

## 12. Zinc

### 12.1 Role of zinc in human metabolic processes

Zinc is present in all body tissues and fluids. The total body zinc content has been estimated to be 30 mmol (2 g). Skeletal muscle accounts for approximately 60% of the total body content and bone mass, with a zinc concentration of 1.5–3  $\mu\text{mol/g}$  (100–200  $\mu\text{g/g}$ ), for approximately 30%. The concentration of zinc in lean body mass is approximately 0.46  $\mu\text{mol/g}$  (30  $\mu\text{g/g}$ ). Plasma zinc has a rapid turnover rate and it represents only about 0.1% of total body zinc content. This level appears to be under close homeostatic control. High concentrations of zinc are found in the choroid of the eye (4.2  $\mu\text{mol/g}$  or 274  $\mu\text{g/g}$ ) and in prostatic fluids (4.6–7.7 mmol/l or 300–500 mg/l) (1).

Zinc is an essential component of a large number (>300) of enzymes participating in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids as well as in the metabolism of other micronutrients. Zinc stabilizes the molecular structure of cellular components and membranes and in this way contributes to the maintenance of cell and organ integrity. Furthermore, zinc has an essential role in polynucleotide transcription and thus in the process of genetic expression. Its involvement in such fundamental activities probably accounts for the essentiality of zinc for all life forms.

Zinc plays a central role in the immune system, affecting a number of aspects of cellular and humoral immunity (2). Shankar and Prasad have reviewed the role of zinc in immunity extensively (2).

The clinical features of severe zinc deficiency in humans are growth retardation, delayed sexual and bone maturation, skin lesions, diarrhoea, alopecia, impaired appetite, increased susceptibility to infections mediated via defects in the immune system, and the appearance of behavioural changes (1). The effects of marginal or mild zinc deficiency are less clear. A reduced growth rate and impairments of immune defence are so far the only clearly demonstrated signs of mild zinc deficiency in humans. Other effects, such as impaired taste and wound healing, which have been claimed to result from a low zinc intake, are less consistently observed.

## 12.2 Zinc metabolism and homeostasis

Zinc absorption is concentration dependent and occurs throughout the small intestine. Under normal physiological conditions, transport processes of uptake are not saturated. Zinc administered in aqueous solutions to fasting subjects is absorbed efficiently (60–70%), whereas absorption from solid diets is less efficient and varies depending on zinc content and diet composition (3).

The major losses of zinc from the body are through the intestine and urine, by desquamation of epithelial cells, and in sweat. Endogenous intestinal losses can vary from 7  $\mu\text{mol/day}$  (0.5 mg/day) to more than 45  $\mu\text{mol/day}$  (3 mg/day), depending on zinc intake—the higher the intake, the greater the losses (4). Urinary and integumental losses are of the order of 7–10  $\mu\text{mol/day}$  (0.5–0.7 mg/day) each and depend less on normal variations in zinc intake (4). Starvation and muscle catabolism increase zinc losses in urine. Strenuous exercise and elevated ambient temperatures can lead to high losses through perspiration.

The body has no zinc stores in the conventional sense. In conditions of bone resorption and tissue catabolism, zinc is released and may be reutilized to some extent. Human experimental studies with low zinc diets containing 2.6–3.6 mg/day (40–55  $\mu\text{mol/day}$ ) have shown that circulating zinc levels and activities of zinc-containing enzymes can be maintained within a normal range over several months (5, 6), a finding which highlights the efficiency of the zinc homeostasis mechanism. Controlled depletion–repletion studies in humans have shown that changes in the endogenous excretion of intestinal, urinary, and integumental zinc as well as changes in absorptive efficiency are how body zinc content is maintained (7–10). However, the underlying mechanisms are poorly understood.

Sensitive indexes for assessing zinc status are unknown at present. Static indexes, such as zinc concentration in plasma, blood cells, and hair, and urinary zinc excretion are decreased in severe zinc deficiency. A number of conditions that are unrelated to zinc status can affect all these indexes, especially zinc plasma levels. Food intake, stress situations such as fever, infection, and pregnancy lower plasma zinc concentrations whereas, for example, long-term fasting increases it (11). However, on a population basis, reduced plasma zinc concentrations seem to be a marker for zinc-responsive growth reductions (12, 13). Experimental zinc depletion studies suggest that changes in immune response occur before reductions in plasma zinc concentrations are apparent (14). To date, it has not been possible to identify zinc-dependent enzymes which could serve as early markers for zinc status.

A number of functional indexes of zinc status have been suggested, for example, wound healing, taste acuity, and visual adaptation to the dark (11).

Changes in these functions are, however, not specific to zinc and these indexes have not been proven useful for identifying marginal zinc deficiency in humans thus far.

The introduction of stable isotope techniques in zinc research (15) has created possibilities for evaluating the relationship between diet and zinc status and is likely to lead to a better understanding of the mechanisms underlying the homeostatic regulation of zinc. Estimations of the turnover rates of administered isotopes in plasma or urine have revealed the existence of a relatively small but rapidly exchangeable body pool of zinc of about 1.5–3.0 mmol (100–200 mg) (16–19). The size of the pool seems to be correlated to habitual dietary intake and it is reduced in controlled depletion studies (18). The zinc pool was also found to be correlated to endogenous intestinal excretion of zinc (19) and to total daily absorption of zinc. These data suggest that the size of the pool depends on recently absorbed zinc and that a larger exchangeable pool results in larger endogenous excretion. Changes in endogenous intestinal excretion of zinc seem to be more important than changes in absorptive efficiency for maintenance of zinc homeostasis (19).

### **12.3 Dietary sources and bioavailability of zinc**

Lean red meat, whole-grain cereals, pulses, and legumes provide the highest concentrations of zinc: concentrations in such foods are generally in the range of 25–50 mg/kg (380–760  $\mu$ mol/kg) raw weight. Processed cereals with low extraction rates, polished rice, and chicken, pork or meat with high fat content have a moderate zinc content, typically between 10 and 25 mg/kg (150–380  $\mu$ mol/kg). Fish, roots and tubers, green leafy vegetables, and fruits are only modest sources of zinc, having concentrations <10 mg/kg (<150  $\mu$ mol/kg) (20). Saturated fats and oils, sugar, and alcohol have very low zinc contents.

The utilization of zinc depends on the overall composition of the diet. Experimental studies have identified a number of dietary factors as potential promoters or antagonists of zinc absorption (21). Soluble organic substances of low relative molecular mass, such as amino and hydroxy acids, facilitate zinc absorption. In contrast, organic compounds forming stable and poorly soluble complexes with zinc can impair absorption. In addition, competitive interactions between zinc and other ions with similar physicochemical properties can affect the uptake and intestinal absorption of zinc. The risk of competitive interactions with zinc seems to be mainly related to the consumption of high doses of these other ions, in the form of supplements or in aqueous solutions. However, at levels present in food and at realistic fortification levels, zinc absorption appears not to be affected, for example, by iron or copper (21).

Isotope studies with human subjects have identified two factors that, together with the total zinc content of the diet, are major determinants of absorption and utilization of dietary zinc. The first is the content of inositol hexaphosphate (phytate) in the diet and the second is the level and source of dietary protein. Phytates are present in whole-grain cereals and legumes and in smaller amounts in other vegetables. They have a strong potential for binding divalent cations and their depressive effect on zinc absorption has been demonstrated in humans (21). The molar ratio between phytates and zinc in meals or diets is a useful indicator of the effect of phytates in depressing zinc absorption. At molar ratios above the range of 6–10, zinc absorption starts to decline; at ratios above 15, absorption is typically less than 15% (20). The effect of phytate is, however, modified by the source and amount of dietary proteins consumed. Animal proteins improve zinc absorption from a phytate-containing diet (22). Zinc absorption from some legume-based diets (e.g. white beans and lupin protein) is comparable with that from animal-protein-based diets despite a higher phytate content in the former (22, 23). High dietary calcium potentiated the antagonistic effects of phytates on zinc absorption in experimental studies. The results from human studies are less consistent and any effects seem to depend on the source of calcium and the composition of the diet (21, 23).

Several recently published absorption studies illustrate the effect of zinc content and diet composition on fractional zinc absorption (19, 24–26). The results from the total diet studies, where all main meals of a day's intake were extrinsically labelled, show a remarkable consistency in fractional absorption despite relatively large variations in meal composition and zinc content (see Table 12.1). Thus, approximately twice as much zinc is absorbed from a non-vegetarian or high-meat diet (25, 26) than from a diet based on rice and wheat flour (19). Data are lacking on zinc absorption from typical diets of developing countries, which usually have high phytate contents.

The availability of zinc from the diet can be improved by reducing the phytate content and including sources of animal protein. Lower extraction rates of cereal grains will result in lower phytate content but at the same time the zinc content is reduced, so that the net effect on zinc supply is limited. The phytate content can be reduced by activating the phytase present in most phytate-containing foods or through the addition of microbial or fungal phytases. Phytases hydrolyse the phytate to lower inositol phosphates, resulting in improved zinc absorption (27, 28). The activity of phytases in tropical cereals such as maize and sorghum is lower than that in wheat and rye (29). Germination of cereals and legumes increases phytase activity and addition of some germinated flour to ungerminated maize or sorghum followed by

TABLE 12.1

**Examples of fractional zinc absorption from total diets measured by isotope techniques**

Subject characteristics (reference)	Diet characteristics	Isotope technique	Zinc content		Phytate-zinc molar ratio	Zinc absorption, % ( $\pm$ SD)
			( $\mu$ mol)	(mg)		
Young adults (n = 8) (24)	High-fibre	Radioisotope	163	10.7	7	27 $\pm$ 6
Young women (n = 10) (19)	Self-selected rice- and wheat-based	Stable isotope	80	8.1	11	31 $\pm$ 9
Women (20–42 years) (n = 21) (25)	Lacto-ovo vegetarian	Radioisotope	139	9.1	14	26 <sup>a</sup>
Women (20–42 years) (n = 21) (25)	Non-vegetarian	Radioisotope	169	11.1	5	33 <sup>a</sup>
Postmenopausal women (n = 14) (26)	Low meat	Radioisotope	102	6.7	—	30 <sup>b</sup>
Postmenopausal women (n = 14) (26)	High meat	Radioisotope	198	13.0	—	28 <sup>b</sup>

SD, standard deviation.

<sup>a</sup> Pooled SD = 5.<sup>b</sup> Pooled SD = 4.6.

soaking at ambient temperature for 12–24 hours can reduce the phytate content substantially (29). Additional reduction can be achieved by the fermentation of porridge for weaning foods or dough for bread making. Commercially available phytase preparations could also be used but may not be economically accessible in many populations.

#### 12.4 Populations at risk for zinc deficiency

The central role of zinc in cell division, protein synthesis, and growth is especially important for infants, children, adolescents, and pregnant women; these groups suffer most from an inadequate zinc intake. Zinc-responsive stunting has been identified in several studies; for example, a more rapid body weight gain in malnourished children from Bangladesh supplemented with zinc was reported (30). However, other studies have failed to show a growth-promoting effect of zinc supplementation. A recent meta-analysis of 25 intervention trials comprising 1834 children under 13 years of age, with a mean duration of approximately 7 months and a mean dose of zinc of 14 mg/day (214  $\mu$ mol/day), showed a small but significant positive effect of zinc supplementation on height and weight increases (13). Zinc supplementation had

a positive effect when stunting was initially present; a more pronounced effect on weight gain was associated with initial low plasma zinc concentrations.

Results from zinc supplementation studies suggest that a low zinc status in children not only affects growth but is also associated with an increased risk of severe infectious diseases (31). Episodes of acute diarrhoea were characterized by shorter duration and less severity in zinc-supplemented groups; reductions in incidence of diarrhoea were also reported. Other studies indicate that the incidence of acute lower respiratory tract infections and malaria may also be reduced by zinc supplementation. Prevention of suboptimal zinc status and zinc deficiency in children by an increased intake and availability of zinc could consequently have a significant effect on child health in developing countries.

The role of maternal zinc status on pregnancy outcome is still unclear. Positive as well as negative associations between plasma zinc concentration and fetal growth or labour and delivery complications have been reported (32). Results of zinc supplementation studies also remain inconclusive (32). Interpretation of plasma zinc concentrations in pregnancy is complicated by the effect of haemodilution, and the fact that low plasma zinc levels may reflect other metabolic disturbances (11). Zinc supplementation studies of pregnant women have been performed mainly in relatively well-nourished populations, which may be one of the reasons for the mixed results (32). A recent study among low-income American women with plasma zinc concentrations below the mean at enrolment in prenatal care showed that a zinc intake of 25 mg/day resulted in greater infant birth weights and head circumferences as well as a reduced frequency of very low-birth-weight infants among non-obese women compared with the placebo group (12).

### 12.5 Evidence used to estimate zinc requirements

The lack of specific and sensitive indexes for zinc status limits the possibilities for evaluating zinc requirements from epidemiological observations. Previous estimates, including those published in 1996 as a result of a collaborative effort by WHO, the Food and Agriculture Organization of the United Nations (FAO) and the International Atomic Energy Agency (IAEA) (33) have relied on the factorial technique, which involves totalling the requirements for tissue growth, maintenance, metabolism, and endogenous losses. Experimental zinc repletion studies with low zinc intakes have clearly shown that the body has a pronounced ability to adapt to different levels of zinc intakes by changing the endogenous intestinal, urinary and integumental zinc losses (5–9, 34). The normative requirement for absorbed zinc was thus defined as the obligatory loss during the early phase of zinc depletion before

adaptive reductions in excretion take place and was set at 1.4 mg/day for men and 1.0 mg/day for women. To estimate the normative maintenance requirements for other age groups, the respective basal metabolic rates were used for extrapolation. In growing individuals the rate of accretion and zinc content of newly-formed tissues were used to derive estimates of requirements for tissue growth. Similarly, the retention of zinc during pregnancy (35) and the zinc concentration in milk at different stages of lactation (36) were used to estimate the physiological requirements in pregnancy and lactation.

The translation of these estimates of absorbed zinc into requirements for dietary zinc involves several considerations. First, the nature of the diet (i.e. its content of promoters and inhibitors of zinc absorption) determines the fraction of the dietary zinc that is potentially absorbable. Second, the efficiency of absorption of potentially available zinc is inversely related to the content of zinc in the diet. The review of available data from experimental zinc absorption studies of single meals or total diets resulted in a division of diets into three categories—high, moderate, and low zinc bioavailability—as detailed in Table 12.2 (33). To take account of the fact that the relationship between efficiency of absorption and zinc content differs for these diets, algorithms were developed (33) and applied to the estimates of requirements for absorbed zinc to achieve a set of figures for the average individual dietary zinc requirements (Table 12.3). The fractional absorption figures applied for the three diet categories at intakes adequate to meet the normative requirements for absorbed zinc were 50%, 30%, and 15%, respectively. From these estimates and from the evaluation of data from dietary intake studies, mean population intakes were identified which were deemed sufficient to ensure a low prevalence of individuals at risk of inadequate zinc intake (33). Assumptions made in deriving zinc requirements for specific population groups are summarized below.

### 12.5.1 Infants, children, and adolescents

Endogenous losses of zinc in human-milk-fed infants were assumed to be 20 µg/kg/day (0.31 µmol/kg/day) whereas 40 µg/kg/day (0.6 µmol/kg/day) was assumed for infants fed formula or weaning foods (33). For other age groups an average loss of 0.002 µmol/basal kJ (0.57 µg/basal kcal) was derived from the estimates in adults. Estimated zinc increases for infant growth were set at 120 and 140 µg/kg/day (1.83–2.14 µmol/kg/day) for female and male infants, respectively, for the first 3 months (33). These values decrease to 33 µg/kg/day (0.50 µmol/kg/day) for ages 6–12 months. For ages 1–10 years, the requirements for growth were based on the assumption that new tissue contains 30 µg/g (0.46 µmol zinc/g) (33). For adolescent growth, a tissue-zinc

TABLE 12.2

**Criteria for categorizing diets according to the potential bioavailability of their zinc**

Nominal category <sup>a</sup>	Principal dietary characteristics
High availability	Refined diets low in cereal fibre, low in phytic acid content, and with phytate–zinc molar ratio <5; adequate protein content principally from non-vegetable sources, such as meats and fish. Includes semi-synthetic formula diets based on animal protein.
Moderate availability	Mixed diets containing animal or fish protein. Lacto-ovo, ovo-vegetarian, or vegan diets not based primarily on unrefined cereal grains or high-extraction-rate flours. Phytate–zinc molar ratio of total diet within the range 5–15, or not exceeding 10 if more than 50% of the energy intake is accounted for by unfermented, unrefined cereal grains and flours and the diet is fortified with inorganic calcium salts (>1 g Ca <sup>2+</sup> /day). Availability of zinc improves when the diet includes animal protein or milks, or other protein sources or milks.
Low availability	Diets high in unrefined, unfermented, and ungerminated cereal grain <sup>b</sup> , especially when fortified with inorganic calcium salts and when intake of animal protein is negligible. Phytate–zinc molar ratio of total diet exceeds 15 <sup>c</sup> . High-phytate, soya-protein products constitute the primary protein source. Diets in which, singly or collectively, approximately 50% of the energy intake is accounted for by the following high-phytate foods: high-extraction-rate (≥90%) wheat, rice, maize, grains and flours, oatmeal, and millet; chapatti flours and <i>tanok</i> ; and sorghum, cowpeas, pigeon peas, grams, kidney beans, black-eyed beans, and groundnut flours. High intakes of inorganic calcium salts (>1 g Ca <sup>2+</sup> /day), either as supplements or as adventitious contaminants (e.g. from calcareous geophagia), potentiate the inhibitory effects and low intakes of animal protein exacerbates these effects.

<sup>a</sup> At intakes adequate to meet the average normative requirements for absorbed zinc (Table 12.3) the three availability levels correspond to 50%, 30% and 15% absorption. With higher zinc intakes, the fractional absorption is lower.

<sup>b</sup> Germination of cereal grains or fermentation (e.g. leavening) of many flours can reduce antagonistic potency of phytates; if done, the diet should then be classified as having moderate zinc availability.

<sup>c</sup> Vegetable diets with phytate–zinc ratios exceeding 30 are not unknown; for such diets, an assumption of 10% availability of zinc or less may be justified, especially if the intake of protein is low, that of inorganic calcium salts is excessive (e.g. calcium salts providing >1.5 g Ca<sup>2+</sup>/day), or both.

Source: adapted from reference (33).

content of 23 µg/g (0.35 µmol/g) was assumed. Pubertal growth spurts increase physiological zinc requirements substantially. Growth of adolescent males corresponds to an increase in body zinc requirement of about 0.5 mg/day (7.6 µmol/day) (33).

TABLE 12.3

**Average individual normative requirements for zinc ( $\mu\text{g}/\text{kg}$  body weight/day) from diets differing in zinc bioavailability<sup>a</sup>**

Group	High bioavailability <sup>b</sup>	Moderate bioavailability <sup>c</sup>	Low bioavailability <sup>d</sup>
<i>Infants and children</i>			
Females, 0–3 months	175 <sup>e</sup>	457 <sup>f</sup>	1067 <sup>g</sup>
Males, 0–3 months	200 <sup>e</sup>	514 <sup>f</sup>	1200 <sup>g</sup>
3–6 months	79 <sup>e</sup>	204 <sup>f</sup>	477 <sup>g</sup>
6–12 months	66 <sup>e</sup> , 186	311	621
1–3 years	138	230	459
3–6 years	114	190	380
6–10 years	90	149	299
<i>Adolescents</i>			
Females, 10–12 years	68	113	227
Males, 10–12 years	80	133	267
Females, 12–15 years	64	107	215
Males, 12–15 years	76	126	253
Females, 15–18 years	56	93	187
Males, 15–18 years	61	102	205
<i>Adults</i>			
Females, 18–60+ years	36	59	119
Males, 18–60+ years	43	72	144

<sup>a</sup> For information on diets, see Table 12.2.

<sup>b</sup> Assumed bioavailability of dietary zinc, 50%.

<sup>c</sup> Assumed bioavailability of dietary zinc, 30%.

<sup>d</sup> Assumed bioavailability of dietary zinc, 15%.

<sup>e</sup> Applicable to infants fed maternal milk alone for which the bioavailability of zinc is assumed to be 80% and infant endogenous losses to be  $20\mu\text{g}/\text{kg}$  ( $0.31\mu\text{mol}/\text{kg}$ ). Corresponds to basal requirements with no allowance for storage.

<sup>f</sup> Applicable to infants partly human-milk-fed or fed whey-adjusted cow milk formula or milk plus low-phytate solids. Corresponds to basal requirements with no allowance for storage.

<sup>g</sup> Applicable to infants receiving phytate-rich vegetable protein-based infant formula with or without whole-grain cereals. Corresponds to basal requirements with no allowance for storage.

Source: adapted from reference (33).

### 12.5.2 Pregnant women

The total amount of zinc retained during pregnancy has been estimated to be  $1.5\text{mmol}$  ( $100\text{mg}$ ) (35). During the third trimester, the physiological requirement of zinc is approximately twice as high as that in women who are not pregnant (33).

### 12.5.3 Lactating women

Zinc concentrations in human milk are high in early lactation, i.e.  $2\text{--}3\text{mg}/\text{l}$  ( $31\text{--}46\mu\text{mol}/\text{l}$ ) in the first month, and fall to  $0.9\text{mg}/\text{l}$  ( $14\mu\text{mol}/\text{l}$ ) after 3 months (36). From data on maternal milk volume and zinc content, it was estimated that the daily output of zinc in milk during the first 3 months of lactation could amount to  $1.4\text{mg}/\text{day}$  ( $21.4\mu\text{mol}/\text{l}$ ), which would theoretically triple the physiological zinc requirements in lactating women compared

with non-lactating, non-pregnant women. In setting the estimated requirements for early lactation, it was assumed that part of this requirement is covered by postnatal involution of the uterus and from skeletal resorption (33).

#### 12.5.4 Elderly

A lower absorptive efficiency has been reported in the elderly, which could justify a dietary requirement higher than that for other adults. On the other hand, endogenous losses seem to be lower in the elderly. Because of the suggested role of zinc in infectious diseases, an optimal zinc status in the elderly could have a significant public health effect and is an area of zinc metabolism requiring further research. Currently however, requirements for the elderly are estimated to be the same as those for other adults.

### 12.6 Interindividual variations in zinc requirements and recommended nutrient intakes

The studies (6–10) used to estimate the average physiological zinc requirements with the factorial technique are based on a relatively small number of subjects and do not make any allowance for interindividual variations in obligatory losses at different intakes. Because zinc requirements are related to tissue turnover rate and growth, it is reasonable to assume that variations in physiological zinc requirements are of the same magnitude as variations in protein requirements (37) and that the same figure (12.5%) for the interindividual coefficient of variation (CV) could be adopted. However, unlike protein requirements, the derivation of dietary zinc requirements involves estimating absorptive efficiencies. Consequently, variations in absorptive efficiency, not relevant in relation to estimates of protein requirements, may have to be taken into account in the estimates of the total interindividual variation in zinc requirements. Systematic studies of the interindividual variations in zinc absorption under different conditions are few. In small groups of healthy well-nourished subjects, the reported variations in zinc absorption from a defined meal or diet are of the order of 20–40% and seem to be largely independent of age, sex, or diet characteristics (see Table 12.1). How much these variations, besides being attributable to methodological imprecision, reflect variations in physiological requirement, effects of preceding zinc intake, etc. is not known. Based on the available data from zinc absorption studies (19, 20, 23–28), it is tentatively suggested that the interindividual variation in dietary zinc requirements, which includes variation in requirement for absorbed zinc (i.e. variations in metabolism and turnover rate of zinc) and variation in absorptive efficiency, corresponds to a CV of 25%. The recom-

TABLE 12.4

**Recommended nutrient intakes (RNIs) for dietary zinc (mg/day) to meet the normative storage requirements from diets differing in zinc bioavailability<sup>a</sup>**

Group	Assumed body weight (kg)	High bioavailability	Moderate bioavailability	Low bioavailability
<i>Infants and children</i>				
0–6 months	6	1.1 <sup>b</sup>	2.8 <sup>c</sup>	6.6 <sup>d</sup>
7–12 months	9	0.8 <sup>b</sup> , 2.5 <sup>e</sup>	4.1	8.4
1–3 years	12	2.4	4.1	8.3
4–6 years	17	2.9	4.8	9.6
7–9 years	25	3.3	5.6	11.2
<i>Adolescents</i>				
Females, 10–18 years	47	4.3	7.2	14.4
Males, 10–18 years	49	5.1	8.6	17.1
<i>Adults</i>				
Females, 19–65 years	55	3.0	4.9	9.8
Males, 19–65 years	65	4.2	7.0	14.0
Females, 65+ years	55	3.0	4.9	9.8
Males, 65+ years	65	4.2	7.0	14.0
<i>Pregnant women</i>				
First trimester	—	3.4	5.5	11.0
Second trimester	—	4.2	7.0	14.0
Third trimester	—	6.0	10.0	20.0
<i>Lactating women</i>				
0–3 months	—	5.8	9.5	19.0
3–6 months	—	5.3	8.8	17.5
6–12 months	—	4.3	7.2	14.4

<sup>a</sup> For information on diets, see Table 12.2. Unless otherwise specified, the interindividual variation of zinc requirements is assumed to be 25%. Weight data interpolated from reference (38).

<sup>b</sup> Exclusively human-milk-fed infants. The bioavailability of zinc from human milk is assumed to be 80%; assumed coefficient of variation, 12.5%.

<sup>c</sup> Formula-fed infants. Applies to infants fed whey-adjusted milk formula and to infants partly human-milk-fed or given low-phytate feeds supplemented with other liquid milks; assumed coefficient of variation, 12.5%.

<sup>d</sup> Formula-fed infants. Applicable to infants fed a phytate-rich vegetable protein-based formula with or without whole-grain cereals; assumed coefficient of variation, 12.5%.

<sup>e</sup> Not applicable to infants consuming human milk only.

mended nutrient intakes (RNIs) derived from the estimates of average individual dietary requirements (Table 12.3) with the addition of 50% (2 standard deviations) are given in Table 12.4.

## 12.7 Upper limits

Only a few occurrences of acute zinc poisoning have been reported. The toxicity signs are nausea, vomiting, diarrhoea, fever, and lethargy and have been observed after ingestion of 4–8 g (60–120 mmol) of zinc. Long-term zinc intakes higher than requirements could, however, interact with the metabolism of other trace elements. Copper seems to be especially sensitive to high zinc doses. A zinc intake of 50 mg/day (760 μmol) affects copper status

indexes, such as CuZn-superoxide dismutase in erythrocytes (39, 40). Low copper and ceruloplasmin levels and anaemia have been observed after zinc intakes of 450–660 mg/day (6.9–10 mmol/day) (41, 42). Changes in serum lipid pattern and in immune response have also been observed in zinc supplementation studies (43, 44). Because copper also has a central role in immune defence, these observations should be studied further before large-scale zinc supplementation programmes are undertaken. Any positive effects of zinc supplementation on growth or infectious diseases could be offset by associated negative effects on copper-related functions.

The upper level of zinc intake for an adult man is set at 45 mg/day (690  $\mu$ mol/day) and extrapolated to other groups in relation to basal metabolic rate. For children this extrapolation means an upper limit of intake of 23–28 mg/day (350–430  $\mu$ mol/day), which is close to what has been used in some of the zinc supplementation studies. Except for excessive intakes of some types of seafood, such intakes are unlikely to be attained with most diets. Adventitious zinc in water from contaminated wells and from galvanized cooking utensils could also lead to high zinc intakes.

## 12.8 Adequacy of zinc intakes in relation to requirement estimates

The risk of inadequate zinc intakes in children has been evaluated by comparing the suggested estimates of zinc requirements (33) with available data on food composition and dietary intake in different parts of the world (45). For this assessment, it was assumed that zinc requirements follow a Gaussian distribution with a CV of 15% and that the correlation between intake and requirement is very low. Zinc absorption from diets in Kenya, Malawi, and Mexico was estimated to be 15%, based on the high phytate–zinc molar ratio (> 25) of these diets, whereas an absorption of 30% was assumed for diets in Egypt, Ghana, Guatemala, and Papua New Guinea. Diets of fermented maize and cassava products (*kenkey*, *banku*, and *gari*) in Ghana, yeast leavened wheat-based bread in Egypt, and the use of sago with a low phytate content as the staple in Papua New Guinea were assumed to result in a lower phytate–zinc molar ratio and a better zinc availability. However, on these diets, 68–94% of children were estimated to be at risk for zinc deficiency in these populations, with the exception of those in Egypt where the estimate was 36% (45). The average daily zinc intakes of the children in the high-risk countries were between 3.7 and 6.6 mg (56–100  $\mu$ mol), and in Egypt, 5.2 mg (80  $\mu$ mol) illustrating the impact of a low availability.

Most of the zinc supplementation studies have not provided dietary intake data, which could be used to identify the zinc intake critical for beneficial

growth effects. In a recent study in Chile, positive effects on height gain in boys after 14 months of zinc supplementation were noted (46). The intake in the placebo group at the start of the study was  $6.3 \pm 1.3$  mg/day ( $96 \pm 20$   $\mu$ mol/day) ( $n = 49$ ). Because only 15% of the zinc intake of the Chilean children was derived from flesh foods, availability was assumed to be relatively low.

Krebs et al. (47) observed no effect of zinc supplementation on human-milk zinc content or on maternal zinc status of a group of lactating women and judged their intake sufficient to maintain adequate zinc status through 7 months or more of lactation. The mean zinc intake of the non-supplemented women was  $13.0 \pm 3.4$  mg/day ( $199 \pm 52$   $\mu$ mol/day).

The efficiency of the homeostatic mechanisms for maintaining body zinc content at low intakes, which formed the basis for the estimates of physiological requirements in the WHO/FAO/IAEA report (33), as well as the presumed negative impact of a high-phytate diet on zinc status, has been confirmed in several experimental studies (10, 46, 48, 49). Reductions in urinary and intestinal losses maintained normal plasma zinc concentrations over a 5-week period in 11 men with zinc intakes of 2.45 mg/day (37  $\mu$ mol/day) (10). In a similar repletion–depletion study with 15 men, an intake of 4 mg/day (61  $\mu$ mol/day) from a diet with a molar phytate–zinc ratio of 58 for 7 weeks resulted in a reduction of urinary zinc excretion from  $0.52 \pm 0.18$  to  $0.28 \pm 0.15$  mg/day ( $7.9 \pm 2.8$   $\mu$ mol/day to  $4.3 \pm 2.3$   $\mu$ mol/day) (48). A significant reduction of plasma zinc concentrations and changes in cellular immune response were observed. Effects on immunity were also observed when five young male volunteers consumed a zinc-restricted diet with a high-phytate content (molar ratio approximately 20) for 20–24 weeks (14). Suboptimal zinc status has also been documented in pregnant women consuming diets with high phytate–zinc ratios ( $>17$ ) (49). Frequent reproductive cycling and high malaria prevalence also seemed to contribute to the impairment of zinc status in this population group.

In conclusion, the approach used for derivation of average individual requirements of zinc used in the 1996 WHO/FAO/IAEA report (33) and the resulting estimates still seem valid and useful for assessment of the adequacy of zinc intakes in population groups and for planning diets for defined population groups.

## 12.9 Recommendations for future research

As already indicated in the 1996 WHO/FAO/IAEA report (33), there is still an urgent need to characterize the early functional effects of zinc deficiency and to define their relation to pathologic changes. This knowledge is vital to

the understanding of the role of zinc deficiency in the etiology of stunting and impaired immunocompetence.

For a better understanding of the relationship between diet and zinc supply, there is a need for further research which evaluates the availability of zinc from diets typical of developing countries. The research should include an assessment of the feasibility of adopting realistic and culturally-accepted food preparation practices, such as fermentation, germination, and soaking, and of including available and inexpensive animal protein sources in plant-food-based diets.

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