Rationale for tolerable upper intake level for zinc

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Outline

- Importance of zinc in human body
- Overview of terminology
- Rationale for upper intake level for zinc as recommended by the US Institute of Medicine (2001)
Biology of zinc

- Zinc participates in all major biochemical pathways in body
- Associated with >100 metalloproteins, including transcription factors
- Nucleic acid, amino acid, protein biosynthesis, including specific hormones like insulin, adrenal corticosteroids, testosterone
- Deficiency produces generalized impairment of multiple functions
Biology of zinc

- Especially important for cells with rapid turnover
  - Immune system
  - Intestinal mucosa

- Increased requirements during rapid growth
Consequences of zinc deficiency

- Immuno-dysfunction, increased morbidity, mortality
- Impaired growth
- Adverse pregnancy outcomes
- Abnormal neuro-behavioral development
Definition of EAR and UL

- **Estimated Average Requirement (EAR)**
  - Usual daily nutrient intake that meets the needs of 50% of healthy individuals in a particular sex & life-stage group
  - Used to estimate prevalence of inadequate intakes

- **Tolerable Upper Intake level (UL)**
  - Highest usual daily nutrient intake level likely to pose *no risk* of adverse health effects for almost all individuals in a particular sex & life-stage group
  - Used to estimate prevalence of excessive intakes
LOAEL & NOAEL

- Lowest Observed Adverse Effect Level (LOAEL)
- No Observed Adverse Effect Level (NOAEL)
Four possible levels:

**EAR**: average nutrient requirement

**LRNI** - Deficient level: 2SD below EAR
(probably below needs of almost all individuals (UK))

**RDA/RNI**: 2SD above EAR. (meets needs of 97-98% population)

**UL** - Tolerable upper level: risk of excessive intakes very low, possibly affecting 3% population
IZiNCG (2004): provide EARs; NOAEL for Zn
  - EAR for mixed/refined vegetarian diets; Phy:Zn: 4 to 18
  - OR unrefined cereal-based diets; Phy:Zn > 18

WHO (2005): give EARs & UL’s
  - EAR based on three levels of Zn bioavailability

Country-specific EARs & ULs if available
  - eg: IOM DRV’s; UK DRI’s etc
  - Bioavailability: based on habitual diets
Hazard identification

- Adverse effects associated with chronic intake of supplemental zinc include:
  - Suppression of immune response
  - Decrease in high-density lipoproteins cholesterol (HDL)
  - Reduction of copper status

- No data indicating adverse interactions between zinc and other nutrients when zinc is found in food.

US Institute of Medicine, 2001
Identification of LOAEL for adults

- Based on results from Yadrick et al (1989):
  - 18 healthy women (aged 18 to 40 yrs)
  - $50 \text{ mg/d}$ supplemental zinc for 10 weeks
  - Dietary zinc intake estimated at $10 \text{ mg/d}$ (based on results from 3rd NHANES Study)
- Significant reduction of ESOD activity

- LOAEL at 60 mg zinc/day

- Support for LOAEL of 60 mg/d provided by other studies (Fischer et al, 1984)

US Institute of Medicine, 2001
Extrapolation from LOAEL to UL with uncertainty factor (UF) of 1.5

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

- Zinc UL for adults \( \geq 19 \) yrs: 40 mg/d of zinc

US Institute of Medicine, 2001
Identification of NOAEL for infants

- Based on results from Walravens & Hambidge (1976):
  - 68 healthy full-term infants
  - Control grp: Formula with 1.8 mg zinc/L
  - Suppl grp: Formula with 5.8 mg zinc/L
  - Duration: 6 months
- No change in copper status
- Consideration of average intake of human milk (0.78 L/d) for infants aged 0-6 months
  - NOAEL at 4.5 mg zinc / day

US Institute of Medicine, 2001
Derivation of UL for infants

- Given that no adverse effects at 4.5 mg/d, uncertainty factor (UF) set at 1.0

  - Zinc UL for infants:
    0 – 6 months : 4 mg/d of zinc
    7 – 12 months : 5 mg/d of zinc

US Institute of Medicine, 2001
No adverse effects of zinc in children and adolescent could be found
Adjustment of UL for older children based on relative body weight

- Zinc UL for children:
  - 1-3 yrs : 7 mg/d of zinc
  - 4-8 yrs : 12 mg/d of zinc
  - 9-13 yrs : 23 mg/d of zinc

- Zinc UL for adolescents
  - 14-18 yrs : 34 mg/d of zinc

US Institute of Medicine, 2001
UL for pregnant and lactating women

- Inadequate data to justify a different UL for pregnant and lactating women
- Same UL as for non-pregnant and non-lactating women

- Zinc UL for pregnant and lactating women:
  - 14 – 18 yrs : 23 mg/d of zinc
  - 19 – 50 yrs : 40 mg/d of zinc

US Institute of Medicine, 2001
Adverse effects resulting from excess zinc intake from food and supplements appears to be low at above described levels.

The UL applies to total zinc intake from food, water and supplements (including fortified foods).

The UL is not meant to apply to individuals who are receiving zinc for treatment purposes.
Today’s question

- Is it time to re-assess the recommended UL for zinc?