A Risk/Benefit Approach to Assess Nutrient Intake: Do we Need a New DRI?

Alicia L. Carriquiry
Iowa State University

Collaborator: Suzanne Murphy, U. of Hawaii
Disclosure statement

• I am a Distinguished Professor of Statistics at Iowa State University. I am also a Special Government Employee with the US-EPA Scientific Advisory Board.
• I am member of the Advisory Council of the Bureau of Transportation Statistics.
• Funding from: National Science Foundation, National Institutes of Health, Iowa Department of Transportation.
• I know of no financial or other interests that might conflict with my presenting a scientifically unbiased report to ILSI.
Outline

• Risk of inadequate intake
• Model for development of ULs
• Risk assessment on the upper intake ranges - the Estimated Average Tolerance ET
• Using the ET to
  – assess populations
  – design food fortification programs
• Next steps.
Risk Assessment in Nutrition

- Nutrients, unlike contaminants, are beneficial if consumed in the right amounts.
- Two types of risk are possible:
  - Risk if *inadequacy* when consumption is too low.
  - Risk of *excess* when consumption is too high.
Risk of inadequacy

• When usual consumption of a nutrient is insufficient to maintain essential functions, we say that the intake is inadequate.

• For a given health endpoint, the average (in a population) dose-response relationship is approximately known for most nutrients.

• Importantly, it is also known that this relationship varies between persons.
Distribution of requirements

• The formulation of distributions of requirements for a nutrient provides the framework needed to assess nutrient intakes from the perspective of risk of inadequacy.

• Implicitly, the dose-response relationship is the basis for determining the distribution of requirements.
The EAR and the RDA

The two DRIs are associated with risk of inadequacy:

- The EAR is the level of intake that meets the requirement for the nutrient of half of the population.
- The RDA is the level of intake that meets requirements of almost all individuals in the population.

We should think of the EAR as a typical requirement in a group.

The RDA is the requirement of the most sensitive persons in the group.
Risk of inadequacy

• Given the dose-response relationship, we estimate the prevalence of inadequacy by the average of the risks at each intake level in the group.
• This is what the probability approach (NRC, 1986) does.
• Calculations can be simplified under some assumptions.
• The simplified approach is the EAR cut-point method (Beaton, 1994; Carriquiry, 1999).
Hypothetical requirements versus intakes
Policy implications

• We think of a *typical person* when we use the EAR to estimate prevalence of inadequacy.

• We plan for low prevalence. Equivalently, we plan for low proportion of intakes below the EAR.

• If we were to plan for low proportion of intakes below the RDA, a significant proportion of persons would be offered too much.
The UL

- The Tolerable Upper Level is defined as the level of usual intake that is likely to pose no risk for most individuals in the group.

- It is not a recommended intake level: intakes above the RDA exceed the needs of most persons.
Assessing intakes with the UL

• What can we say when we compare usual intakes to the UL for a nutrient?
  – Intakes below the UL are likely to pose no risk.
  – We do not know what to say about intakes above the UL.

• At high doses, we do not know much about the dose-response relationship for most nutrients.
Same UL, two dose-response curves
The model for setting ULs

• First define an adverse health endpoint.
• Using animal studies (most likely) determine the NOAEL (or LOAEL).
  – Safety factor to compute NOAEL from LOAEL.
  – Safety factor to extrapolate from sub-chronic to chronic exposure.
  – Safety factor to extrapolate from animals to humans.
  – Additional safety factor to extrapolate across age groups.
• Yet additional safety factor to account for differences between persons in a life-stage group.
RESULTING ULs CAN BE QUITE LOW

E.G. ZINC IN CHILDREN
Vitamin E (IOM, 2000)

- At high doses, vitamin E has been linked to hemorrhagic events.
- A LOAEL of 500 mg / kg / day established from studies in rats.
- Safety factors:
  - NOAEL from LOAEL 2
  - Sub-chronic to chronic 2
  - Rats to humans 3
  - Between person variability 3
Vitamin E (cont’d)

- Multiplying the various safety factors, we get a value of 36.
- The UL is computed as:

\[
UL = \frac{LOAEL}{36}
\]

- The UL for vitamin E for adults is 14 mg / kg / day.
- For an “average” person who weighs 70 kg, the UL is approximately 1000 mg/day.
Conceptualizing the UL

• Imagine a distribution of *tolerances* to excessive nutrient intake in a population sub-group.

• The UL corresponds to the lower tail of the distribution: it is the highest level of intake that is *tolerable* by most members of the group.

• Most persons tolerate higher exposures.
Distribution of tolerances and the Estimated Average Tolerance

• We propose that the risk of excess be approached just as we approach the risk of inadequacy:
  – Estimate an Average Tolerance (AT) for population sub-groups and for each nutrient.
  – Formulate a distribution of tolerances in the group, with a variance that reflects between-person differences.
The AT: Estimated Average Tolerance

• To establish the AT, proceed as we do now, by dividing a NOAEL or a LOAEL by a safety factor that accounts for
  – LOAEL to NOAEL
  – Sub-chronic to chronic exposure effects
  – Extrapolation from animals to humans

• Do not include a factor to account for variability between persons.
Between person variability in tolerances

• The physiological variability between persons determines whether the UL is close to the AT or far from it.

• If we expect lots of differences among persons in the same life-stage group, then UL <<<< AT.
Revisiting vitamin E in adults

• For vitamin E, the LOAEL is 500 mg/kg/day and the safety factor is 36.

• The factor that accounts for variability among persons is 3.

• The UL is then: \[ \frac{500}{(12 \times 3)} = 14 \text{ mg/kg/day}. \]
Vitamin E for adults (cont’d)

• For vitamin E, the AT is:
  \[
  \frac{500}{12} = 42 \text{ mg/kg/day}.
  \]

• The 2.5\textsuperscript{th} percentile of the tolerance distribution is the UL, obtained by applying the last safety factor of 3 to the AT.

• The SD of tolerance can be calculated...
CV of tolerance

• We computed the UL as:
  \[ UL = \frac{AT}{\text{Between-person SF}} \]
• If tolerances are normal and UL is the 2.5\(^{th}\) percentile of tolerance, then:
  \[ UL = AT - 2SD \]
• Since \( UL = \frac{AT}{\text{Between-person SF}} \), we find that the implicit CV of tolerance is
  \[ CV = \frac{1}{2} \left( 1 - \frac{1}{SF} \right) 100 = 33\% \]
Between-person SF and CV of tolerance

- The larger the safety factor to account for between-person variability, the larger the implicit CV of tolerance.
  - SF = 5      \( \rightarrow \) CV = 40%
  - SF = 2      \( \rightarrow \) CV = 25%
  - SF = 1      \( \rightarrow \) CV = 0% (no variability)
The UL as a mirror image of the RDA

• We propose that the UL should be viewed as the mirror image of the RDA.

• **Thus, the UL should not be used to assess intakes of groups.**

• The proportion of persons with intakes above the UL is likely to overestimate the proportion of individuals at risk of excess.
Estimating the prevalence of excess

- Consider the AT cut-point method:

  The proportion of persons with usual intakes exceeding their tolerance is estimated as the proportion of persons with usual intakes above the AT.
Hypothetical tolerances vs. intakes
Planning intakes

• To plan intakes for groups, we use:
  1. The EAR to set the target median intake in the group.
  2. The AT to monitor whether some individuals will be at risk.

• To plan intakes for an individual, we use the UL because we are conservative.
Conclusions I

• There is general agreement about using the EAR to assess and to plan intakes of groups.
• We must re-think that current approach to assess excessive intakes.
• Determining excess against a UL is likely to result in conservative decisions.
• An approach that is consistent with risk assessment norms would require that we define an ET and a distribution of tolerances.
Conclusions II

• For some nutrients, the SF for physiological differences has been set to 1.
• Implication is that all persons are equally tolerant to high exposure.
• Under our model, AT = UL for those nutrients.
• Using average body weights is not a good idea. For vitamin E:
  – Woman who weighs 50.5 kg (5th percentile) is exposed to 20 mg/k/day at current UL.
  – Man who weighs 120 kg (95th percentile) is exposed to 8 mg/k/day.
Where to next?

• To determine whether the AT model is reasonable, must revisit the Uls for all nutrients.
• What are policy implications of using an AT for planning?
• For some nutrients (e.g., vitamin D) we use biomarkers to assess prevalence. We need to explore how to extend the AT model to the biomarker context.
THANK YOU

Alicia Carriquiry
Distinguished Professor of Statistics
Iowa State University
alicia@iastate.edu