

Zinc requirements, the recommended dietary allowance and the reference dose

by Harold H Sandstead, MD¹

Human zinc deficiency was described about three decades ago by Prasad, Halsted, and others (1-4). Subsequently, zinc nutriture was shown to affect many systems. The most prominent clinical features of zinc deficiency are growth failure, developmental delay, poor immunity, impaired healing, dermatitis, abnormal reproduction, and impairment of special senses (including taste, smell and vision) and cognition (5-7).

The primary cause of zinc deficiency is consumption of a diet insufficient in bioavailable zinc. Zinc absorption is facilitated by certain amino acids (8) and depressed by phytate and other ligands with which it forms insoluble chelates (8-16).

The inhibition of zinc retention by dietary factors was shown by balance studies (table 1) (17-20). The data in table 1 illustrate the inhibitory effects of phytate, fiber, and cow milk proteins on zinc retention. Diet A was the control diet. It was low in fiber and phytate and provided about 60 g of protein. Diet B was similar to diet A except that 26 g of various sources of fiber and phytate were added individually to the bread. Diet C was similar to diet A except that the protein content was nearly doubled by the addition of cow milk proteins. Diet D was similar to diet C except that 26 g of the individual sources of fiber and phytate were added. Regression analysis of the retention data found the levels of zinc needed for balance. Availability decreased as the intake of substances that interfere with zinc retention increased.

Human zinc requirements can also be estimated by factorial calculations that account for needs for growth, losses, and bioavailability (21-23). Factorially estimated requirements (FER), set by a committee of the World Health Organization (WHO), are shown in table 2 (22). Of interest is a comparison of the WHO FER with more recent estimates of zinc requirements (table 3) by King & Turnland (23).

Their estimates were based on entirely different data (including metabolic studies and on factorial calculations) than the WHO estimates. The similarity of the data supports the validity of the estimates.

Estimates of needs for zinc during pregnancy are an example of the disparity between apparent requirements and reported intakes. Swanson & King (23, 24) calculated a requirement for the first half of pregnancy (table 3) that, at 20% bioavailability, is about 5 mg higher than the 8 mg mean intake of young women who participated in the Second National Health and Nutritional Examination (NHANES II) (25). It is also notable that the requirement for the last half of pregnancy in tables 2 and 3 is equal to or greater than the 15-mg recommended dietary allowance (RDA). These findings suggest that many women are at risk of zinc deficiency during pregnancy. Evidence of zinc deficiency during pregnancy was reviewed by Swanson & King (24) and has been reported more recently by Cherry et al (26) and Neggers et al (27).

The 1989 RDA values (28) were based on data from selected balance studies and reported endogenous losses of zinc. A 10% coefficient of variation in requirements and 20% availability were assumed. Table 4 compares the RDA with the WHO FER. In some instances there is a substantial disparity between these two estimates of need.

The other end of the zinc nutriture spectrum is zinc excess. Impairment of copper retention and the induction of copper deficiency appear to be potentially important consequences of high intakes of zinc. The sensitivity of the copper absorption mechanism to zinc is illustrated by the need for increased dietary copper when dietary zinc is increased (29). The significance of this association for health is unclear. One suspects that persons who select diets low in copper are at risk of copper deficiency when they consume diets or pharmacologic supplements rich in bioavailable zinc.

One mechanism of zinc interference with copper metabolism involves the induction of metallothionein synthesis in the intestinal mucosa (30). Metallothionein avidly binds copper and thus lowers the amount of copper entering the body through intestinal mucosal cells (31).

Studies on rats found that copper deficiency causes substantial changes in cholesterol metabolism which

¹ Department of Preventive Medicine and Community Health, Division of Human Nutrition, The University of Texas Medical Branch, Galveston, Texas, United States.

Address for correspondence: Professor HH Sandstead, PM&CH, UTMB, J-09, Galveston, Texas 77555-1009, USA.

include increases in total cholesterol and decreases in high-density lipoprotein cholesterol (32–35).

For humans, Hooper et al (36) found that 150 mg of zinc daily given to young men caused a substantial and significant decrease in high-density lipoprotein cholesterol. Others (37–39) confirmed these findings, though the effects on females were transitory.

Another manifestation of copper deficiency is a decrease in the activity of copper-zinc superoxide dismutase in erythrocytes (E-SOD). Two studies reported supplementation with as little as 50 mg of zinc daily lowered the activity of E-SOD. Fischer et al (40) gave 26 men a supplement of 25 mg of zinc or a placebo twice daily for six weeks. In the zinc-treated group the mean plasma zinc was significantly increased after two weeks, and the mean E-SOD activity was significantly decreased after six weeks. Zinc supplementation had no apparent effect on copper or ceruloplasmin activity in plasma. In the second study Yadick et al (41) found that 50 mg of zinc daily for 10 weeks significantly increased serum zinc and lowered the mean E-SOD and serum ferritin of nine premenopausal women. The ceruloplasmin protein concentration was unaffected.

The effects of copper on the E-SOD were used by a committee of the United States Environmental Protection Agency (EPA) as the basis for calculating a reference dose (RfD) for zinc.

The lowest-observed adverse-effect level (LOAEL) was 60 mg of zinc daily, a value based on the 50-mg zinc supplement and an assumed 10 mg of zinc in the diet. An uncertainty factor of 3 was proposed instead of the standard factor of 10 because of the uncertainty about the significance of the decrease in E-SOD. No modifying factors such as the effects of bioavailability were proposed.

The RfD from these assumptions was $0.33 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$:

$$\text{RfD} (\text{mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}) = [\text{NOAEL (or LOAEL)}] / [\text{UF} \cdot \text{MF}]$$

$$\text{RfD} = [(50 + 10) \text{ mg}] / (3 \cdot 60) = 60/180 = 0.33 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$$

This RfD seems inappropriate because the level is below the RDA or the WHO FER or both at 15% availability for children and adolescents (figure 1). Therefore, zinc RfD values that are related to zinc bioavailability might be appropriate. For example, if it is assumed that about 90% of the zinc from pharmacologic supplements is bioavailable and that the retention of zinc from the diet is essentially zero when pharmacologic doses of zinc are given, because of saturation of absorption mechanisms, it follows that the subjects in the studies of Fischer et al (40) and Yadick et al (41) absorbed 45 mg of zinc and that this was the amount of zinc that inhibited copper retention. Entering 45 mg in the RfD formula

Table 1. Zinc balance and diet composition. (CV = coefficient of variation, RDA = recommended dietary allowance)

Diet ^a	Number of subjects	Zinc (mg)				Availability ^b (%)
		Mean	SD	CV	RDA	
A	64	7.18	0.72	10	8.6	37.6
B	30	9.13	2.03	22	13.2	29.6
C	41	12.17	2.56	21	17.3	22.2
D	47	14.74	2.26	15	19.3	18.3

^a A: low fiber and phytate, 8% protein; B: 26 g fiber and phytate, 8% protein; C: low fiber and phytate, 15% protein by added dairy products; and D: 26 g fiber and phytate, 15% protein by added dairy products.

^b Availability, based on turnover of 2.7 mg daily (17).

Table 2. Zinc requirements (taken from reference 22).

Group	Need ^a ($\text{mg} \cdot \text{d}^{-1}$)	Availability ^b ($\text{mg} \cdot \text{d}^{-1}$)	
		10%	20%
Infants (0–4 months)	1.25	12.5	6.3
Infants (5–12 months)	1.1	11.0	5.5
Children (1–10 years)	1.6	16.0	8.0
Boys (11–18 years)	2.8	28.0	14.0
Men (19–≥51 years)	2.2	22.0	11.0
Girls (10–13 years)	2.65	26.5	13.3
Girls (14–18 years)	2.2	22.0	11.0
Women (19–≥51 years)	2.2	22.0	11.0
Pregnant (0–20 weeks)	2.55	25.5	12.8
Pregnant (20–30 weeks)	2.9	29.0	14.5
Pregnant (30–40 weeks)	3.0	30.0	15.0
Lactating women	5.45	54.5	27.3

^a Surface loss, menses, growth, pregnancy, lactation.

^b Diet availability.

Table 3. Zinc requirements (taken from reference 23).

Group	Zinc ($\text{mg} \cdot \text{d}^{-1}$)
Adults, 20–35 years	2.5
Adults, >65 years	1.5
Pregnant, 0–10 weeks	2.6
10–20 weeks	2.7
20–30 weeks	3.0
30–40 weeks	3.2
Lactating women, 1 month	4.62 (SD 1.80)
2 months	3.44 (SD 0.68)
3 months	3.18 (SD 0.36)
Infant boys, 0–1 years	1.0–1.2
Infant girls, 0–1 years	0.9–1.05

Table 4. Recommended dietary allowance (RDA) set by the United States Food and Nutrition Board (28) and the factorially estimated requirement (FER) of the World Health Organization (22) with approximately 20% availability.

Group	RDA ($\text{mg} \cdot \text{d}^{-1}$)	FER ($\text{mg} \cdot \text{d}^{-1}$)
Infants (0–0.5 years)	5	6.3
Infants (0.5–1 years)	5	5.5
Children (1–10 years)	10	8
Boys (11–18 years)	15	14
Men (19–≥51 years)	15	11
Girls (10–13 years)	12	13.3
Girls (14–18 years)	12	11
Women (19–≥50 years)	12	11
Pregnant (20–30 weeks)	15	14.5
Lactating women	19	27.3

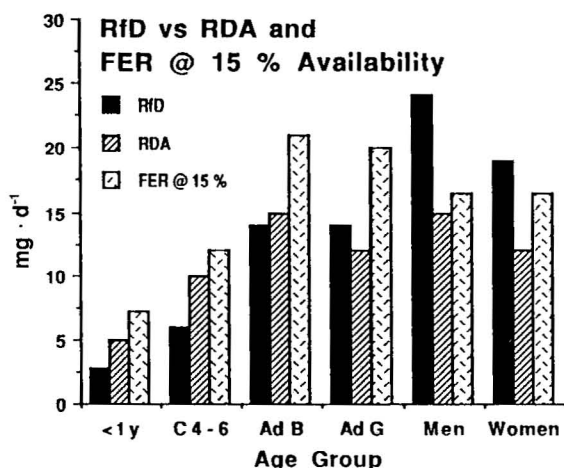


Figure 1. Reference dose (RfD) versus the recommended daily allowance (RDA) and the factorially estimated requirement (FER) for various age groups. (y = year, C = children, Ad B = adolescent boys, Ad G = adolescent girls)

gives a value of $0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for individuals who are consuming supplements:

$$\text{RfD} = (0.9 \cdot 50 \text{ mg}) / (3 \cdot 60 \text{ kg}) = 0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1},$$

$$\text{safe dose for OTC medications: } 0.25 \cdot 60 = 15 \text{ mg} \cdot \text{d}^{-1}.$$

Calculating RfD values that are related to dietary zinc requires adjustments for bioavailability. About 30% of zinc is retained from high bioavailability diets, and less than 15% is retained from low bioavailability diets. Therefore 150 mg is the amount of zinc necessary in a high bioavailability diet to provide the 45 mg that Fisher et al (40) and Yadick et al (41) found impaired copper metabolism. When 150 mg is entered in the RfD formula the result is $0.83 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$:

$$\text{RfD} = 45 \text{ mg} / (0.30 \cdot 3 \cdot 60 \text{ kg}) = 0.83 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1},$$

$$\text{safe dose for high bioavailability diet zinc: } 0.83 \cdot 60 = 50 \text{ mg} \cdot \text{d}^{-1}.$$

For low bioavailability diets (15%) the RfD would be $1.66 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$:

$$\text{RfD} = 45 \text{ mg} / (0.15 \cdot 3 \cdot 60 \text{ kg}) = 1.66 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1},$$

$$\text{safe dose for low bioavailability diet zinc: } 1.66 \cdot 60 = 100 \text{ mg} \cdot \text{d}^{-1}.$$

Summary

1. The 1989 zinc RDA is not congruent with many of the estimates of requirements determined by factorial or metabolic methods.

2. The proposed zinc RfD was based on the finding of lower activity of E-SOD after the administration of zinc in a form that might be consumed in an un-prescribed medication. This lower activity was taken as a marker of toxicity.

3. The proposed zinc RfD is incompatible with the 1989 RDA and the 1973 WHO FER or requirements published by King & Turnland (23).

4. A calculation of the RfD that accounts for bioavailability gives RfD values for OTC medications, and high and low bioavailability diets of 0.25, 0.83 and $1.66 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, respectively.

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