

# Rationale for tolerable upper intake level for zinc

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# Outline

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- 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

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- 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

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- Especially important for cells with rapid turnover
  - Immune system
  - Intestinal mucosa
- Increased requirements during rapid growth

# Consequences of zinc deficiency

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- Immuno-dysfunction, increased morbidity, mortality
- Impaired growth
- Adverse pregnancy outcomes
- Abnormal neuro-behavioral development

# Definition of EAR and UL

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- 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

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- Lowest Observed Adverse Effect Level (LOAEL)
- No Observed Adverse Effect Level (NOAEL)

# Framework for multiple nutrient reference levels

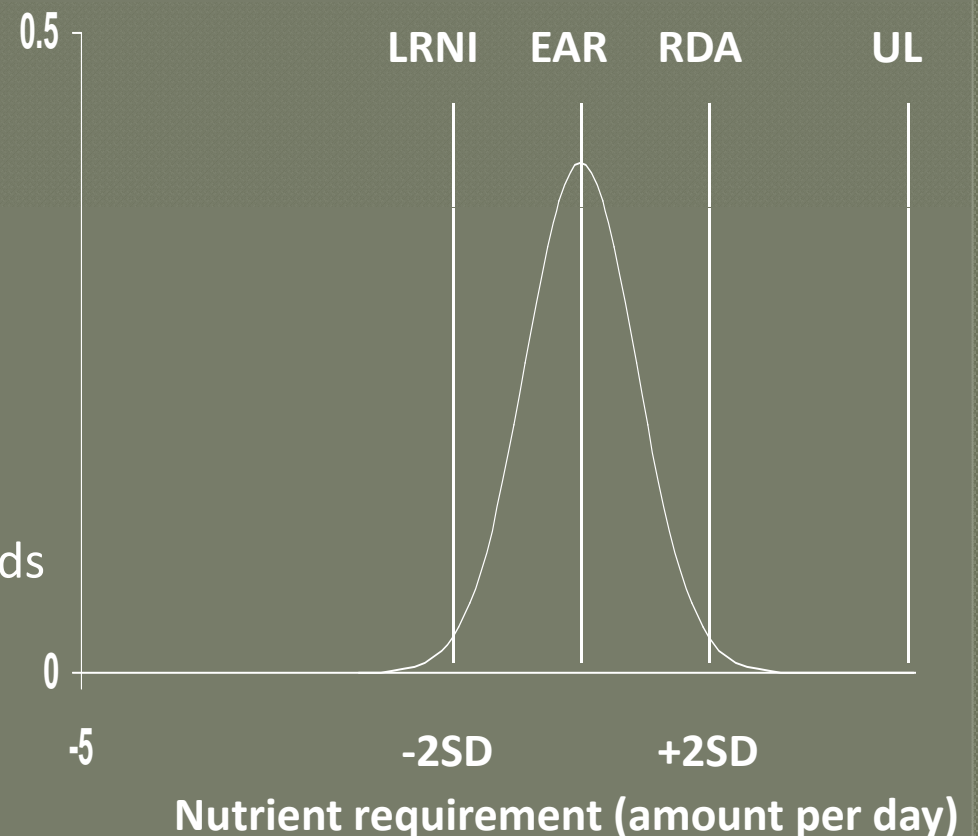
Four possible levels:

**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





# Different available recommendations for safe upper levels of zinc intake

- **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

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- 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.

# Identification of LOAEL for adults

- Based on results from Yadrick et al (1989):
  - 18 healthy women (aged 18 to 40 yrs)
  - 50 mg/d supplemental zinc for 10 weeks
  - Dietary zinc intake estimated at 10 mg/d (based on results from 3<sup>rd</sup> 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)

# Derivation of UL for adults

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- Extrapolation from LOAEL to UL with uncertainty factor (UF) of 1.5

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

➤ Zinc UL for adults  $\geq 19$  yrs: 40 mg/d of zinc

# 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

# Derivation of UL for infants

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- 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

# Derivation of UL for children and adolescents

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- 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

## UL for pregnant and lactating women

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- 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



# Risk characterization

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- 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

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