Zinc

Common Acronyms

CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
ICMR-NIN	Indian Council of Medical Research - National Institute of Nutrition
IOM	Institute of Medicine
IU	international unit
KNS	Korean Nutrition Society
LOAEL	lowest observed adverse effect level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NOAEL	no observed adverse effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Zinc is an essential element that demonstrates a classic U-shaped dose-response curve in which adverse effects are associated with receiving either too little or too much zinc. Zinc deficiency resulting from inadequate dietary intake can lead to a variety of physiological effects. For example, impaired growth and development has been observed in some countries, as evidenced by areas of endemic hypogonadism and dwarfism in rural Iran (Cousins 1996; King and Keen 1999; Hidgon 2001; EC SCF 2003; Li et al. 2022). Conditioned (secondary) zinc deficiency related to diseases, iatrogenic causes, impaired absorption, or excess zinc loss can also result in a variety of negative health effects (Hidgon 2001; Li et al. 2022; Sangeetha et al. 2022).

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Zinc is essential for the functions of numerous enzymes, including many involved in acid-base balance, amino acid metabolism, protein synthesis, and nucleic acid synthesis and function (Hidgon 2001; Sangeetha et al. 2022). For example, a zinc-dependent enzyme facilitates the conversion of food forms of folic acid (pteroylpolyglutamates) to free folic acid (pteroylmonoglutamate) to permit the body's utilization of food folates. Subsequently, the conversion of pteroylheptaglutamate to free folic acid is impaired with zinc deficiency.

Safety Considerations

Zinc toxicity can occur either acutely or chronically. Acute zinc toxicity symptoms include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headache (IOM 2001, 2006; EC SCF 2003). The acute effects of zinc excess typically result from ingesting gram quantities of zinc, which could occur by consuming 40 to 60 servings of a typical multivitamin that provides RDA levels (e.g., 8-12 mg per day in adults; IOM [2001, 2006]) of essential nutrients. For example, vomiting has been associated with intakes of 225-450 mg zinc (Higdon 2001; IOM 2006).

Chronic adverse effects of zinc excess are more subtle. Impacts on copper status have been identified previously by CRN, as well as global authoritative agencies, as the most critical safety-related endpoint. Specifically, reductions in serum copper levels have been reported in human clinical trials following zinc supplementation (Higdon 2001; IOM 2001; EC SCF 2003). At high supplemental intakes (e.g., 100-150 mg per day), overt effects of copper deficiency have been observed, including anemia and neutropenia (EC SCF, 2003). The effect of zinc intake on copper status has been shown to have a dose response, with effects found inconsistently below intake levels of 100 mg per day (EC SCF, 2003).

In some clinical trials, the activity of the erythrocyte enzyme, copper-zinc superoxide dismutase (ESOD), has been assessed as an indicator of copper status. For example, in one small clinical trial, ESOD levels in healthy females (N=18) were significantly reduced following 50 mg per day zinc supplementation for ten weeks (Yadrick et al. 1989). This study served as the basis of the IOM (2011) UL value and part of the basis for the EVM (2003) UL value (both discussed

below), with the reduction of copper-dependent ESOD identified as the most sensitive endpoint. However, selection of a NOAEL or LOAEL based on this endpoint may be overly conservative, as the researchers in this study did not determine how much reserve functional capacity is available for this enzyme and whether a small decrease in activity would have any relevant clinical impact. In fact, the EC SCF (2003) reviewed the available data on decreased copper-dependent ESOD following zinc supplementation and concluded the physiological relevance of such to be unclear, as this finding "is not accompanied by adverse effects and is not considered to be a marker of decreased copper status".

Reductions in copper status have been reported in at least one clinical trial in an unhealthy population at supplemental zinc levels lower than 50 mg per day. In two publications reporting on the same trial, patients on maintenance hemodialysis received 50 mg per day (as zinc acetate hydrate) or 34 mg per day (as polaprezinc) for three months (Okamoto et al. 2020a, 2020b). Serum copper levels were significantly reduced in the 50 mg per day group from baseline levels but not in the lower zinc group; however, copper deficiency (serum copper level < 60 μg/dL) was reported in patients of both groups. Effects on copper levels have also been reported in non-dialysis patients with chronic kidney disease, where an increase in serum copper levels was observed in patients decreasing from 25 mg per day to 7.5 mg per day of zinc (Nazari-Taloki et al. 2023). As reviewed by Nazari-Taloki and colleagues, several other studies (case studies and clinical trials) reported decreased serum copper levels with zinc supplementation in kidney disease patients. Given the health status of these patients, they are excluded from the target population for a UL.

No adverse effects have been observed, including on copper status, in other (double blind) clinical trials in healthy and some unhealthy populations at supplemental zinc intakes of 30-60 mg per day for 6-14 weeks in double blind trials (Davis et al. 2000; Milne et al. 2001; Bonham et al. 2003a, 2003b; DiSilvestro et al. 2015; Barnett et al. 2016; Katayama et al. 2020; Nazem et al. 2023; see also table below of key studies).

Some other effects reported with zinc supplementation have been reported. For example, supplemental zinc has been shown to influence several biomarkers that may have clinical

relevance in certain populations. Zinc supplements of 150 and 300 mg per day for 6 weeks have been shown to cause impaired immune function (Chandra 1984; Greger 1994; IOM 2006). Conversely, too little zinc has also been associated with impaired immune response (Higdon 2001). Zinc supplements have been associated with effects on lipoproteins and cholesterol metabolism (EC SCF 2003; IOM 2006); 50 mg or more per day have been shown to decrease serum HDL cholesterol levels (Hooper et al. 1980; Freeland-Graves et al. 1982; Black et al. 1988). In addition, total intakes of 60 mg of zinc decreased levels of iron in the Yadrick et al. (1989) study. Reports of anemia related to zinc intakes above 110 mg per day all describe the microcytic, hypochromic anemia associated with copper deficiency, a condition that could also interfere with iron utilization (Frambach and Bendel 1991; Gyorffy and Chan 1992; Summerfield et al. 1992; Greger 1994).

There are several medications that can interact with zinc, including antibiotics such as quinoline compounds and penicillamine, as well as several diuretics, such as hydrochlorothiazide. Zinc supplementation can interfere with the activity of medications, or in some cases medication can result in zinc depletion. A full discussion of drug-nutrient interactions is beyond the scope of this report, and individuals taking prescription medication should be advised to consult with their health care provider about potential drug-nutrient interactions.

Certain zinc–folic acid interactions are well documented (Butterworth and Tamura 1989). But the crucial issue is whether higher intakes of either zinc or folic acid may disrupt the bioavailability or function of the other and, if so, what the intakes associated with such effects are. Some reports of zinc–folic acid interactions suggest the possibility that supplemental folic acid could adversely affect zinc nutriture (Milne et al. 1984; Mukherjee et al. 1984; Simmer et al. 1987), but more recent reports have not uncovered any such interaction (Tamura et al. 1992; Kauwell et al. 1995).

The observation of adverse effects in some studies at lower zinc doses may be attributable to the variation in the dietary intake of phytate between populations. The inhibitory effect of phytate on zinc absorption has been evaluated extensively since the publication of the 3rd edition of this book. Findings suggest that absorption of zinc has likely previously been overestimated, indicating the need for revision to DRI values (Armah 2016; Hambidge 2008). In 2014, EFSA revised its DRIs

for zinc based on saturation response modeling (up to 20 mg zinc per day) and taking into account the inverse relationship between dietary phytate and zinc absorption (Miller et al. 2007; Hambidge et al. 2008, 2020; EFSA 2014). The EFSA DRI values derived for adults were increased from previous values derived by the EC SCF, with the population reference intake (PRI) values ranging from 7.5-16.3 mg zinc/day, depending on body weight and dietary phytate consumption (EFSA 2014).

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IOM (2001). The IOM found the adverse effects of excess zinc to include a suppressed immune response, decreased HDL cholesterol levels, and a reduced copper status. The IOM did not find adverse effects on human reproduction from excess zinc in their study. Of the various effects, the IOM selected the reduced copper status as the critical effect for deriving a UL for zinc. Specifically, the IOM used the data showing suppression of copper-dependent superoxide dismutase at 50 mg of zinc supplementation (Yadrick et al. 1989) to identify a LOAEL. Although no zinc intake from food was identified by Yadrick and colleagues, the IOM used population data to estimate a dietary zinc intake of 10 mg for the study. Thus, the IOM identified a LOAEL of 60 mg per day for total intake from all sources. A UF of 1.5 was selected to correct for uncertainty in extrapolation from a LOAEL to a NOAEL; the UF of 1.5 was judged to be adequate because reduced copper status is rare. Thus, the IOM UL for zinc is 40 mg per day for total intake from all sources.

European Commission, Scientific Committee on Food (EC SCF 2003). The EC SCF identified a NOAEL for zinc of approximately 50 mg per day. This NOAEL represents an overall conclusion based upon several studies. Although zinc intakes as low as 18.2 mg may decrease copper retention (Festa et al. 1985), this effect is readily corrected by adequate copper intake. Studies looking at the interplay between zinc and copper (Davis et al. 2000; Milne et al. 2001) indicate that copper balance and other indicators of copper status can be maintained when zinc intake is as high as 53 mg. No adverse effects were observed with 30 mg of supplemental zinc when dietary zinc was near 10 mg (Bonham et al. 2003a, 2003b). From these data collectively, the EC SCF identified its NOAEL of 50 mg of zinc and proposed a UF of 2 to derive a UL of 25 mg for total intake from all sources. Of note, the EFSA NDA Panel has been

asked by the European Commission to provide updated scientific opinions on the UL values for various vitamins and minerals. As of the time of this review, such a report has not been released by EFSA for zinc; however, re-evaluations of other vitamins and minerals are noted by EFSA to be "ongoing" (EFSA, 2024).

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM identified the key adverse effect for zinc intake to be reduction of copper absorption, with reduction of copper-dependent superoxide dismutase being the most sensitive endpoint. EVM selected a LOAEL of 50 mg for supplemental zinc based on several studies (Black et al. 1988; Yadrick et al. 1989; Cunningham et al. 1994; Davis et al. 2000). To extrapolate from a LOAEL to a NOAEL, the EVM selected a UF of 2, resulting in a derived SUL of 25 mg per day for supplemental zinc. The EVM (2003) noted that the total daily intake of 42 mg per day would not be expected to result in any adverse effects.

Chinese Nutrition Society (CNS 2023). An UL value for zinc of 40 mg per day in adults was set by the CNS.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN 2020). The ICMR-NIN determined the UL for zinc in adults to be 40 mg per day, consistent with IOM (2001) and based on an updated review of available literature.

Korean Nutrition Society (KNS 2020). The KNS published its general approach to evaluating data for setting DRI values. Based on this approach, UL values of 35 and 33 mg per day were derived for zinc in adults ages ≥19 and 18 years, respectively.

CRN Recommendations

The goal of the current update to CRN's supplemental UL for zinc was to determine whether more recent human clinical data are available that might impact the conclusions published in the 3rd edition. While not all human clinical trials are specifically designed to evaluate adverse effects, no new trials were identified following CRN's updated methodology that reported serum copper reducing effects or other serious adverse effects associated with zinc intervention in

healthy volunteers, as well as most trials in unhealthy populations. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the UL are recognized. As discussed above, other methodologies have been used by some government agencies that included review of available human and animal data, ultimately relying on other human clinical trials to derive associated UL values.

CRN's safety methodology for deriving a supplemental intake UL prioritizes data from human studies, when available. The table below summarizes the key human clinical and epidemiological studies considered in deriving an updated UL for supplemental intakes by CRN according to its principal points of departure for risk assessment (as described in the Methods).

Key Studies Considered for the CRN UL for Zinc

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg per day)	Duration	NOAEL (mg/day)	LOAEL (mg/day)
Key studies from 3rd edition							
Bonham et al. 2003a	Double blind trial	Healthy male volunteers	38	0, 30[a]	14 weeks	30	N/A
Bonham et al. 2003b	Double blind trial	Healthy male volunteers	38	0, 30[a]	14 weeks	30	N/A
Yadrick et al. 1989	Double blind trial	Healthy female volunteers	18	50	10 weeks	N/A	50[b]
Davis et al. 2000	Double blind trial	Healthy female volunteers (post-menopausal)	25	53	90 days	53	N/A
Milne et al. 2001	Double blind trial	Healthy female volunteers (post-menopausal)	21	53	90 days	53	N/A
Key studies identified in update							
Barnett et al. 2016	Double blind trial	Nursing home elderly with zinc deficiency	31	0, 30	3 months	30	N/A
Katayama et al. 2020	Double blind trial	Patients with chronic liver disease and zinc deficiency	57	0, 50	8 weeks	50	N/A
Nazem et al. 2023	Double blind trial	Patients with type 2 diabetes	70	0, 50	8 weeks	50	N/A
DiSilvestro et al. 2015	Double blind trial	Healthy female volunteers	30	0, 60	6 weeks	60	N/A

N/A, not applicable
[a] Fourteen weeks of zinc supplement followed by eight weeks of 3 mg/day copper
[b] Based on decreased superoxide dismutase activity

There are no known adverse effects of zinc at chronic supplemental levels of 30 mg per day (Bonham et al. 2003a, 2003b; Barnett et al. 2016). This is supported by a lack of adverse effects in many studies with higher doses in healthy and unhealthy populations (Davis et al. 2000; Milne et al. 2001; DiSilvestro et al. 2015; Katayama et al. 2020; Nazem et al. 2023). This level also provides a substantial margin of safety below the levels associated with adverse effects have been reported (at least 50 mg of supplemental zinc). Therefore, 30 mg per day is identified as the NOAEL for zinc following the CRN process. As described in the Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology, an UF of 1 is applied to yield an UL of 30 mg per day for adults for supplemental zinc. Assuming a dietary zinc intake of 10 mg, the CRN UL for supplements is compatible with the 40 mg IOM UL for total intake.

Quantitative Summary for Zinc for Adults

CRN (2024) UL, supplemental intake	30 mg/day[a]
IOM (2001) UL, total intake	40 mg/day
EC SCF (2003) UL, total intake	25 mg/day
EVM (2003), guidance level	25 mg/day supplemental intake; 42 mg/day total intake
CNS (2023), total intake	40 mg/day
ICMR-NIN (2020), total intake	40 mg/day
KNS (2020), total intake	35 mg/day (33 mg/day for ages 15-18 years)

[a] Assuming a dietary zinc intake of 10 mg, the CRN UL for supplements is compatible with the 40 mg IOM UL for total intake.

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