Excess Iron Intake: Defining Toxic Effects and Upper Limits in Vulnerable Populations

Dr. Stanley Zlotkin

November 2019


vitamin & mineral
food supplement


Кубанская
семечка

…but what is “excess intake”?

Tolerable Upper Intake Level or Upper Limit (UL)

The maximum amount of chronic daily intake of a nutrient that is unlikely to pose risk of *adverse health effects (toxicity)* in almost all (97.5%) healthy individuals in an age- and sex-specific population group.

Set at different levels by various groups – no universal agreement on upper limits (ULs)

Adverse Effects (toxicity)

Adverse effects = “any significant alteration in the structure or function of the human organism or any impairment of a physiologically important function”, including one nutrient’s negative impact on the absorption or effectiveness of another.

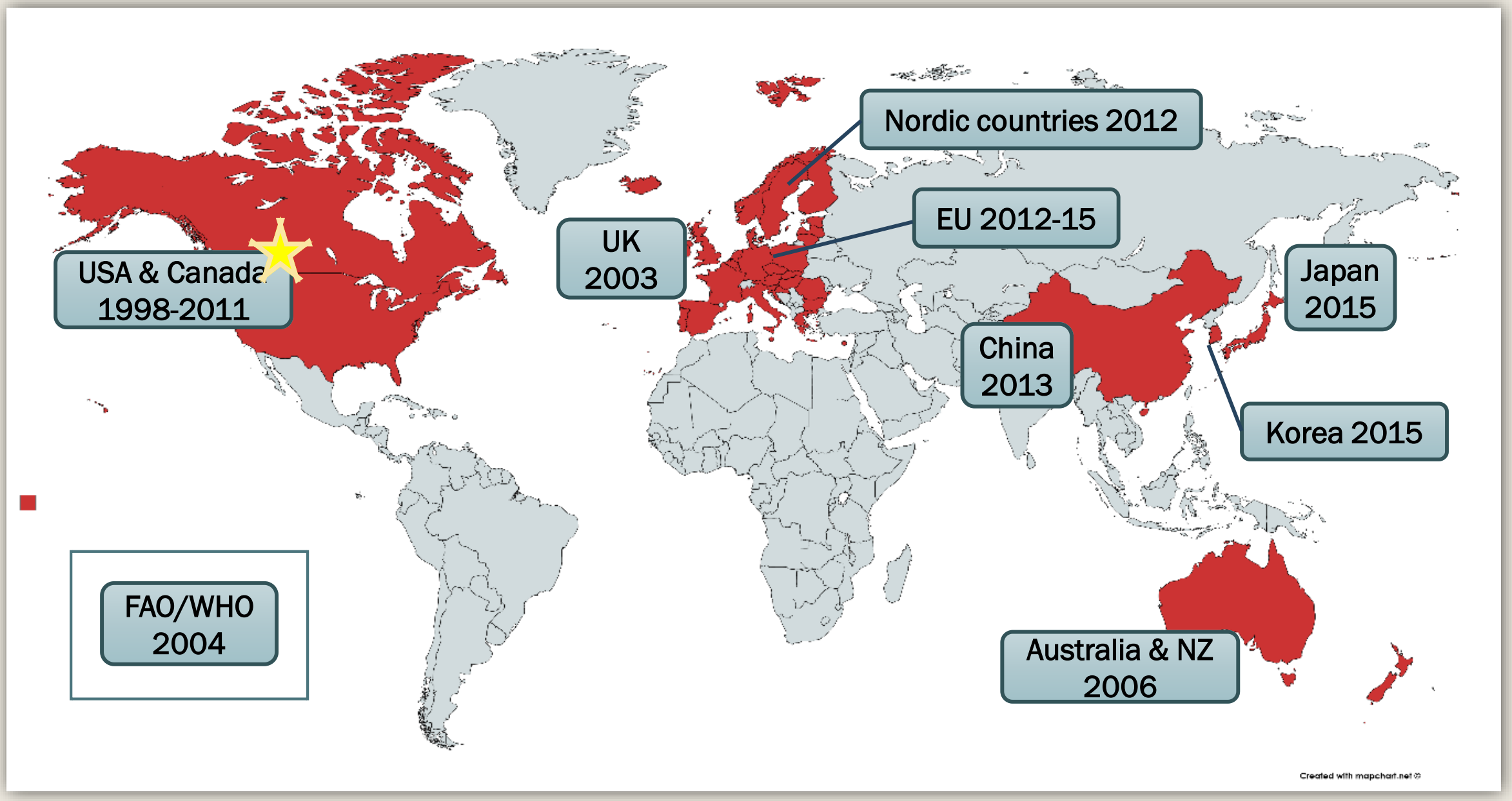
Selected Adverse Effects of Excess Intake

	Iron	Folic Acid	Vitamin A	Vitamin D
Acute	GI distress and corrosion Organ damage Lethal at extremely high doses	Antagonist to antifolate drugs	Increased intracranial pressure (bulging fontanelles, headaches), blurred vision, vertigo GI symptoms	Hypercalcemia GI symptoms Impaired renal function Lethal at extremely high doses
Chronic	Liver fibrosis Carcinogenesis Inhibition of zinc absorption	Neurological damage via masking of vitamin B12 deficiency	Hepatotoxicity Reduced bone mineral density Birth defects	Irreversible calcification of tissues and bone demineralization Kidney stones Infant growth retardation

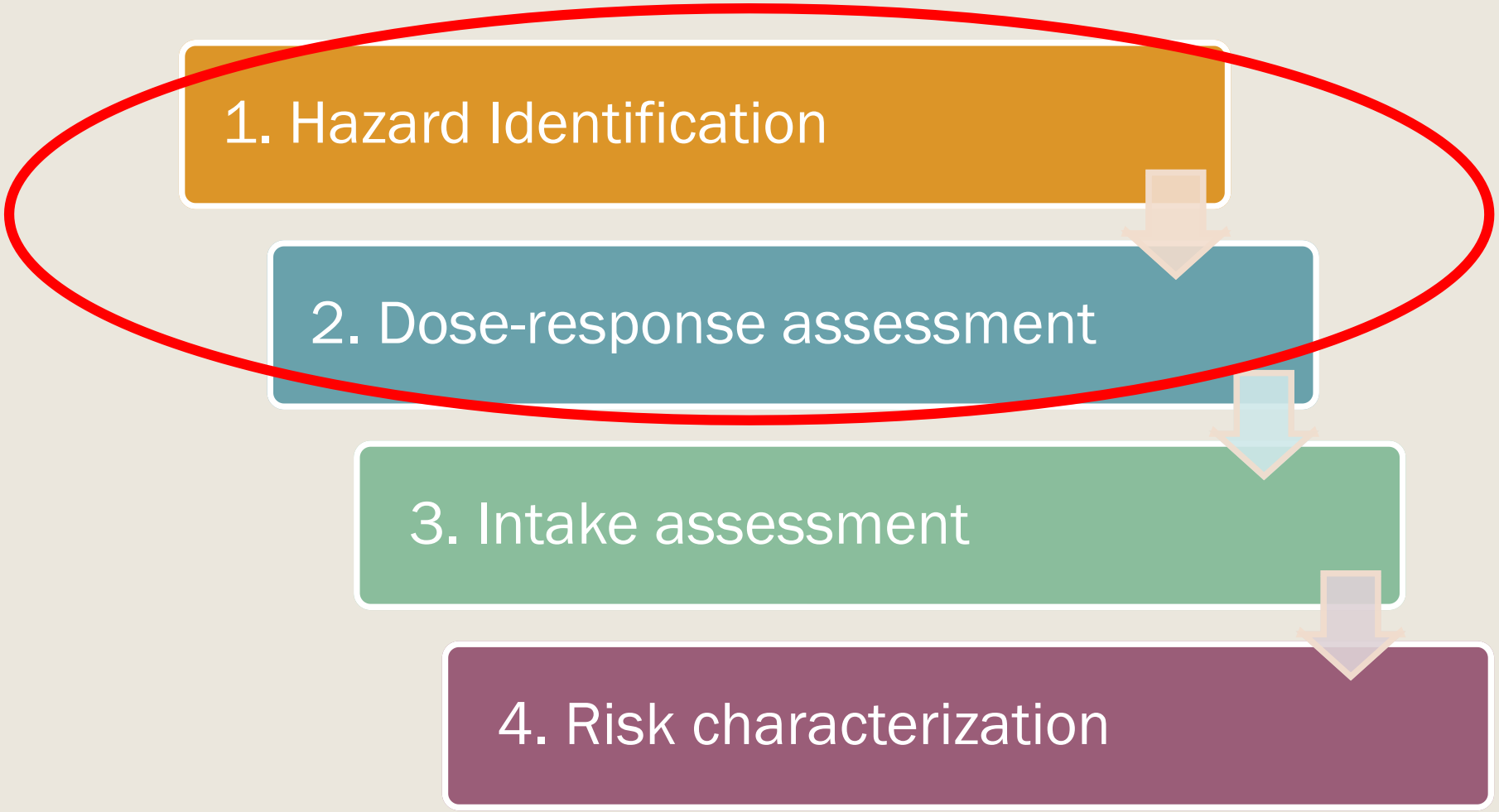
Published UL Recommendations

- 8 from government + FAO/WHO recommendations
- Consistency in approach: risk assessment framework
- Variability in application of framework
- Incongruence in outcomes

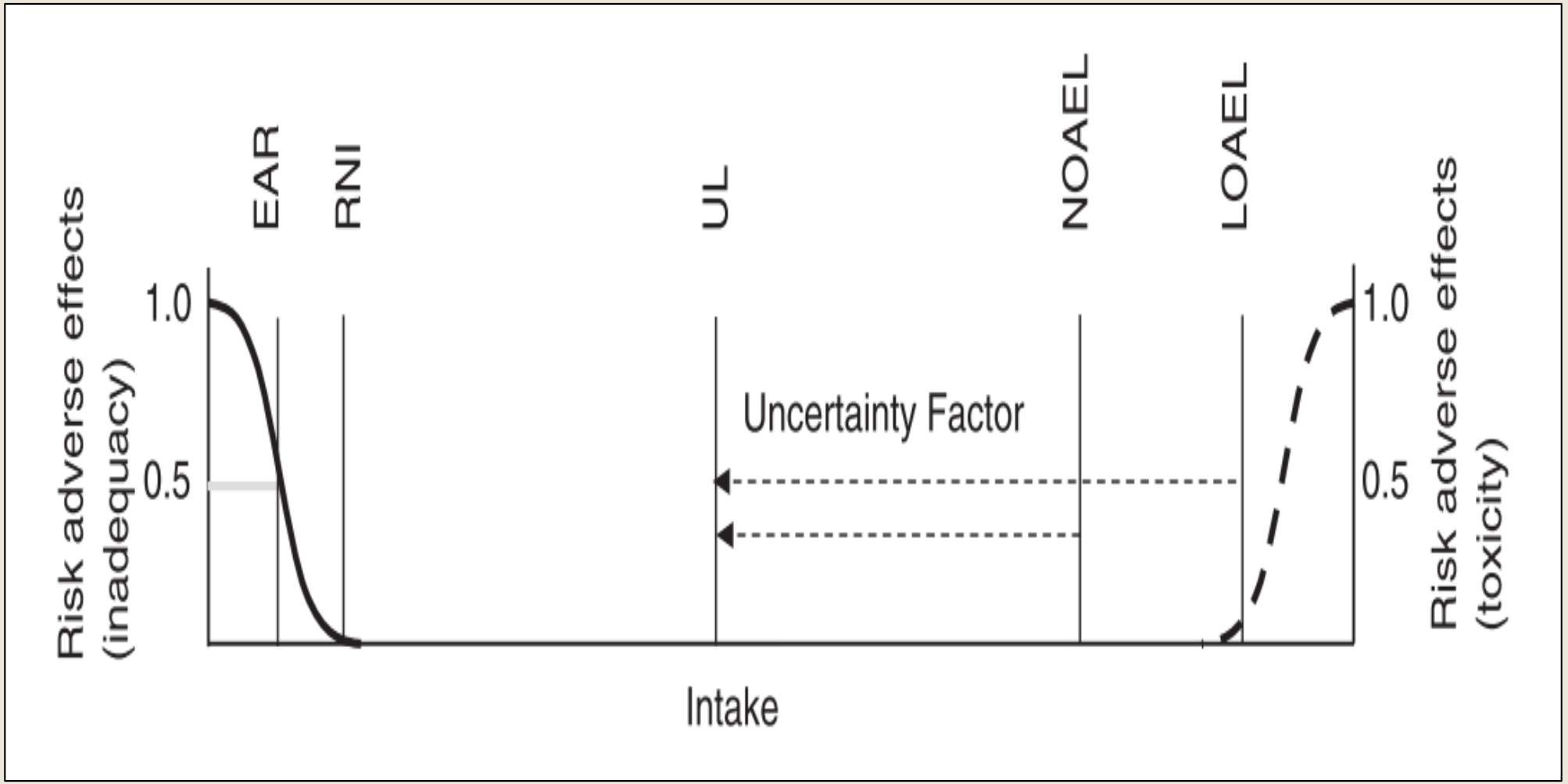
Published UL Recommendations

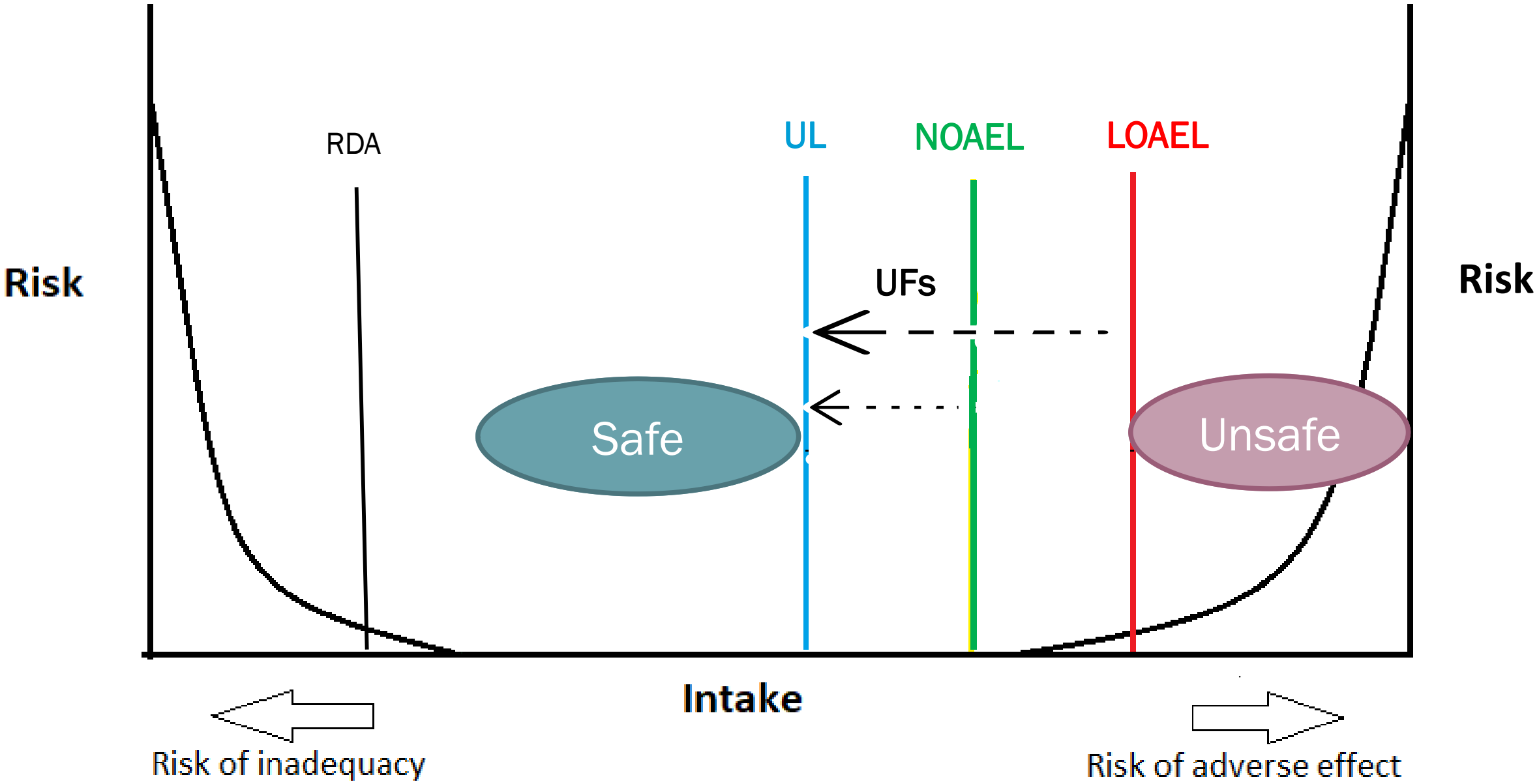


Risk Assessment: 4 steps



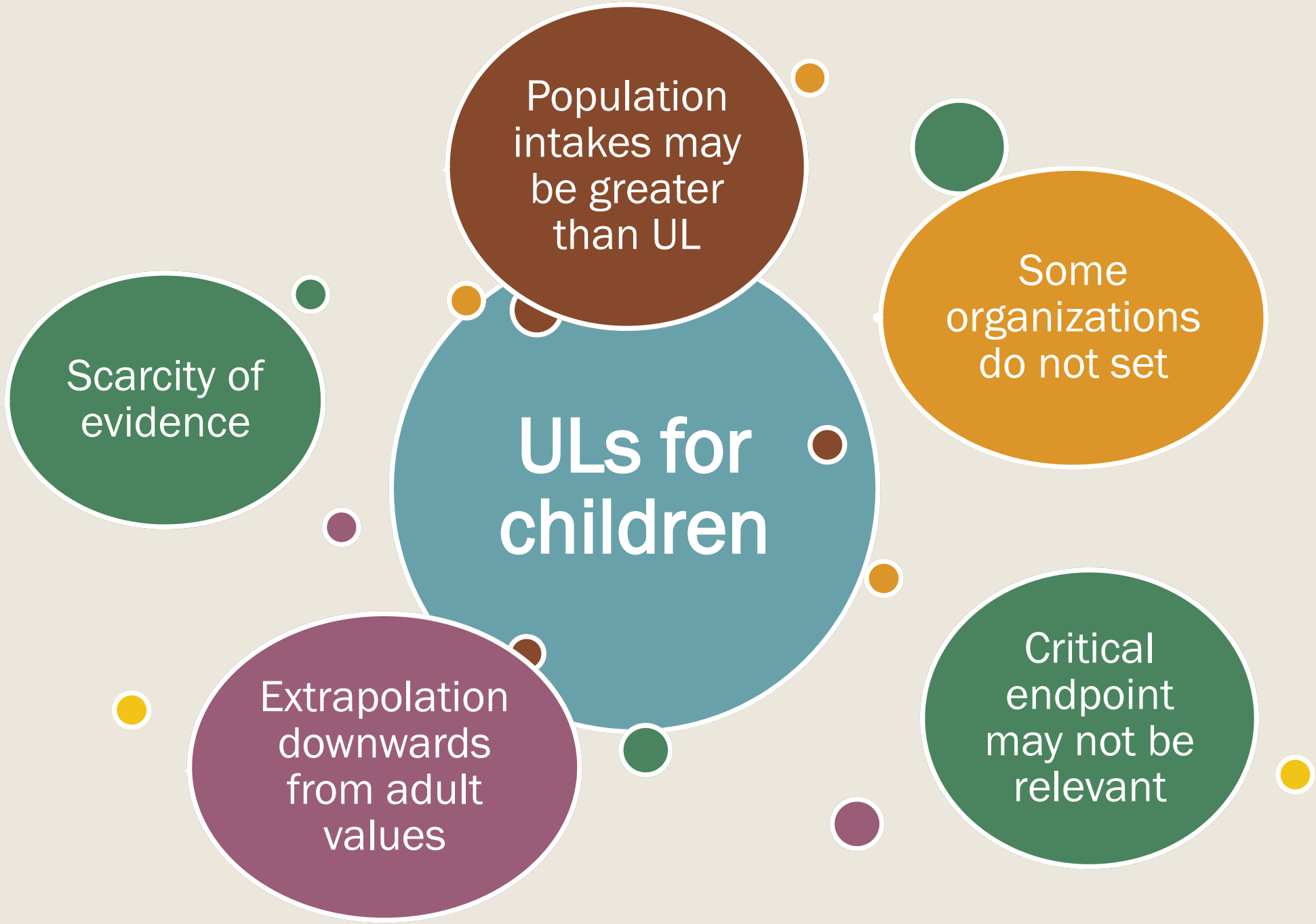
The Big Picture




RDA
UL
NOAEL
LOAEL
Risk
UFs
Risk
Safe
Unsafe
Intake
Risk of inadequacy
Risk of adverse effect

Variabilities in Application of Risk Assessment (cont'd)

- Whether ULs reflect total or supplementary intake
- Whether ULs were set for children (and how)
  - *If extrapolated, which equation and which reference weights were used*
- Level of confidence in ULs set (e.g., "guidance levels" with significant uncertainty)


Population intakes may be greater than UL
Some organizations do not set
Scarcity of evidence
ULs for children
Extrapolation downwards from adult values
Critical endpoint may not be relevant

UL Ranges for Infants and Young Children vs Population Intakes

	0-12 month UL range (total intake)	1-3 years UL range (total intake)	Intake from national surveys
Iron	20-40 mg	20-40 mg	NHANES 2-5y: Mean 12.3 mg; 95th percentile 13.1 mg ENFCS 6-35m: Median 10 mg
Folic acid	no UL	200-300 µg	NHANES 2-5y: Mean 309 µg; 95th percentile 536 µg ENSANUT 1-4y: Mean 246 µg
Vitamin A	600 µg*	600-800 µg*	NHANES 2-5y: Mean 549 µg; 95th percentile 607 µg ENFCS 6-35m: Median 9 µg ENSANUT 1-4y: Mean 563 µg
	* NNR UL is 3 mg/day for "entire population"		

Challenges with Risk Assessment in UL-setting

- Scarcity of quality data, especially for children
  - *Ethical limitations*
  - *Studies often not designed to assess adverse effects*
  - *Small, short duration*
  - *Heterogeneity in types of evidence*
- ULs assume chronic intake but are often based on acute adverse effects
- Lack of understanding of how nutrients interact with each other in excess

Ultimately…

- There is considerable uncertainty in UL values, especially for children
- ULs were developed to apply to healthy populations and should not be assumed directly applicable to malnourished populations
- Caution must be exercised in interpreting risk for populations receiving public health interventions
  - *E.g. high-dose vitamin A supplementation*
- For nutrients with limited evidence of toxicity in children, population intake data may provide better insight for setting ULs than inappropriate extrapolation form adult ULs

Iron Supplementation in Malaria Endemic Areas

© UNICEF/UN0150202/Dejongh

- Taking iron does not make a child more likely to be infected with malaria
- However, children taking iron may get sicker than children not taking iron:
  - IF they become infected and;
  - IF they do not receive treatment promptly
- Iron supplementation is important in treating anemia
  - Providing iron in the context of malaria control will have a greater impact on anemia than malaria control alone
- Therefore, iron-containing MNP must always be provided in the context of an active malaria control program

Key Health Messages

MNP program beneficiaries should be told:

- Malaria is a preventable and treatable illness which people can get from a mosquito bite
- Malaria causes fever
- All children, including those receiving MNP, should sleep under a bed net every night
- Children with a fever should be tested for malaria without delay
- Children who test positive should be treated with the first line antimalarial

Coordination of efforts between malaria control and nutrition programs providing MNP can help to ensure improved health outcomes for children

© UNICEF/UN022008/Ayene

World Health Organization

SickKids®
Centre for Global Child Health

Thank you!