dietary zinc intakes straddle the vicinity of the average requirement, and therefore use of those concentrations for estimating an average requirement is limited. Furthermore, plasma and serum zinc concentrations do not seem to be sufficiently sensitive to serve as a subsidiary indicator.

**Zinc Concentration in Erythrocytes**

Erythrocyte zinc concentration is depressed at moderately severe levels of dietary zinc restriction (Thomas et al., 1992), but the sensitivity of this assay is inadequate to provide more than a secondary supportive indicator of dietary zinc requirements. Sample preparation may account for some of the lack of sensitivity. Results from experimental depletion studies (Baer and King, 1984; Bales et al., 1994; Grider et al., 1990; Ruz et al., 1992; Thomas et al., 1992) have been mixed, and the value of erythrocyte zinc concentrations as an indicator of zinc nutritional status is not well defined.

**Zinc Concentration in Hair**

Associations between low zinc concentration in hair and poor growth have been documented (Ferguson et al., 1993; Gibson et al., 1989; Hambidge et al., 1972; Walravens et al., 1983). In three of these studies, low zinc concentration in hair was used as a criterion for zinc supplementation in children and resulted in increased growth velocity. Low zinc concentrations in hair have also been reported in Canadian children with low meat consumption (Smit-Vanderkooy and Gibson, 1987). Subjects whose habitual diets are high in phytate or who have very high phytate:zinc molar ratios have also been noted to have relatively low zinc concentrations in hair. However, there is a lack of uniformity in apparently low zinc concentrations in hair, and no lower cut-off values have been defined clearly for any age group or either gender. The use of zinc in hair as a supportive indicator for establishing zinc requirements needs further research.

**Activity of Zinc-Dependent Enzymes**

With the large number of zinc-dependent enzymes that have been identified, it is perhaps remarkable that no single zinc-dependent enzyme has found broad acceptance as an indicator of zinc status or
requirement. This state of affairs is attributable to a number of factors, including the homeostatic processes that maintain zinc occupancy of the catalytic sites of these enzymes and the lack of consistency in findings between studies. Other factors include a lack of sensitivity, the inaccessibility of optimal tissues to assay, or, simply, inadequate research. The lack of baseline dietary data also negates the potential value of some reports. Given these limitations, limited dose-response data, and inconsistent responses to dietary zinc (Bales et al., 1994; Davis et al., 2000; Paik et al., 1999; Ruz et al., 1992; Samman et al., 1996), the activities of zinc-dependent enzymes, including alkaline phosphatase, copper-zinc superoxide dismutase, and lymphocyte 5′-nucleotidase, can at most serve as supportive indicators of dietary zinc requirements at this time. Although it is not consistently responsive to zinc intake, the activity of plasma 5′-nucleotidase (Beck et al., 1997a), which is derived from the CD73 cell surface markers of B and T cells, merits specific recognition as a potential marker of zinc status (Failla, 1999).

Metallothionein and Zinc-Regulated Gene Markers

Erythrocyte metallothionein concentrations have been reported to be responsive to both increased and restricted dietary zinc (Grider et al., 1990; Thomas et al., 1992), but the sensitivity and precision of this index has not been thoroughly evaluated. Monocyte metallothionein messenger RNA responds rapidly to in vivo zinc supplementation (Sullivan et al., 1998) and merits additional research. Moreover, this approach points the way for future exploration of molecular markers of zinc status including, for example, a whole family of zinc transporters that are now being identified (Failla, 1999; McMahon and Cousins, 1998).

Indexes of Immune Status

Zinc is essential for the integrity of the immune system, and inadequate zinc intake has many adverse effects (Shankar and Prasad, 1998). Though the immune system, which is thought to underlie several of the most important sequelae of mild zinc deficiency, is sensitive to even mild zinc deficiency, the effects on functional indexes of zinc status are not specific. At this time, therefore, changes in indexes of immune status with manipulation of dietary zinc can serve only as a limited indicator for dietary zinc requirements.
Hormones

The biology of zinc is linked extensively to hormone metabolism. Notable examples are the zinc finger motifs of regulatory proteins required for hormonal signals to regulate gene transcription (Cousins, 1994; Klug and Schwabe, 1995). Zinc has been reported to have roles in the synthesis, transport, and peripheral action of hormones. Low dietary zinc status has been associated with low circulating concentrations of several hormones including testosterone (Prasad et al., 1996), free T4 (Wada and King, 1986), and IGF-1 (Ninh et al., 1996). Zinc supplementation has been associated with an increase in both circulating IGF-1 concentration and growth velocity (Ninh et al., 1996). However, no studies have directly related hormone concentrations to decreases or increases in zinc intake.

Circulating Hepatic Proteins

Reductions in retinol binding protein, albumin, and pre-albumin concentrations have been reported with moderate dietary zinc restriction (Wada and King, 1986). Serum zinc and retinol binding protein concentrations are significantly correlated in zinc-deficient Thai children (Udomkesmalee et al., 1990). Changes in circulating concentrations of these proteins with changes in dietary zinc may serve as minor supportive indicators. The relationship of such indicators to general malnutrition or to dietary deficiency that is not related to zinc status supports their being minor indicators for zinc requirements.

FACTORS AFFECTING THE ZINC REQUIREMENT

Bioavailability

Bioavailability of zinc can be affected by many factors at many sites. The intestine is the major organ in which variations in bioavailability affect dietary zinc requirements. These effects occur through two key regulatory processes: absorption of exogenous zinc and reabsorption of endogenous zinc. Dietary factors that affect bioavailability can have an impact on each of these processes (Cousins, 1989b; Lonnerdal, 1989).

Zinc absorption from foods and supplements has received extensive study. The environment within the gastrointestinal tract drastically influences zinc solubility and absorptive efficiency. The propensity of zinc to bind tenaciously to ligands provided by dietary...
constituents is accentuated at the near neutral pH in the intestinal lumen. The exact nature of the form in which zinc is needed for uptake has not been established. Some transporters responsible for transcellular zinc movement may require the free ion, but cotransport with small peptides and nucleotides has not been ruled out. Absorption of zinc, when consumed as a chelate, has not been investigated extensively. The option for zinc to be absorbed by the paracellular route adds to the lack of a unified form or path of zinc absorption from foods. Furthermore, the methods used to assess zinc absorption have varied widely, including balance studies, intestinal perfusion, responses of plasma zinc to single meals or aqueous doses, and tracer studies with intrinsically or extrinsically stable or radioactive zinc isotopes (Sandstrom and Lonnerdal, 1989).

Nutrient-Nutrient Interactions

Iron

Daily intake of iron at levels such as those found in some supplements could decrease zinc absorption (O’Brien et al., 2000; Solomons and Jacob, 1981; Valberg et al., 1984). This relationship is of some concern in management of iron supplementation during pregnancy and lactation (Fung et al., 1997). Recent studies of the mechanism of nonheme iron absorption suggest that upregulation of an iron transport protein occurs in iron deficiency (Gunshin et al., 1997). The comparable affinity of this transporter for zinc suggests that, during low iron intake, zinc absorption may be stimulated and suggests one possible locus for a zinc-iron interaction. The influence of heme iron on zinc absorption has not received much attention. The activity of other divalent metal transporters may also affect zinc absorption.

Calcium and Phosphorus

The importance of calcium in the diet and the mass of the element that must be consumed daily to maintain maximum bone density suggest that special attention should be given to its potential inhibitory effect on zinc absorption. Nutrition experiments with swine have shown conclusively that excess dietary calcium produces a decrease in zinc absorption, which leads to a skin condition called parakeratosis. Experiments in humans have been equivocal, with calcium phosphate (1,360 mg/day of calcium) decreasing zinc absorption (Wood and Zheng, 1997) and calcium as the citrate-malate
complex (1,000 mg/day of calcium) having no statistically significant effect on zinc absorption (McKenna et al., 1997). Differences could be related to the calcium sources, techniques used, and the extent of luminal zinc solubility. At present, data suggest consumption of a calcium-rich diet does not have a major effect on zinc absorption at an adequate intake level of the nutrient. Calcium effects at low dietary zinc intakes have not been adequately investigated. Dietary phosphorus-containing salts over an extensive intake range have not been shown to influence zinc balance (Greger and Snedeker, 1980; Spencer et al., 1984). Other dietary sources of phosphorus include phytate and phosphorus-rich proteins, for example, milk casein and nucleic acids, all of which bind zinc tenaciously and decrease zinc absorption.

Copper

Large-scale studies on the influence of dietary copper intake on zinc absorption and utilization have not been carried out with human subjects. Various experimental approaches with animals have not revealed a uniform influence of copper on intestinal zinc uptake (Cousins, 1985; Sandstrom and Lonnerdal, 1989). Rather, evidence for an interaction derives from the therapeutic effect of zinc in reducing copper absorption in patients with Wilson’s disease (Yuzbasiyan-Gurkan et al., 1992). This action includes the induction of intestinal metallothionein by zinc and the subsequent binding of excess copper by this metalloprotein, which may limit transcellular copper absorption. The relationship may have relevance in situations where zinc supplements are consumed with marginal dietary copper intake.

Folate

Folate bioavailability is enhanced when polyglutamate folate is hydrolyzed by the zinc-dependent enzyme, polyglutamate hydrolase, to the monoglutamate. This occurrence suggests a possible point of interaction. Some studies have shown a relationship between folate and zinc (Milne et al., 1984), with low zinc intake decreasing folate absorption/status. More recent evidence does not support any effect of low zinc intake on folate utilization and shows that folate supplementation does not adversely affect zinc status (Kauwell et al., 1995). Extensive studies on this potential relationship have not been carried out in women. Given that these nutrients have important functions in both fetal and postnatal development, the relationship requires further study.
Protein

Zinc binds tenaciously to proteins at near neutral pH. Consequently, the amount of protein in the diet is a factor contributing to the efficiency of zinc absorption. As protein digestion proceeds, zinc becomes more accessible for zinc transport mechanisms of intestinal cells. The relative abundance of zinc as small molecular weight complexes of low binding affinity enhances the process. Small changes in protein digestion may produce significant changes in zinc absorption (Sandstrom and Lonnerdal, 1989). These changes in absorption may explain the correlation between zinc deficiency symptoms and certain malabsorption disorders (Cousins, 1996). The markedly greater bioavailability of zinc from human milk than from cow’s milk is an example of how protein digestibility, which is much lower in casein-rich cow’s milk than in human milk, influences zinc absorption (Roth and Kirchgessner, 1985). In general, zinc absorption from a diet high in animal protein will be greater than from a diet rich in proteins of plant origin such as soy (King and Keen, 1999).

Other Food Components

Phytic Acid

Plants contain phytic acid (myo-inositol hexaphosphate) for use as a storage form of phosphorus. Consequently, plant-based foods, particularly grains and legumes, have a significant phytic acid content. Enzymatic action of yeast during the leavening of bread and other fermentations reduce phytate levels, whereas extrusion processes (used in preparation of some breakfast cereals), may not (Williams and Erdman, 1999). In Caco-2 cells, the metal binding property of phytic acid decreases proportionally as fewer than six phosphate groups are bound to each inositol molecule (Han et al., 1994). Phytate binding of zinc has been demonstrated as a contributing factor for the zinc deficiency related to consumption of unleavened bread seen in certain population groups in the Middle East (Prasad, 1991). The overall effect of phytate is to reduce zinc absorption from the gastrointestinal tract through complexation and precipitation (Oberleas et al., 1966). These chemical effects appear to be enhanced by simultaneous binding of calcium. Phytate binding in the intestinal lumen includes zinc of both food origin and endogenous origin. Since zinc homeostasis is controlled in part by endogenous secretions, consumption of phytate-rich foods may
be of practical importance as a factor that limits absorption and maintenance of zinc balance. While high-fiber-containing foods tend also to be phytate-rich, fiber alone may not have a major effect on zinc absorption.

**Picolinic Acid**

A metabolite of tryptophan metabolism, picolinic acid has a high metal binding affinity. Picolinate complexes of zinc and chromium are not formed in nature in appreciable amounts, but are sold commercially as dietary supplements. Zinc picolinate as a zinc source for humans has not received extensive investigation. In an animal model, picolinic acid supplementation promoted negative zinc balance (Seal and Heaton, 1985), presumably by promoting urinary excretion.

**Algorithms**

To date, a useful algorithm for establishing dietary zinc requirements based on the presence of other nutrients and food components has not been established, and much information is still needed to develop one that can predict zinc bioavailability (Hunt, 1996). Algorithms for estimating dietary zinc bioavailability will need to include the dietary content of phytic acid, protein, zinc, and possibly calcium, iron, and copper. The World Health Organization (WHO, 1996) developed zinc requirements from low, medium, and high bioavailability diets on the basis of estimates of fractional absorption on single test meals with varying zinc and phytate content. The results of single test meals for measuring zinc absorption, however, may be different from the long-term response of zinc absorption, as has been shown to be the case for iron (see Chapter 9).

**FINDINGS BY LIFE STAGE AND GENDER GROUP**

*Infants Ages 0 through 6 Months*

No functional criteria of zinc status have been demonstrated that reflect response to dietary intake in infants. Thus, recommended intakes of zinc are based on an Adequate Intake (AI) that reflects the observed mean zinc intake of infants exclusively fed human milk.
**Method Used to Set the Adequate Intake**

Using the method described in Chapter 2, an AI has been used as the goal for intake during the first 6 months of life. The AI is based on the maternal zinc supply to the infant exclusively fed human milk.

There is an unusually rapid physiologic decline in the zinc concentration of human milk and consequently in the zinc supplied to infants fed human milk during the first 6 months of lactation (Krebs et al., 1985, 1994, 1995; Moser and Reynolds, 1983) (Figure 12-3). Concentrations of zinc in human milk decline from approximately 4 mg/L at 2 weeks to 3 mg/L at 1 month, 2 mg/L at 2 months, 1.5 mg/L at 3 months, and 1.2 mg/L at 6 months postpartum (Krebs et al., 1995; see Table 12-1). With a standard volume of intake of 0.78 L/day (Chapter 2), calculated zinc intakes are 2.15 mg/day at 1 month, 1.56 mg/day at 2 months, 1.15 mg/day at 3 months, and 0.94 mg/day at 6 months (Table 12-1). Measured zinc intake of infants fed human milk was 2.3 mg/day at 2 weeks and 1 mg/day at 3 months (Krebs et al., 1994).

**FIGURE 12-3** Average zinc consumption from human milk during the first 12 months of lactation.

SOURCE: Table 12-1.
### TABLE 12-1 Zinc Concentration in Human Milk

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Group</th>
<th>Maternal Intake (mg/d)</th>
<th>Stage of Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picciano and Guthrie, 1976</td>
<td>50 women</td>
<td>Not reported</td>
<td>6–12 wk</td>
</tr>
<tr>
<td>Johnson and Evans, 1978</td>
<td>10 women</td>
<td>Not reported</td>
<td>2 mo–2 y</td>
</tr>
<tr>
<td>Vuori et al., 1980</td>
<td>15 women, 24–35 y</td>
<td>13.7 ± 2.7 mg/d</td>
<td>6–8 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.8 ± 2.8 mg/d</td>
<td>17–22 wk</td>
</tr>
<tr>
<td>Fransson and Lonnerdal, 1982</td>
<td>25 women</td>
<td>Not reported</td>
<td>Various s</td>
</tr>
<tr>
<td>Moser and Reynolds, 1983</td>
<td>23 women, 30 y</td>
<td>9.4</td>
<td>1 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.8</td>
<td>3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.6</td>
<td>6 mo</td>
</tr>
<tr>
<td>Casey et al., 1985</td>
<td>11 women, 26–39 y</td>
<td>Not reported</td>
<td>8 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28 d</td>
</tr>
<tr>
<td>Casey et al., 1989</td>
<td>22 women</td>
<td>10.9</td>
<td>7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 mo</td>
</tr>
<tr>
<td>Sievers et al., 1992</td>
<td>10 women</td>
<td>Not reported</td>
<td>17 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56 d</td>
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<td></td>
<td></td>
<td></td>
<td>85 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>117 d</td>
</tr>
<tr>
<td>Anderson, 1993</td>
<td>6 women, 20–30 y</td>
<td>Not reported</td>
<td>Up to 5 mo</td>
</tr>
<tr>
<td>Krebs et al., 1995</td>
<td>71 women, 30 y</td>
<td>13–25.7</td>
<td>0.5 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 mo</td>
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<td></td>
<td></td>
<td></td>
<td>3 mo</td>
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<td></td>
<td></td>
<td></td>
<td>4 mo</td>
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<td></td>
<td></td>
<td></td>
<td>5 mo</td>
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<td>6 mo</td>
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<td></td>
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<td></td>
<td>7 mo</td>
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<td></td>
<td></td>
<td></td>
<td>8 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 mo</td>
</tr>
<tr>
<td>Aquilio et al., 1996</td>
<td>14 women, 21–29 y</td>
<td>Not reported</td>
<td>2–6 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12–16 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 d</td>
</tr>
<tr>
<td>Biego et al., 1998</td>
<td>17 milk samples</td>
<td>Not reported</td>
<td>Mature m</td>
</tr>
</tbody>
</table>

*Zinc intake based on reported data or concentration (mg/L) × 0.78 L/day for 0–6 months postpartum and concentration (mg/L) × 0.6 L/day for 7–12 months postpartum.*
<table>
<thead>
<tr>
<th>Intake</th>
<th>Stage of Lactation</th>
<th>Milk Concentration (mg/L)</th>
<th>Estimated Zinc Intake of Infants (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced</td>
<td>6–12 wk</td>
<td>1.7</td>
<td>1.33</td>
</tr>
<tr>
<td>Reduced</td>
<td>2 mo–2 y</td>
<td>1.8</td>
<td>1.40</td>
</tr>
<tr>
<td>Reduced 17 mg/d</td>
<td>6–8 wk</td>
<td>1.89</td>
<td>1.47</td>
</tr>
<tr>
<td>Reduced 8 mg/d</td>
<td>17–22 wk</td>
<td>0.72</td>
<td>0.56</td>
</tr>
<tr>
<td>Reduced Various stages</td>
<td></td>
<td>1.1</td>
<td>0.86</td>
</tr>
<tr>
<td>1 mo</td>
<td></td>
<td>2.6</td>
<td>2.03</td>
</tr>
<tr>
<td>3 mo</td>
<td></td>
<td>1.3</td>
<td>1.01</td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td>1.1</td>
<td>0.86</td>
</tr>
<tr>
<td>Reduced 8 d</td>
<td>8 d</td>
<td>4.74</td>
<td>3.69</td>
</tr>
<tr>
<td></td>
<td>14 d</td>
<td>3.88</td>
<td>3.03</td>
</tr>
<tr>
<td></td>
<td>21 d</td>
<td>3.71</td>
<td>2.89</td>
</tr>
<tr>
<td></td>
<td>28 d</td>
<td>2.98</td>
<td>2.32</td>
</tr>
<tr>
<td></td>
<td>7 d</td>
<td>4.7</td>
<td>3.66</td>
</tr>
<tr>
<td></td>
<td>1 mo</td>
<td>2.9</td>
<td>2.26</td>
</tr>
<tr>
<td></td>
<td>12 mo</td>
<td>0.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Reduced 17 d</td>
<td>17 d</td>
<td>3.6</td>
<td>2.81</td>
</tr>
<tr>
<td></td>
<td>35 d</td>
<td>2.6</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>56 d</td>
<td>1.7</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>85 d</td>
<td>1.3</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>117 d</td>
<td>1.2</td>
<td>0.94</td>
</tr>
<tr>
<td>Reduced 2 mo–6 d</td>
<td>Up to 5 mo</td>
<td>1.1–3.4</td>
<td>0.86–2.65</td>
</tr>
<tr>
<td></td>
<td>0.5 mo</td>
<td>4</td>
<td>3.12</td>
</tr>
<tr>
<td></td>
<td>1 mo</td>
<td>2.75</td>
<td>2.15</td>
</tr>
<tr>
<td></td>
<td>2 mo</td>
<td>2</td>
<td>1.56</td>
</tr>
<tr>
<td></td>
<td>3 mo</td>
<td>1.5</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td>4 mo</td>
<td>1.4</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>5 mo</td>
<td>1.2</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>1.2</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>7 mo</td>
<td>0.8</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>8 mo</td>
<td>0.9</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>9 mo</td>
<td>0.8</td>
<td>0.48</td>
</tr>
<tr>
<td>Reduced 12–16 d</td>
<td>2–6 d</td>
<td>2.2</td>
<td>1.72</td>
</tr>
<tr>
<td></td>
<td>12–16 d</td>
<td>2.3</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>21 d</td>
<td>2.3</td>
<td>1.79</td>
</tr>
<tr>
<td>Reduced Mature milk</td>
<td></td>
<td>2</td>
<td>1.6</td>
</tr>
</tbody>
</table>
In order to match the zinc intake of the infant in early weeks (Figure 12-3), the AI is set at 2.0 mg/day (2.5 mg/L × 0.78 L/day). This amount appears to be generous at ages 4 to 6 months when evaluated by zinc intake from human milk at this age, and human milk has been shown to result in weight gain and body lengths similar to those of infants provided complementary foods at 4 to 6 months (Dewey et al., 1999). A positive association between zinc content of human milk at 5 months and changes in the weight-for-age Z scores for the 5- to 7-month interval have, however, been documented (Krebs et al., 1994). There is also some evidence, however, that growth-limiting zinc deficiency can occur in infants principally fed human milk after the age of 4 months (Walravens et al., 1992).

Factorial estimates of requirements (i.e., 2.1 mg/day at 1 month and 1.54 mg/day at 5 months) are consistent with this AI for infants ages 0 through 6 months. These factorial estimates are based on measurements of zinc intake of infants fed human milk, fractional absorption, and endogenous losses (Krebs et al., 1996). Integumental and urine losses are from published calculations (Krebs and Hambidge, 1986). Also consistent with this AI is an earlier report that physical growth of male infants fed a zinc-fortified cow milk formula (5.8 mg/L) was greater than that of infants receiving the same formula but with a zinc concentration of 1.8 mg/L, which provided about 1.4 mg/day of zinc (Walravens and Hambidge, 1976).

Zinc AI Summary, Ages 0 through 6 Months

AI for Infants

0–6 months 2.0 mg/day of zinc

Special Considerations

The zinc concentration in cow milk ranges from 3 to 5 mg/L (Lonnerdal et al., 1981) which is greater than the average concentration in human milk (Table 12-1). Singh and coworkers (1989) reported that approximately 32 percent of zinc in cow milk is bound to casein and the majority of the remaining zinc (63 percent) is bound to colloidal calcium phosphate. The absorption of zinc from human milk is higher than from cow milk-based infant formula and cow milk (Lonnerdal et al., 1988; Sandstrom et al., 1983). The zinc bioavailability from soy formulas is significantly lower than from milk-based formulas (Lonnerdal et al., 1988; Sandstrom et al., 1983).
Infants and Children Ages 7 Months through 3 Years

Evidence Considered in Estimating the Average Requirement

Intake from Human Milk. Zinc nutriture in later infancy is quite different from that in the younger infant. It is likely that neonatal hepatic stores, which may contribute to metabolically usable zinc pools in early postnatal life, have been dissipated (Zlotkin and Cherian, 1988). Human milk provides only 0.5 mg/day of zinc by 7 months postpartum (Krebs et al., 1994), and the concentration declines even further by 12 months (Casey et al., 1989). It is apparent, therefore, that human milk alone is an inadequate source of zinc after the first 6 months. As a result, extrapolation from human milk intake during the 0 through 6 months postpartum period, which yields 2.4 mg/day, does not reflect adequate zinc intake during the second 6 months.

Intake from Human Milk and Complementary Foods. Data from the Third National Health and Nutrition Examination Survey indicate that the median intake of zinc from complementary foods is 1.48 mg/day (n = 45) for older infants consuming human milk. Thus, the average zinc intake from human milk and complementary foods is estimated to be approximately 2 mg/day (0.5 + 1.48).

Factorial Analysis. Excretion of endogenous zinc is used to estimate the physiological requirement of zinc in older infants and young children. The Estimated Average Requirement (EAR) for zinc is determined by dividing the physiological requirement by the fractional zinc absorption. Apart from some data on excretion of zinc in the urine (Alexander et al., 1974; Cheek et al., 1968; Ziegler et al., 1978), direct measurements of endogenous zinc excretion are not available for older infants, children, or adolescents. These endogenous zinc losses (intestinal, urinary, and integumental), therefore, are estimated by extrapolation from measured values for either adults (see “Adults Ages 19 Years and Older”) or younger infants. These extrapolations have been based on a reference weight.

Intestinal losses vary directly with the quantity of zinc absorbed (see “Adults Ages 19 Years and Older”). The average intestinal excretion of endogenous zinc in infants aged 2 to 4 months who receive human milk is approximately 50 µg/kg/day (Krebs et al., 1996). There is a “critical” level of intestinal excretion of endogenous zinc...
in adults at which the quantity of absorbed zinc is equal to the total endogenous zinc losses. This critical level, derived from all available sets of data for adult men, yields an average excretion of 34 µg/kg/day of zinc and is used for children beyond 1 year of age and adolescents. Therefore, 50 µg/kg/day is used for older infants and 34 µg/kg/day for children aged 1 through 3 years. It is recognized that this is an approximation, not only because of the extrapolation of values but also because intestinal excretion of endogenous zinc is strongly correlated with zinc absorption.

**Urinary losses** of zinc are approximately 7.5 µg/kg/day for both men and women (see “Adults Ages 19 Years and Older”). After early infancy, excretion rates for children on a body weight basis seem to differ very little from adult values (Krebs and Hambidge, 1986). No data are available on the *integumental losses* in children, so estimates for children are derived from data in adult men (Johnson et al., 1993), which provide an estimate of 14 µg/kg/day of zinc. Therefore, the estimated total endogenous excretion of zinc is 64 µg/kg/day for older infants and 48 µg/kg/day for children aged 1 through 3 years.

**Requirements for Growth.** These requirements have been estimated from chemical analyses of infants and adults, which give an average concentration of 20 µg/g wet weight of zinc (Widdowson and Dickerson, 1964). It is assumed that each gram of new lean and adipose tissue requires this amount of zinc. The average amount of new tissue accreted for older infants and young children is 13 and 6 g/day, respectively (Kuczmarski et al., 2000).

With the estimates above, the total amount of absorbed zinc required for infants ages 7 through 12 months is 836 µg/day (Table 12-2). The corresponding value for children ages 1 through 3 years is 744 µg/day (Table 12-3).

**Fractional Absorption of Dietary Zinc.** Fractional absorption probably has the greatest variation of any of the above physiological factors, depending as it does on numerous factors including quantity of ingested zinc, nutritional status, and bioavailability. Although a “critical” average fractional absorption of 0.4 has been derived from the data sets used for adult men (see “Adults Ages 19 Years and Older”), a more conservative value of 0.3 is used for preadolescent children. This value is based on studies of infants and young children reported by Fairweather-Tait and coworkers (1995) and Davidsson and coworkers (1996). To calculate the dietary zinc requirement based on
TABLE 12-2 Requirement for Absorbed Zinc for Infants Aged 7 through 12 Months

<table>
<thead>
<tr>
<th>Losses</th>
<th>Absorbed Zinc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal losses 50 µg/kg/day</td>
<td>450 µg/day</td>
</tr>
<tr>
<td>Urinary and integumental losses</td>
<td>126 µg/day</td>
</tr>
<tr>
<td>Requirement for growth 13 g/day</td>
<td>260 µg/day</td>
</tr>
</tbody>
</table>

Required absorbed zinc = 836 µg/day

TABLE 12-3 Requirement for Absorbed Zinc for Children Aged 1 through 3 Years

<table>
<thead>
<tr>
<th>Losses</th>
<th>Absorbed Zinc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal losses 34 µg/kg/day</td>
<td>442 µg/day</td>
</tr>
<tr>
<td>Urinary and integumental losses</td>
<td>182 µg/day</td>
</tr>
<tr>
<td>Requirement for growth 6 g/day</td>
<td>120 µg/day</td>
</tr>
</tbody>
</table>

Required absorbed zinc = 744 µg/day

the fractional zinc absorption, it is assumed that the older infant continues to be fed human milk between 7 and 12 months of age along with complementary foods. The fractional absorption of zinc from human milk continues to approximate 0.5 (Abrams et al., 1997). Based on an average intake of 500 µg/day from human milk and a fractional absorption of 0.5, the amount of zinc ingested from milk is approximately 250 µg/day. Therefore the estimated absorbed zinc required from complementary foods is 586 µg/day (836 – 250). Applying a fractional absorption of 0.3, zinc intake required from complementary foods is 1.95 mg/day (586 ÷ 0.3). Therefore, the EAR for infants ages 7 through 12 months is 2.5 mg/day (0.5 + 1.95). For children ages 1 through 3 years, a fractional absorption of 0.3 is used to estimate the required dietary zinc resulting in an EAR of 2.5 mg/day (744 ÷ 0.3), after rounding.

Extrapolation from Adults. An average requirement of 2.3 and 3.0 mg/day for older infants and young children, respectively, is calculated with use of the method described in Chapter 2 that extrapolates from the adult EAR based on body size.

Growth. Limited dietary zinc data are available for children in this age group. In a 6-month, placebo-controlled, randomized zinc supplementation study (Walravens et al., 1989), a major criterion for
inclusion was a weight-for-age less than the tenth percentile in apparently healthy young children with no organic disease and no detectable family dynamic issues that might explain failure to thrive. Compared with placebo-treated control subjects, the zinc-supplemented children had a significantly greater increase in mean weight-for-age Z-scores. Inspection of the individual data points indicated that 87.5 percent of zinc-supplemented subjects had an increase in weight-for-age Z-scores compared with 52 percent of control subjects. These results indicate that 35.5 percent of 10 percent, or 3.6 percent of the overall population in this age group, had growth-limiting zinc deficiency. The calculated mean dietary intake at baseline for the placebo-treated children was $4.1 \pm 0.8$ mg/day (standard deviation [SD]) of zinc. Subtraction of two SDs from this population mean gives an EAR of 2.5 mg/day. It is likely that this calculation errs on the low side because of the variability associated with 24-hour recall dietary information and because some children with weight-for-age greater than the tenth percentile are also likely to have mild growth-limiting zinc deficiency. Hence this value corresponds reasonably well with the EAR determined from the factorial approach.

**Zinc EAR and RDA Summary, Ages 7 Months through 3 Years**

**EAR for Infants**
- 7–12 months: 2.5 mg/day of zinc

**EAR for Children**
- 1–3 years: 2.5 mg/day of zinc

The Recommended Dietary Allowance (RDA) for zinc is set by using a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, the zinc RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 1 mg.

**RDA for Infants**
- 7–12 months: 3 mg/day of zinc

**RDA for Children**
- 1–3 years: 3 mg/day of zinc
Evidence Considered in Estimating the Average Requirement

Factorial Analysis. Factorial analysis is used to determine the EAR for children ages 4 through 8 years. The nonintestinal endogenous losses and requirement for growth are based on data previously discussed (see “Infants and Children Ages 7 Months through 3 Years”). For this age group, the average intestinal losses are 34 µg/kg/day of zinc and the amount of new tissue accreted is 7 g/day (Kuczmarski et al., 2000). Based on the summation of zinc losses and requirements for growth, the required amount of absorbed zinc for this age group is approximately 1.2 mg/day (Table 12-4). With a fractional absorption of 0.3 based on studies in infants and young children (Davidsson et al., 1996; Fairweather-Tait et al., 1995), the EAR is 4.0 mg/day of zinc.

Extrapolation from Adults. The average requirement for zinc is 4 mg/day as determined by the method described in Chapter 2, which extrapolates from the adult EAR.

Growth. Some dietary data are available from children aged 4 through 8 years whose growth percentiles were at the lower end of the normal range and who were subjects in placebo-controlled, randomized trials of dietary zinc supplementation. In each of two studies, one in Canada (Gibson et al., 1989) and the other in the United States (Walravens et al., 1983), zinc supplementation was associated with greater linear growth gain. Mean dietary intakes of the placebo-treated controls in the Canadian and U.S. studies were 6.4 and 4.6 mg/day of zinc, respectively. No growth response was observed with zinc supplementation of healthy children of either gender, unselected for growth, whose average calculated zinc intake was 6.3 mg/day (Hambidge et al., 1979a). The SDs were too

<table>
<thead>
<tr>
<th>Requirement for Absorbed Zinc for Children Aged 4 through 8 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal losses 34 µg/kg/day × 22 kg = 748 µg/day</td>
</tr>
<tr>
<td>Urinary and integumental losses 14 µg/kg/day × 22 kg = 308 µg/day</td>
</tr>
<tr>
<td>Requirement for growth 7 g/day × 20 µg/g = 140 µg/day</td>
</tr>
<tr>
<td>Required absorbed zinc = 1,196 µg/day</td>
</tr>
</tbody>
</table>
large (likely attributable to methodological limitations) to use these data with any confidence in setting an EAR. However, these data are consistent with the EAR derived from a factorial approach.

**Zinc EAR and RDA Summary, Ages 4 through 8 Years**

**EAR for Children**

4–8 years 4 mg/day of zinc

The RDA for zinc is set by using a CV of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, the zinc RDA is 120 percent of the EAR). The calculated RDA was rounded to the nearest 1 mg.

**RDA for Children**

4–8 years 5 mg/day of zinc

**Children Ages 9 through 13 Years**

**Evidence Considered in Estimating the Average Requirement**

**Factorial Analysis.** Estimates used for factorial analysis are similar for boys and girls, and therefore calculations are used to estimate a single average requirement for both genders. With use of the same values as for younger children, an average accretion of 10 g/day of new tissue (Kuczmarski et al., 2000), and a reference weight of 40 kg, the required amount of absorbed zinc is 2.1 mg/day (Table 12-5). Based on a fractional absorption of 0.3 observed in infants and young children (Davidsson et al., 1996; Fairweather-Tait et al., 1995), the EAR is 7 mg/day.

**TABLE 12-5** Requirement for Absorbed Zinc for Children Aged 9 through 13 Years

<table>
<thead>
<tr>
<th>Requirement for Absorbed Zinc for Children Aged 9 through 13 Years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal losses</td>
<td>34 µg/kg/day × 40 kg = 1,360 µg/day</td>
</tr>
<tr>
<td>Urinary and integumental losses</td>
<td>14 µg/kg/day × 40 kg = 560 µg/day</td>
</tr>
<tr>
<td>Requirement for growth</td>
<td>10 g/day × 20 µg/g = 200 µg/day</td>
</tr>
<tr>
<td>Required absorbed zinc</td>
<td>2,120 µg/day</td>
</tr>
</tbody>
</table>
Extrapolation from Adults. As determined by the extrapolation method described in Chapter 2, the average requirement for boys and girls is 6.7 and 5.6 mg/day of zinc, respectively.

Zinc EAR and RDA Summary, Ages 9 through 13 Years

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EAR for Boys</td>
<td>7 mg/day</td>
</tr>
<tr>
<td>9–13 years</td>
<td></td>
</tr>
<tr>
<td>EAR for Girls</td>
<td>7 mg/day</td>
</tr>
<tr>
<td>9–13 years</td>
<td></td>
</tr>
</tbody>
</table>

The RDA for zinc is set by using a CV of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, the zinc RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 1 mg.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RDA for Boys</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>9–13 years</td>
<td></td>
</tr>
<tr>
<td>RDA for Girls</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>9–13 years</td>
<td></td>
</tr>
</tbody>
</table>

Adolescents Ages 14 through 18 Years

Evidence Considered in Estimating the Average Requirement

Factorial Analysis. Endogenous losses are calculated as for younger age groups by using the reference weights (see Chapter 2) with the addition of 100 µg/day of zinc to allow for calculated average semen or menstrual losses (see “Adults Ages 19 Years and Older”, which follows). For this age group, a fractional absorption of 0.4 is used; it corresponds to the average “critical” value for adult men from the data sets used in estimating adult requirements (see below). Gender differences are sufficient at this age for boys and girls requirements to be calculated separately. As determined by the summation of average zinc losses and the zinc requirement for growth (Kuczmański et al., 2000; Widdowson and Dickerson, 1964), the amount of absorbed zinc that is required for boys and girls is approximately 3.4 and 3.0 mg/day, respectively (Table 12-6). On the basis of a fractional zinc absorption of 0.4 that was derived for men
(see below), the EARs for adolescent boys and girls are calculated to be 8.5 and 7.3 mg/day of zinc, respectively.

**Extrapolation from Adults.** Based on the extrapolation method described in Chapter 2, the average requirement for adolescent boys and girls is 9.5 and 6.4 mg/day, respectively.

**Zinc EAR and RDA Summary, Ages 14 through 18 Years**

**EAR for Boys**
14–18 years 8.5 mg/day of zinc

**EAR for Girls**
14–18 years 7.3 mg/day of zinc

The RDA for zinc is set by using a CV of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, the zinc RDA is 120 percent of the EAR). The calculated RDA is rounded up to the nearest 1 mg.

**RDA for Boys**
14–18 years 11 mg/day of zinc

**RDA for Girls**
14–18 years 9 mg/day of zinc
Evidence Considered in Estimating the Average Requirement

As discussed earlier, there are no adequately documented functional or simple laboratory indexes of zinc nutriture that can provide a principal indicator of zinc requirements in adults. However, sufficient data are now available to apply a factorial approach to determine the EAR for adults. With this approach, the principal indicator selected is the minimal quantity of absorbed zinc that is adequate to replace endogenous zinc losses. The EAR is the average zinc intake that provides this quantity of absorbed zinc. An outline of these calculations follows.

Step 1: Calculation of Endogenous Losses of Zinc via Routes Other than the Intestine. Urinary zinc excretion declines only with extreme dietary zinc restriction and is not correlated with zinc ingested by young adult men over a range of 4 to 25 mg zinc/day (Baer and King, 1984; Behall et al., 1987; Coudray et al., 1997; Hallfrisch et al., 1987; Holbrook et al., 1989; Hunt JR et al., 1992; Jackson et al., 1984; Johnson et al., 1982, 1993; Lee et al., 1993; Mahalko et al., 1983; Milne et al., 1983; Snedeker et al., 1982; Spencer et al., 1979; Turnlund et al., 1984, 1986; Wada et al., 1985). In men, therefore, zinc excretion via the kidney should be regarded as a constant in calculating zinc requirements, the average excretion being 0.63 mg/day. Though fewer data are available, the same constancy appears to be true for combined integumental and sweat losses (Johnson et al., 1993) and losses in semen (Hunt CD et al., 1992; Johnson et al., 1993) for which the zinc losses average 0.54 and 0.1 mg/day, respectively. Therefore, losses of endogenous zinc via routes other than the intestine can be regarded as a constant over the range of dietary zinc intake that encompasses zinc requirements. This average constant for men has been calculated to be 1.27 mg/day (0.63 + 0.54 + 0.1) of zinc. An equal quantity of zinc must be absorbed to match this loss.

In 10 studies, the mean urinary loss of zinc from women was 0.44 mg/day (Colin et al., 1983; Greger et al., 1978; Hallfrisch et al., 1987; Hunt JR et al., 1992, 1998; Miller et al., 1998; Swanson and King, 1982; Taper et al., 1980; Turnlund et al., 1991; Wisker et al., 1991). Reported integumental losses for men are multiplied by 0.86 to adjust for the different average surface area of women, and accordingly the average total zinc endogenous losses are 0.46 mg/day for women. Menstrual zinc losses are assumed to average 0.1
mg/day (Hess et al., 1977). Therefore, the calculated total loss of endogenous zinc for women via routes other than the intestine is 1.0 mg/day (0.44 + 0.46 + 0.10).

**Step 2: Relationship Between Excretion of Endogenous Zinc via the Intestine and Quantity of Zinc Absorbed.** In contrast to other endogenous zinc losses, the quantity of endogenous zinc excreted via the intestine is positively correlated with the quantity of zinc absorbed over a wide range. This correlation is shown in Figure 12-1. This figure is based on 10 sets of balance data from seven studies (Hunt JR et al., 1992; Jackson et al., 1984; Lee et al., 1993; Taylor et al., 1991; Turnlund et al., 1984, 1986; Wada et al., 1985) of healthy young men, which also included isotopic tracer measurements of fractional zinc absorption. This correlation, in turn, allows for the quantification of daily zinc absorption and intestinal excretion of endogenous zinc. Importantly, this linear relationship, which indicates that for each milligram of zinc absorbed the intestine excretes approximately 0.6 mg/day of endogenous zinc, has been demonstrated only for zinc absorption ranging from 0.8 to 5.5 mg/day. It is also noted that most of these data were relatively short-term, and these variables were not examined while the participants were consuming habitual diets. However, the studies did extend as long as 6 months, a duration that suggests the observed relationship between absorption and endogenous losses via the intestine is a long-term phenomenon. Therefore, in contrast to other endogenous losses of zinc, losses from the intestine cannot be treated as a constant.

To achieve balance, absorption must match the sum of nonintestinal and intestinal endogenous zinc losses. The minimum amount of zinc that must be absorbed before absorption matches the losses is determined in step 3 below.

Corresponding data for women are both limited and divergent (Hunt JR et al., 1992, 1998; Sian et al., 1996; Turnlund et al., 1991). It has therefore been assumed that there are no significant gender differences for this relationship between absorbed zinc and intestinal excretion of endogenous zinc.

**Step 3: Determination of Minimal Zinc Absorption Required to Replace Total Endogenous Zinc Excretion.** The sum of nonintestinal endogenous zinc losses (1.27 mg/day for men and 1.0 mg/day for women) is added to the linear regression line for excretion of endogenous zinc in the feces versus absorbed zinc (Figure 12-1). These “adjusted” lines depict the quantitative relationship between absorbed zinc and total endogenous zinc losses for men and women.
The intercept between the dashed line (line of equality for absorbed zinc) and the gender-specific lines is then used to determine the minimal quantity of absorbed zinc required to replace endogenous zinc losses.

With this approach, the calculated average total minimal quantity of absorbed zinc required for the men in these studies is 3.84 mg/day (1.27 mg to match endogenous zinc losses from nonintestinal sources and, therefore, 2.57 mg/day to match intestinal endogenous zinc losses). The corresponding value for women is 3.3 mg/day (1.0 mg/day to match endogenous zinc losses from nonintestinal sources and, therefore, 2.3 mg/day to match intestinal endogenous zinc losses).

These calculated average minimal values for absorbed zinc are then used as the principal indicator for establishing an EAR in step 4.

Step 4: Determination of the Average Zinc Intake Required to Achieve Absorption of the Quantity of Zinc Necessary to Match Total Endogenous Losses. The EAR is determined from the asymptotic regression of absorbed zinc on zinc intake (Figure 12-2) that was derived from the same data sets used for Figure 12-1. Thus, if 3.84 mg/day of absorbed zinc is required for men, the amount of ingested zinc, and therefore the EAR, is 9.4 mg/day. When this approach is used for women, the EAR is 6.8 mg/day. This value corresponds to average fractional absorptions of 0.41 and 0.48 for men and women, respectively. A similar fractional absorption of 0.4 was observed for adult men fed experimental diets from which zinc bioavailability is likely to be favorable (August et al., 1989).

Other Criteria for Men. Zinc deficiency has not been documented in healthy adult men in North America with the assessment methods currently in use. Some supportive data have been derived from one of the studies included in the factorial approach outlined above (Wada et al., 1985). This study included six men who received a diet containing 5.5 mg/day of zinc for an 8-week period. At the end of this period, several zinc-responsive biochemical changes had occurred, including declines in serum retinol binding protein, albumin, prealbumin, and thyroxin concentrations (Wada and King, 1986).

Other data from experimental zinc depletion studies are also consistent but at lower levels of intake (zinc intakes of 3 to 5 mg/day). These data include decreased erythrocyte metallothionein (Grider et al., 1990; Thomas et al., 1992) and zinc concentrations, decreased...
5′-nucleotidase activity (Beck et al., 1997a), and various abnormalities of laboratory indexes of immune status (Beck et al., 1997b).

Other Criteria for Women. Twenty-six percent of a group of apparently healthy Canadian omnivore women had prebreakfast serum zinc concentrations below the cut-off of 70 µg/dL (Gibson et al., 2000). The zinc intake of these subjects averaged 7.3 mg/day, which by this criterion is slightly above the EAR. These data are consistent with an EAR of 6.8 mg/day.

Elderly. Reported values on the fractional absorption of zinc in the elderly have been quite variable (Couzy et al., 1993; Hunt et al., 1995; Turnlund et al., 1982, 1986), and no consistent evidence indicates that aging affects absorption adversely. Results of balance studies are again, predictably, variable (Bunker et al., 1982; Hallfrisch et al., 1987; Wood and Zheng, 1997). No evidence suggests that the zinc requirements of the elderly are higher than those of younger adults, but possible differences in zinc metabolism (Wastney et al., 1986) merit further investigation.

Other Criteria for the Elderly. Zinc supplementation of 53 elderly men and women whose diet contained an average of 9.2 mg/day of zinc was not associated with any detectable benefits (Swanson et al., 1988). Specifically, there were no changes in circulating protein or immunoglobulin concentrations. In contrast, dietary zinc was positively correlated with serum albumin in a group of 82 elderly Canadians whose zinc intakes averaged 5 mg/day for women and 6.5 mg/day for men (Payette and Gray-Donald, 1991). Several studies in which improvements in laboratory indexes of zinc status with zinc supplementation were reported did not, unfortunately, include information on habitual zinc intake (Boukaiba et al., 1993; Cakman et al., 1997; Duchateau et al., 1981; Fortes et al., 1998). Fifteen older men and women whose habitual dietary zinc averaged 8.8 mg/day had a significant decline in the activity of 5′-nucleotidase activity after a 2-week period during which zinc intake was restricted to 4 mg/day (Bales et al., 1994). Subsequently, a 6-day supplementation period in which total zinc intake averaged 28 mg/day was associated with a significant increase in 5′-nucleotidase activity, but not beyond baseline levels. In 119 elderly women, serum IGF-1 concentration was weakly correlated with dietary zinc over a range of 5 to 17 mg/day (Devine et al., 1998). A nonplacebo controlled study of zinc supplementation in 13 elderly subjects, part of a larger group of 180 subjects whose average calculated zinc intake was 9 mg/day,
was reported to result in normalization of zinc in granulocytes and lymphocytes and improvement in various immune parameters (Prasad et al., 1993). Ethanol tolerance tests indicated a change in ethanol metabolism when dietary zinc intake of postmenopausal women was restricted to 2.6 mg/day (Milne et al., 1987).

**Zinc EAR and RDA Summary, Ages 19 Years and Older**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>EAR for Men (mg/day)</th>
<th>EAR for Women (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19–30 years</td>
<td>9.4</td>
<td>6.8</td>
</tr>
<tr>
<td>31–50 years</td>
<td>9.4</td>
<td>6.8</td>
</tr>
<tr>
<td>51–70 years</td>
<td>9.4</td>
<td>6.8</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>9.4</td>
<td>6.8</td>
</tr>
</tbody>
</table>

The RDA for zinc is set by using a CV of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for zinc the RDA is 120 percent of the EAR). The calculated RDA was rounded to the nearest 1 mg.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>RDA for Men (mg/day)</th>
<th>RDA for Women (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19–30 years</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>31–50 years</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>51–70 years</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>
Evidence Considered in Estimating the Average Requirement

Factorial Approach. The average daily rates of zinc accumulation by maternal and embryonic/fetal tissues during the four quarters of pregnancy are 0.08, 0.24, 0.53, and 0.73 mg (Swanson and King, 1987). On the assumption of no compensatory change in intestinal excretion of endogenous zinc, it is concluded that increasing daily zinc absorption by these amounts is desirable.

The average fractional absorption of zinc was 27 percent for non-pregnant women from eight studies in which dietary zinc averaged 10 mg/day (Fung et al., 1997; Hunt JR et al., 1992, 1998; Miller et al., 1998; Sian et al., 1996; Turnlund et al., 1991). Increases in fractional absorption during pregnancy have been reported to be non-significant (Fung et al., 1997), but this outcome may reflect inadequate power of the study design. Therefore, increases in dietary zinc requirements during pregnancy are calculated to be the following:

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Fractional Absorption</th>
<th>Additional Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quarter</td>
<td>0.08 ÷ 0.27 = 0.3 mg/day of zinc</td>
<td></td>
</tr>
<tr>
<td>Second quarter</td>
<td>0.24 ÷ 0.27 = 0.9 mg/day of zinc</td>
<td></td>
</tr>
<tr>
<td>Third quarter</td>
<td>0.53 ÷ 0.27 = 2.0 mg/day of zinc</td>
<td></td>
</tr>
<tr>
<td>Fourth quarter</td>
<td>0.73 ÷ 0.27 = 2.7 mg/day of zinc</td>
<td></td>
</tr>
</tbody>
</table>

To set a single EAR for pregnant women, the EAR is based on the additional requirement during the fourth quarter (2.7 mg/day) of pregnancy plus the EAR for nonpregnant adolescent girls and women. It should be noted, however, that the zinc requirement during the first quarter of pregnancy is only minimally greater than the preconceptional requirement.

Other Criteria. Dietary supplementation reduced the decline in plasma/serum zinc concentration across pregnancy in a large cohort of Peruvian women whose dietary zinc intake was estimated to be 7 mg/day (Caulfield et al., 1999a), but not in North American women whose dietary zinc intake averaged 11 mg/day (Hambidge et al., 1983). Correlations observed between maternal biochemical indexes of zinc status and complications of pregnancy, delivery, and fetal development have been inconsistent.

Gravid women with a zinc intake of 6 mg/day or less were found to have a high incidence of premature deliveries (Scholl et al., 1993). Increased gestational age at delivery and increased birth size
have been reported to result from zinc supplementation of pregnant African-American women whose baseline dietary zinc intake was calculated to be 13 mg/day (Goldenberg et al., 1995). This calculated dietary zinc intake is notably high in comparison with other data for African-American women (Mares-Perlman et al., 1995). Without additional supporting documentation, it is difficult to reconcile the implications of the results of this study (with respect to dietary zinc requirements during pregnancy) with the EARs derived from a factorial approach. Nor is it easy to reconcile these findings with the results of other intervention studies. For example, no effect of zinc supplements on birth size was observed in a recent large-scale study of Peruvian women whose dietary zinc intake was estimated to be 7 mg/day (Caulfield et al., 1999b). There was, however, evidence of improved fetal neurobehavioral development (Merialdi et al., 1998).

A report that zinc intakes of less than 7.5 mg/day during the third trimester are associated with lower zinc concentrations in human milk is consistent with the EAR (Ortega et al., 1997).

Zinc EAR and RDA Summary, Pregnancy

**EAR for Pregnancy**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Zinc Intake (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>10.0</td>
</tr>
<tr>
<td>19–30 years</td>
<td>9.5</td>
</tr>
<tr>
<td>31–50 years</td>
<td>9.5</td>
</tr>
</tbody>
</table>

The RDA for zinc is set by using a CV of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for zinc the RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 1 mg.

**RDA for Pregnancy**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Zinc Intake (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>12</td>
</tr>
<tr>
<td>19–30 years</td>
<td>11</td>
</tr>
<tr>
<td>31–50 years</td>
<td>11</td>
</tr>
</tbody>
</table>

**Lactation**

**Evidence Considered in Estimating the Average Requirement**

*Losses in Human Milk.* Average concentrations of zinc in human milk decline physiologically from approximately 4 mg/L at 2 weeks
postpartum to 3 mg/L at 4 weeks, 2 mg/L at 8 weeks, 1.5 mg/L at 12 weeks, and 1.2 mg/L at 24 weeks (Krebs et al., 1995; Moser-Veillon and Reynolds, 1990). With use of a standard volume of 0.78 L/day of human milk secreted per day (Chapter 2), calculated zinc losses via the mammary gland are 2.15 mg/day at 4 weeks, 1.56 mg/day at 8 weeks, 1.17 mg/day at 12 weeks, and 0.94 mg/day at 24 weeks.

Postpartum involution of the uterus and decreased maternal blood volume should release approximately 30 mg of zinc that has been accumulated during pregnancy (King and Turnlund, 1989); that is, an average of approximately 1 mg/day for the first month. It is reasonable to assume that this endogenous zinc is available for reutilization. Thus, 1 mg/day is subtracted from the amount of zinc lost during the first 4 weeks of lactation. The loss of zinc for weeks 8, 12 and 24 are averaged:

- Week 4: \( (2.15 - 1.0) = 1.15 \text{ mg/day of zinc} \)
- Week 8: \( (2.15 + 1.56) \div 2 = 1.85 \text{ mg/day of zinc} \)
- Week 12: \( (1.56 + 1.17) \div 2 = 1.36 \text{ mg/day of zinc} \)
- Weeks 12–24: \( (1.17 + 0.94) \div 2 = 1.05 \text{ mg/day of zinc} \)

The average calculated increased requirement for absorbed zinc during lactation is 1.35 mg/day.

Reported values for fractional absorption of zinc for adult women outside the reproductive cycle averages 27 percent (Fung et al., 1997; Hunt JR et al., 1992, 1998; Sian et al., 1996; Turnlund et al., 1991). If this value were applied to the calculation of increased dietary zinc required during lactation (1.35 ÷ 0.27), the average dietary requirement would increase by 5 mg/day. However, the fractional absorption of zinc increases during lactation by 0.107 (Fung et al., 1997). Therefore, the fractional absorption would be increased to 0.716 (0.27 ÷ 0.377) to give an additional requirement of 3.6 mg/day (5 × 0.716). This value is added to the EAR for adolescent girls and women to set the EAR during lactation.

Other Criteria. Typically, human milk zinc concentrations are not increased by the administration of a daily zinc supplement across lactation (Kirksey et al., 1979; Krebs et al., 1995; Moser-Veillon and Reynolds, 1990). In one study, however, a modest but statistically significant reduced rate of decline in zinc concentrations in milk across lactation was observed with a zinc supplement (Krebs et al., 1985). The dietary zinc in the placebo group averaged 10.7 mg/day. In a subsequent study, in which the average dietary zinc was
higher at 13.0 mg/day, there was no evidence of an effect of zinc supplementation on zinc concentration in milk.

**Zinc EAR and RDA Summary, Lactation**

**EAR for Lactation**

- 14–18 years: 10.9 mg/day of zinc
- 19–30 years: 10.4 mg/day of zinc
- 31–50 years: 10.4 mg/day of zinc

The RDA for zinc is set by using a CV of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for zinc the RDA is 120 percent of the EAR). The calculated RDA is rounded to the nearest 1 mg.

**RDA for Lactation**

- 14–18 years: 13 mg/day of zinc
- 19–30 years: 12 mg/day of zinc
- 31–50 years: 12 mg/day of zinc

**Special Considerations**

**Vegetarianism**

Cereals are the primary source of dietary zinc for vegetarians (Gibson, 1994). The bioavailability of zinc in vegetarian diets is reduced if the phytate content in the diet is high (Gibson, 1994), and this may result in low zinc status (Freeland-Graves et al., 1980b). Absorption of zinc from vegetarian diets is lower than from non-vegetarian diets (Hunt et al., 1998; Kies, 1988); however, relatively minor changes to the diet can improve zinc absorption (Gibson et al., 1997; Harland et al., 1988). Vegetarian diets rich in calcium may negatively affect zinc bioavailability (Ellis et al., 1987).

Zinc intake from vegetarian diets has been found to be both similar to intake from nonvegetarian diets (Alexander et al., 1994; Berglund et al., 1994; Donovan and Gibson, 1996; Johansson and Widerstrom, 1994; Kelsay et al., 1988; Levin et al., 1986; Srikumar et al., 1992) and lower than intake from nonvegetarian diets (Faber et al., 1986; Freeland-Graves et al., 1980a; Harland and Peterson, 1978; Hunt et al., 1998; Janelle and Barr, 1995). In most older adult and elderly populations, vegetarians have lower zinc intakes than non-
Among vegetarians, zinc concentrations in serum, plasma, hair, urine, and saliva are either the same as or lower than those of nonvegetarians (Anderson et al., 1981; Freeland-Graves et al., 1980a, 1980b; Hunt et al., 1998; Kadrabova et al., 1995; King et al., 1981; Krajcovicova-Kudlackova et al., 1995; Levin et al., 1986; Srikumar et al., 1992). The variations in these status indicators are most likely due to the amount of phytate, fiber, calcium, or other inhibitors of zinc absorption in the vegetarian diets. Individuals consuming vegetarian diets were found to be in positive zinc balance (Ganapathy et al., 1981; Hunt et al., 1998).

The requirement for dietary zinc may be as much as 50 percent greater for vegetarians and particularly for strict vegetarians whose major food staples are grains and legumes and whose dietary phytate:zinc molar ratio exceeds 15:1. At this time there are not sufficient data to set algorithms for establishing dietary requirements for zinc on the basis of the presence and concentration of other nutrients and food components.

**Alcohol**

Long-term alcohol consumption is associated with impaired zinc absorption and increased urinary zinc excretion. Low zinc status is observed in approximately 30 to 50 percent of alcoholics. Thus, with long-term alcohol consumption, the daily requirement for zinc will be greater than that estimated via the factorial approach.

**INTAKE OF ZINC**

**Food Sources**

The dietary sources of zinc vary widely. Zinc is abundant in red meats, certain seafood, and whole grains. Because zinc is mainly located in the germ and bran portions of grains, as much as 80 percent of the total zinc is lost during milling. Many breakfast cereals are fortified with zinc. Studies measuring zinc content in human milk are summarized in Table 12-1.

**Dietary Intake**

Data from nationally representative U.S. surveys are available to estimate zinc intakes (Appendix Tables C-25, C-26, D-4, E-9). Median intakes of zinc for adult men aged 19 to 50 years, based on the
Third National Health and Nutrition Examination Survey and the Continuing Survey of Food Intakes by Individuals, were approximately 14 mg/day (Appendix Tables C-25 and D-4). The median intakes for women in the same age range were approximately 9 mg/day. These values are similar to those found for zinc intakes of Canadian adults (Appendix Table F-3).

Intake from Supplements

In 1986, approximately 16 percent of Americans took supplements that contained zinc (Moss et al., 1989; see Table 2-2). The median total (food plus supplements) zinc intakes by adults taking supplements were similar to those of adults who did not take zinc supplements (Appendix Table C-26). Intake of zinc supplements, however, greatly increased the intakes in the upper quartile compared to those who did not take zinc supplements.

TOLerable Upper Intake Levels

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. In addition, the UL is not meant to apply to individuals who are receiving zinc under medical supervision.

Hazard Identification

Although no evidence of adverse effects from intake of naturally occurring zinc in food was found, the UL derived here applies to total zinc intake from food, water, and supplements (including fortified food). Adverse effects associated with chronic intake of supplemental zinc include suppression of immune response, decrease in high-density lipoprotein (HDL) cholesterol, and reduced copper status.
Adverse Effects

Acute Effects. Acute adverse effects of excess zinc have been reported. These include epigastric pain, nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches (Prasad, 1976; Samman and Roberts, 1987). Fosmire (1990) estimated that an emetic dose of zinc sulfate was approximately 1 to 2 g of the salt (225 to 450 mg of zinc). Gastrointestinal distress has been reported at doses of 50 to 150 mg/day of supplemental zinc (Freeland-Graves et al., 1982).

Immunological Response. Intake of 300 mg/day of supplemental zinc as the sulfate for 6 weeks has been shown to cause some functional impairment in immunological response as well as significantly decreased concentrations of HDL cholesterol (Chandra, 1984).

Lipoprotein and Cholesterol. Two studies (Black et al., 1988; Hooper et al., 1980) have found that zinc at doses between 50 and 160 mg/day decreased serum lipoprotein and cholesterol concentrations in men. Samman and Roberts (1988), however, reported no depression of HDL concentrations in men at 150 mg/day of zinc and found some indication of a depression of low-density lipoproteins (LDL) in women. The different response to excess zinc in women was supported by an earlier study by Freeland-Graves and coworkers (1982). The reduction in HDL cholesterol concentration was shown to be transient and not dose related.

Reduced Copper Status. Reduced copper status has been associated with increased zinc intake (Boukaiba et al., 1993; Burke et al., 1981; Festa et al., 1985; Fischer et al., 1984; Prasad et al., 1978; Samman and Roberts, 1988; Yadrick et al., 1989) (Table 12-7). In all studies in which the interaction of excess zinc and copper was measured, there was a consistent decrease in erythrocyte copper-zinc superoxide dismutase (ESOD) activity, an erythrocyte enzyme indicative of copper status. Yadrick and coworkers (1989) reported this effect after total zinc intakes of about 60 mg/day (50-mg supplement plus 10 mg of dietary zinc) for up to 10 weeks. Although the clinical significance of the depressed ESOD activity is unknown, this marker enzyme is known to be a sensitive indicator of the effect of high zinc levels on copper homeostasis.

Zinc-Iron Interactions. Zinc and iron are known to interact, and Whittaker (1998) has reviewed the available studies (also see "Fac-
tors Affecting the Zinc Requirement”). The primary effect appears to be a decreased absorption of zinc at an iron:zinc ratio of 3:1 when the iron was administered in water. However, when iron was administered during a meal, no such effect was found. Similarly, when iron was present as heme iron, no effect was noted. One study found a 56 percent decline in iron absorption when the zinc:iron ratio was 5:1 and was administered in water (Rossander-Hultén et al., 1991). However, when this ratio of zinc and iron was administered in a hamburger meal, no effect on iron absorption was noted.

Other Endpoints. No evidence was found of reproductive effects in humans from zinc intake. There is one case report of three premature deliveries and one stillborn infant after excess zinc intake during pregnancy (Kumar, 1976). Because details on other contributing factors were not provided, interpretation of these results is limited. There is insufficient evidence of carcinogenicity from human or animal studies.

Summary

Although there are no data indicating adverse interactions between zinc and other nutrients when zinc is found in food, adverse nutrient interactions are present after feeding zinc in the form of dietary supplements. The adverse effect of excess zinc on copper metabolism (i.e., reduced copper status) was chosen as the critical effect on which to base a UL for total daily intake of zinc from food, water, and supplements in humans. This selection is based on (1) the consistency of findings from studies measuring the interaction of zinc and copper (Fischer et al., 1984; Samman and Roberts, 1988; Yadrick et al., 1989), (2) the sensitivity of ESOD activity as a marker for this effect, and (3) the quality and completeness of the database for this endpoint. The data on the effects of zinc on HDL cholesterol concentration were not consistent from study to study and therefore were not used to derive a UL.

Dose-Response Assessment

Adults

Data Selection. Data on reduced copper status in humans were used to derive a UL for zinc (Table 12-7). Studies measuring ESOD activity (which is a sensitive indicator of copper status) or other indicators
TABLE 12-7 Effect of Increasing Doses of Zinc (Zn) Intake on Copper (Cu) Status

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Zinc Intake (mg/d)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasad et al., 1978</td>
<td>1 black man, 26 y w/sickle cell anemia</td>
<td>150–200</td>
<td>2 y</td>
</tr>
<tr>
<td>Greger et al., 1978</td>
<td>14 girls, 12–14 y</td>
<td>7.4 (food)</td>
<td>30 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.4 (food)</td>
<td>30 d</td>
</tr>
<tr>
<td>Burke et al., 1981</td>
<td>5 men, 6 women, 56–83 y</td>
<td>7.8 (fortified food)</td>
<td>30 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.26 (fortified food)</td>
<td>30 d</td>
</tr>
<tr>
<td>Fischer et al., 1984</td>
<td>26 healthy adult men</td>
<td>Placebo</td>
<td>6 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 (as gluconate)</td>
<td>6 wk</td>
</tr>
<tr>
<td>Festa et al., 1985</td>
<td>9 healthy men, 21–27 y</td>
<td>1.8 (food)</td>
<td>1 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.0 (food)</td>
<td>1 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.0 (food)</td>
<td>1 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.0 (food)</td>
<td>1 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.5 (food)</td>
<td>2 wk</td>
</tr>
<tr>
<td>Samman and Roberts, 1988</td>
<td>Healthy men and women</td>
<td>150 (as sulfate)</td>
<td>12 wk</td>
</tr>
<tr>
<td>Yadrick et al., 1989</td>
<td>18 healthy women, 25–40 y</td>
<td>50 (as gluconate)</td>
<td>10 wk</td>
</tr>
<tr>
<td>Boukaiba et al., 1993c</td>
<td>44 older adults, 73–106y</td>
<td>Placebo</td>
<td>8 wk</td>
</tr>
</tbody>
</table>

\( ^{a} \) The authors note it was not possible to separate the effects of sickle cell disease and copper depletion.

\( ^{b} \) Copper status was assessed by the activities of the copper-metalloenzymes, plasma ferroxidase (ceruloplasmin), and erythrocyte Cu,Zn-superoxide dismutase. No significant differences in the plasma copper levels or the ferroxidase activities between the supplemented and control groups could be detected at 2, 4, or 6 weeks. ESOD = erythrocyte copper-zinc superoxide dismutase.

Identification of a No-Observed-Adverse-Effect Level (NOAEL) and Lowest-Observed-Adverse-Effect Level (LOAEL). A LOAEL of 60 mg/day is based on the study of Yadrick and coworkers (1989) who evaluated copper status after supplemental intake of 50 mg/day as zinc glu-
<table>
<thead>
<tr>
<th>Duration</th>
<th>Cu Intake (mg/d)</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 y</td>
<td>Not provided</td>
<td>Cu deficiency anemia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased serum Cu and ceruloplasmin</td>
</tr>
<tr>
<td>30 d</td>
<td>2.8 (food)</td>
<td>No significant change</td>
</tr>
<tr>
<td>30 d</td>
<td>2.8 (food)</td>
<td>No significant change</td>
</tr>
<tr>
<td>30 d</td>
<td>2.33 (fortified food)</td>
<td>Significant decrease in Cu retention</td>
</tr>
<tr>
<td>6 wk</td>
<td>Not provided</td>
<td>No effect</td>
</tr>
<tr>
<td>6 wk</td>
<td></td>
<td>Significant decrease in ESOD activity&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 wk</td>
<td>2.6 (food)</td>
<td>No effect</td>
</tr>
<tr>
<td>1 wk</td>
<td>2.6 (food)</td>
<td>No effect</td>
</tr>
<tr>
<td>1 wk</td>
<td>2.6 (food)</td>
<td>No effect</td>
</tr>
<tr>
<td>1 wk</td>
<td>2.6 (food)</td>
<td>No effect</td>
</tr>
<tr>
<td>2 wk</td>
<td>2.6 (food)</td>
<td>Increase in Cu excretion/ decrease in retention</td>
</tr>
<tr>
<td>12 wk</td>
<td>Not provided</td>
<td>Decrease in ESOD (women only)</td>
</tr>
<tr>
<td>10 wk</td>
<td>Not provided</td>
<td>Significant decrease in ESOD activity</td>
</tr>
<tr>
<td>8 wk</td>
<td>Not provided</td>
<td>No effect</td>
</tr>
<tr>
<td>8 wk</td>
<td></td>
<td>Significant decrease in serum Cu</td>
</tr>
</tbody>
</table>

<sup>a</sup> Boukaiha et al. (1993) is a crossover study designed to determine the effects of low-dose zinc supplementation on food intake, nutritional status, immune and lipid indexes. The 16-week study period was divided into two experimental treatment periods, each lasting 8 weeks. Serum Zn concentrations were depressed.

conate in 18 healthy women (aged 25 to 40 years) for 10 weeks. ESOD activity was significantly lower than pretreatment values. Although no dietary zinc or copper intakes were reported, a level of dietary zinc can be estimated at approximately 10 mg/day for women (aged 19 to 50 years) from the 1988–1994 Third National Health and Nutrition Examination Survey (Appendix Table C-26). A LOAEL of 60 mg/day was calculated by adding the supplemental
intake of 50 mg/day with the rounded estimate of dietary intake, 10 mg/day. Support for a LOAEL of 60 mg/day is provided by other studies showing altered copper balance after zinc supplementation (Fischer et al., 1984) (Table 12-7).

Uncertainty Assessment. An uncertainty factor (UF) of 1.5 was selected to account for interindividual variability in sensitivity and for extrapolation from a LOAEL to a NOAEL. Because reduced copper status is rare in humans, a higher UF was not justified.

Derivation of a UL. A LOAEL of 60 mg/day was divided by a UF of 1.5 to derive a UL of 40 mg/day for total intake of zinc from food, water, and supplements.

\[
UL = \frac{LOAEL}{UF} = \frac{60 \text{ mg/day}}{1.5} = 40 \text{ mg/day}
\]

Zinc UL Summary, Ages 19 Years and Older

UL for Adults
\[\geq 19 \text{ years} \quad 40 \text{ mg/day of zinc}\]

Infants, Children, and Adolescents

Data Selection. There is only one case report of zinc-induced copper deficiency anemia in a young child (Botash et al., 1992): a 13-month-old girl was given 16 mg/day of zinc for 6 months followed by 24 mg/day for 1 month. There are no reports on the adverse effects of zinc on copper status in children or adolescents. The UL values for infants are based on a study by Walravens and Hambidge (1976).

Identification of a NOAEL. Walravens and Hambidge (1976) fed 68 healthy, full-term infants either formula containing 1.8 mg/L of zinc (control) or the same formula supplemented with an additional 4 mg/L (total of 5.8 mg/L) of zinc for 6 months. No effects of zinc on serum copper or cholesterol concentrations or other adverse effects were found. Thus, 5.8 mg/L is the NOAEL selected. Multiplying the NOAEL for infants 0 through 6 months of age by the estimated average intake of human milk of 0.78 L/day (Allen et al., 1991; Butte et al., 1984; Heinig et al., 1993) results in a NOAEL of 4.5 mg/day.

Uncertainty Assessment. The length of the study by Walravens and
Hambidge (1976) and the high number of infants justifies a UF of 1.0, given that there is no evidence that intakes from formula of 5.8 mg/L of zinc result in infant toxicity.

Derivation of a UL. The NOAEL of 4.5 mg/day was divided by a UF of 1.0 to obtain a UL of 4 mg/day (rounded down) for infants ages 0 through 6 months. No adverse effects of zinc in children and adolescents could be found. Due to a dearth of information, the UL for young infants was adjusted for older infants, children, and adolescents on the basis of relative body weight as described in Chapter 2 and using reference weights from Chapter 1 (Table 1-1). Values have been rounded down.

Zinc UL Summary, Ages 0 through 18 Years

UL for Infants
- 0–6 months: 4 mg/day of zinc
- 7–12 months: 5 mg/day of zinc

UL for Children
- 1–3 years: 7 mg/day of zinc
- 4–8 years: 12 mg/day of zinc
- 9–13 years: 23 mg/day of zinc

UL for Adolescents
- 14–18 years: 34 mg/day of zinc

Pregnancy and Lactation

Because the UL is based on reduced copper status and because there are inadequate data to justify a different UL for pregnant and lactating women, the UL for pregnant and lactating women is the same as that for nonpregnant and nonlactating women.

Zinc UL Summary, Pregnancy and Lactation

UL for Pregnancy
- 14–18 years: 34 mg/day of zinc
- 19–50 years: 40 mg/day of zinc

UL for Lactation
- 14–18 years: 34 mg/day of zinc
- 19–50 years: 40 mg/day of zinc
Special Considerations

Individuals with Menke’s disease may be distinctly susceptible to the adverse effects of excess zinc intake. Since Menke’s disease is a defect in the ATPase involved in copper efflux from enterocytes, supplying extra zinc will likely further limit copper absorption (Yuzbasiyan-Gurkan et al., 1992). Brewer and coworkers (1993) demonstrated the effectiveness of zinc therapy in reducing copper accumulation in individuals with Wilson’s disease. The UL is not meant to apply to individuals who are being treated with zinc under close medical supervision.

Intake Assessment

Utilizing the Third National Health and Nutrition Examination Survey data, the highest reported intake of dietary zinc at the ninety-fifth percentile for all adults was 24 mg/day in men aged 19 to 30 years (Appendix Table C-25), which is lower than the UL of 40 mg/day. In 1986, approximately 17 percent of women and 15 percent of men consumed supplements that contained zinc (Moss et al., 1989; see Table 2-2). The ninety-fifth percentile intake of zinc coming from food and supplements for adult men and nonpregnant women was approximately 25 to 32 mg/day (Appendix Table C-26). For pregnant and lactating women, the zinc intake from food and supplements was approximately 40 and 47 mg/day, respectively, at the ninety-fifth percentile.

Risk Characterization

The risk of adverse effects resulting from excess zinc intake from food and supplements appears to be low at the highest intakes noted above. High intakes of zinc are due to the use of supplements, especially during lactation and pregnancy. Doses approaching or equal to the UL are currently being tested in the treatment of diarrhea, pneumonia, and acute respiratory infections, especially in developing countries. The UL is not meant to apply to individuals who are receiving zinc for treatment purposes.

RESEARCH RECOMMENDATIONS FOR ZINC

• Biomarkers of zinc status based on functional outcomes; these may be gene products derived from zinc-influenced systems and...
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may include transporter proteins that provide homeostatic regulation of zinc intake and cellular processing.

• Information on the relationship of oxidative stress to zinc status; zinc is used therapeutically for treatment of some medical problems, but how this relates to daily dietary zinc intake is not clear.

• Effectiveness and potential toxicity of zinc as a dietary supplement; on which systems should zinc’s potential effectiveness be based, and which systems become dysfunctional with excessive zinc intake.

• The role of zinc and the immune system, particularly those related to T-cell function at marginal status.

• Quantitative data on human zinc homeostasis under a wide range of dietary conditions and at all ages using recent advances in zinc stable isotope methodology; quantification of what happens to zinc homeostasis as zinc intakes and absorption are increased and decreased beyond the range typically seen until recently; these metabolic studies need to be long-term.

REFERENCES


Zinc supplementation reconstitutes the production of interferon-α by leukocytes from elderly persons. *J Interferon Cytokine Res* 17:469–472.


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