EVIDENCE REQUIREMENTS FOR DEVELOPING ULs AND CDRRs, AND RISK FRAMEWORKS FOR APPLYING THE EVIDENCE

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NASEM 4 January 2021
Washington, DC

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TRADITIONAL DRIs FOR NUTRIENTS

1) **Estimated Average Requirement (EAR):** Average daily intake meeting requirement for half of healthy individuals.
2) **Recommended Dietary Allowance (RDA):** Average daily intake meeting requirements of 97-98% of healthy individuals.
3) **Adequate Intake (AI):** Observed daily intakes – developed when insufficient evidence to estimate EAR or RDA.
4) **Tolerable Upper Intake Level (UL):** Highest daily intake level likely to pose no risk of adverse health effects.

DRIs also developed for Macronutrients and Energy Requirements.

Used to plan and assess diets of apparently healthy people.

TOLERABLE UPPER INTAKE LEVEL (UL)

- Highest daily intake without adverse health effects
  - Intakes greater than UL may result in adverse health effects.
  - Until recently, no distinctions were made regarding the types of adverse effects considered suitable for UL development.

UL CRITICAL ADVERSE EFFECTS (1997-2004)

Nutrient	Adverse Effect
Calcium	Milk-alkali syndrome
Phosphorus	Elevated serum P_i
Magnesium	Osmotic diarrhea
Vitamin D	Serum calcium > 11 mg/dl
Fluoride	Children: moderate dental fluorosis Adults: moderate skeletal fluorosis
Niacin	Flushing
Vitamin B_6	Sensory neuropathy
Folate	Neuropathy in B_{12}-deficient individuals
Choline	Hypotension, fishy body odor
Sodium	Coronary heart disease (BP as surrogate)

SOURCES OF EVIDENCE FOR ULs

- Observational studies
- Clinical Trials – Adverse Event Reports
- Case Reports of Adverse Events
- Animal toxicology studies
- Studies of mechanisms of toxic action

UL DERIVATION

- Data on adverse effects from observations in humans
- Data on adverse effects from animal studies may sometimes be used

- Dose-response critical: Identify

No Observed Adverse Effect Level

NOAEL

- UL= $\frac{\textbf{NOAEL}}{\textbf{UFs}}$

UF= Uncertainty Factors

- Variability
- Data Uncertainties

UL – FOLATE (IOM, 1998)

- Adults → 1000 ug/day from fortified foods/supplements
- Primary Evidence ("limited but suggestive"): Case Reports (>100) of progression of neuropathy of neurological disorders in patients with B12 deficiency
- Supporting Evidence
  - Studies in monkeys and fruit bats
  - Documented metabolic interaction
- Other Evidence Considered but Found Insufficient
  - Reproductive, Developmental Effects
  - Carcinogenicity
  - Hypersensitivity
  - Zinc Absorption

DERIVATION OF FOLATE UL (IOM, 1998)

- Almost all cases involved > 5 mg/day folate, although some occurred at < 5

  → 5 mg/day described as "Lowest Observed Adverse Effect Level" (LOAEL)

  → No NOAEL identified

- Uncertainty factor of 5 selected

  → Thus UF larger than most used for nutrients:

    - Severity of disorder
    - LOAEL rather than NOAEL

DATA LIMITATIONS AND UNCERTAINTIES FOR FOLATE UL DEVELOPMENT

Typical of those encountered with other nutrients

- Limitations in acquiring sufficient evidence in humans regarding causality
- Relevance to humans of experimental toxicity studies
- Lack of consensus on use of mechanistic data
- Little rigorous basis for selecting UFs

These issues are still with us…

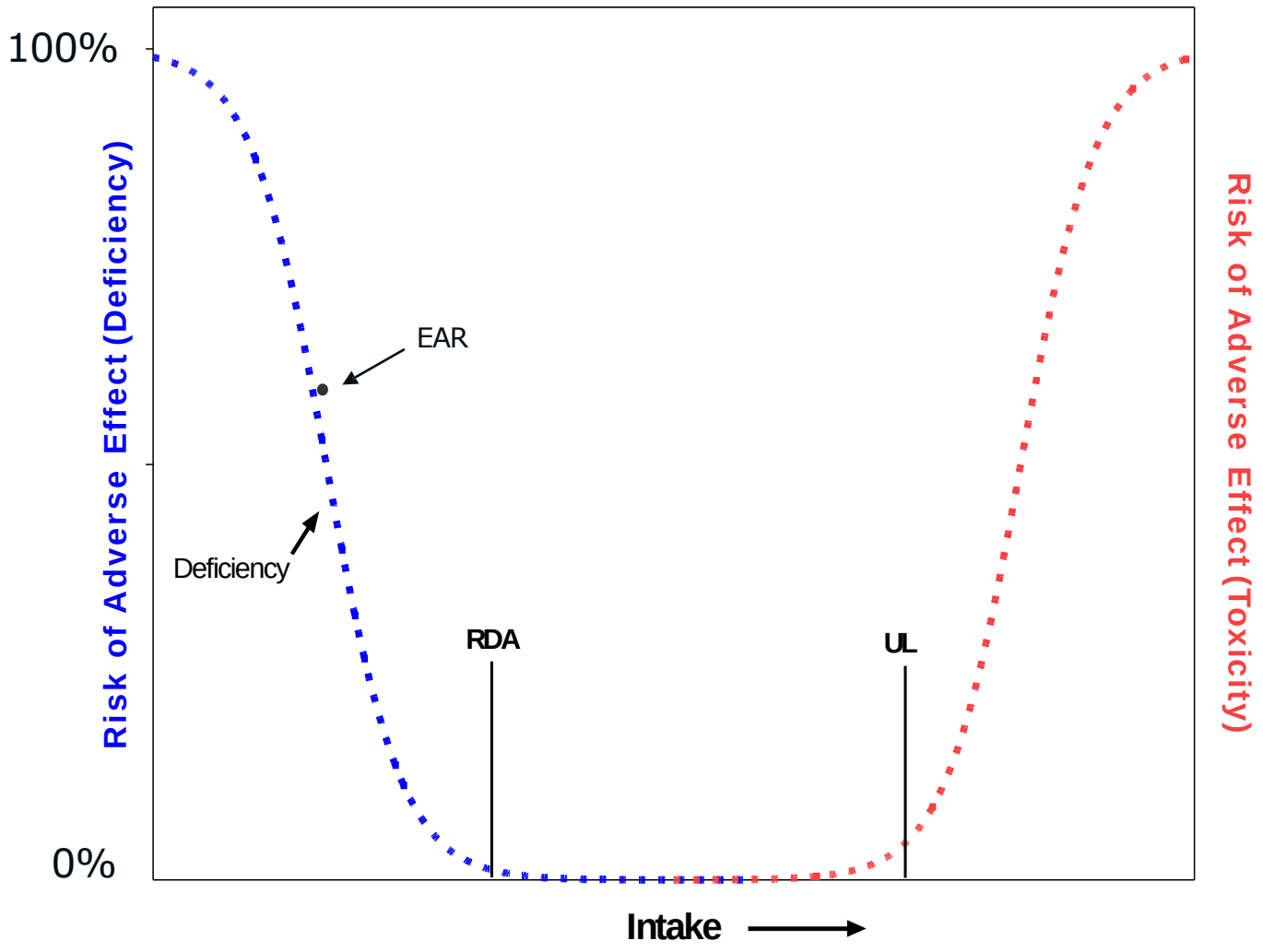
RIBOFLAVIN

- Previous DRI Committee (1998) Found No Evidence to support a UL for **RIBOFLAVIN**
  - Based on observations of no adverse effects in short term studies in humans, including high doses from supplements.
  - Limited absorption from GI tract.

Based on my own (limited) literature search this situation seems not to have changed.

INTAKE-RESPONSE

Relationships of Intakes and Adverse Effects of Substances that are Nutritionally Necessary



Characteristics of Substances that Exhibit Intake-Response Relationships as Described in Figure

1. They are nutritionally necessary
2. The are, *by themselves,* **NECESSARY AND SUFFICIENT** to completely avoid deficiency disease
3. Their complete absence will lead to disease in 100% of the population.

IMPORTANT

The intake-response relationships depicted in Figure 1 -- *do not apply* to constituents of the diet that affect chronic disease risks.

No single substance would be necessary and sufficient **TO CAUSE OR COMPLETELY AVOID A CHRONIC DISEASE IN MORE THAN A FRACTION OF THE POPULATION.**

In other words:
Some substances may, at most, increase or decrease the **RISK** of a chronic disease.

RISK = probability of disease

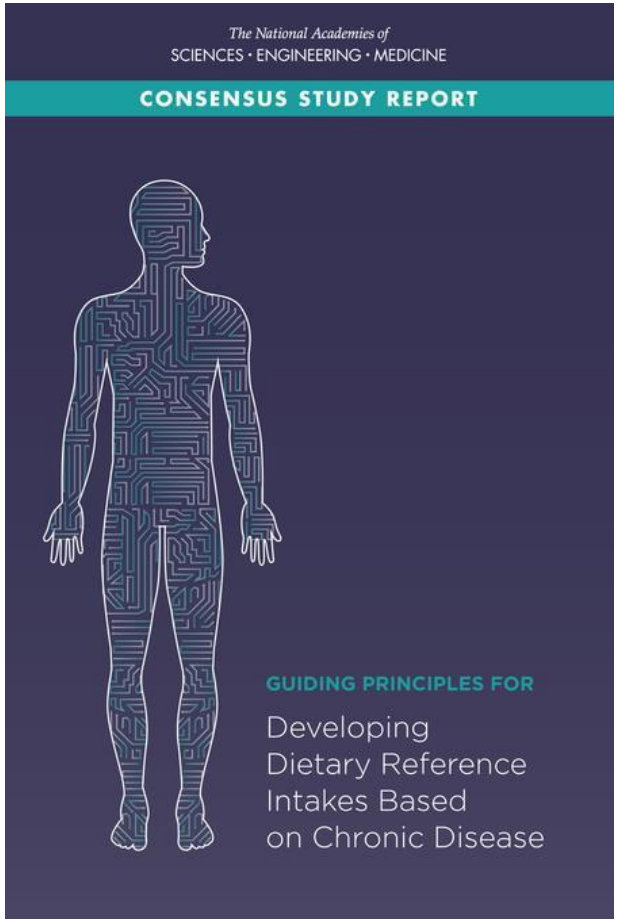
NASEM CONSENSUS STUDY REPORT, 2017

Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease

Applies to both…

Nutrients
Other (Natural) Constituents of Food

NOFS = Nutrients and Other Food Substances



Guidance for Future DRI Committees

NASEM GUIDELINES: SCIENTIFIC REQUIREMENTS TO ESTABLISH DRIs BASED ON CHRONIC DISEASE ENDPOINTS

1. Evidence supporting ***causal*** relationship between intake of a nutrient/food substance and risk of chronic disease
2. Evidence supporting ***quantitative intake-risk*** relationship
3. Specification of ***intake range*** over which risk is reduced

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The method of evaluation used to support 1 and 2 must provide a **systematic way** to identify the certainty of the finding.

HOW CERTAIN DO WE NEED TO BE?

A KEY RECOMMENDATION FROM THE GUIDING PRINCIPLES REPORT

DRI committees should

use GRADE* to assess the ***certainty of the evidence to support***

1. Causal relationship between a NOFS and a chronic disease
2. Intake-response relationship for that relationship

*Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a widely used, transparent approach to grading quality (or certainty) of evidence and strength of recommendations. http://www.gradeworkinggroup.org/

RATING THE CERTAINTY OF EVIDENCE FOR A CAUSAL ASSOCIATION ACCORDING TO GRADE GUIDANCE

Certainty of the evidence is rated for each outcome, across studies **Randomized controlled trials begin with a high rating, observational studies with a low rating**	
Rating is then modified downward:	*Rating is then modified upward:*
✓ Risk of bias	✓ Large magnitude of effect
✓ Imprecision	✓ Intake-response is observed
✓ Inconsistency of results (heterogeneity)	✓ Confounders likely minimize the effect
✓ Indirectness	
Final rating for each outcome is 'high', 'moderate', or 'low'	

EVIDENCE RATINGS:

A=high certainty; B=moderate; C=low; D=substantial uncertainty

GRADE YIELDS FOUR LEVELS OF CERTAINTY REGARDING AND INTAKE-RESPONSE RELATIONSHIP CAUSALITY

- DRIs require at least a moderate level of certainty in the evidence for causation. (Level B)

- DRIs require at least a moderate level of certainty in the relationship between intake and response. (Level B)

DRIS FOR CHRONIC DISEASES WILL BE EXPRESSED AS RANGES

DRIs will be RANGES OF INTAKES OVER WHICH

Increasing intakes

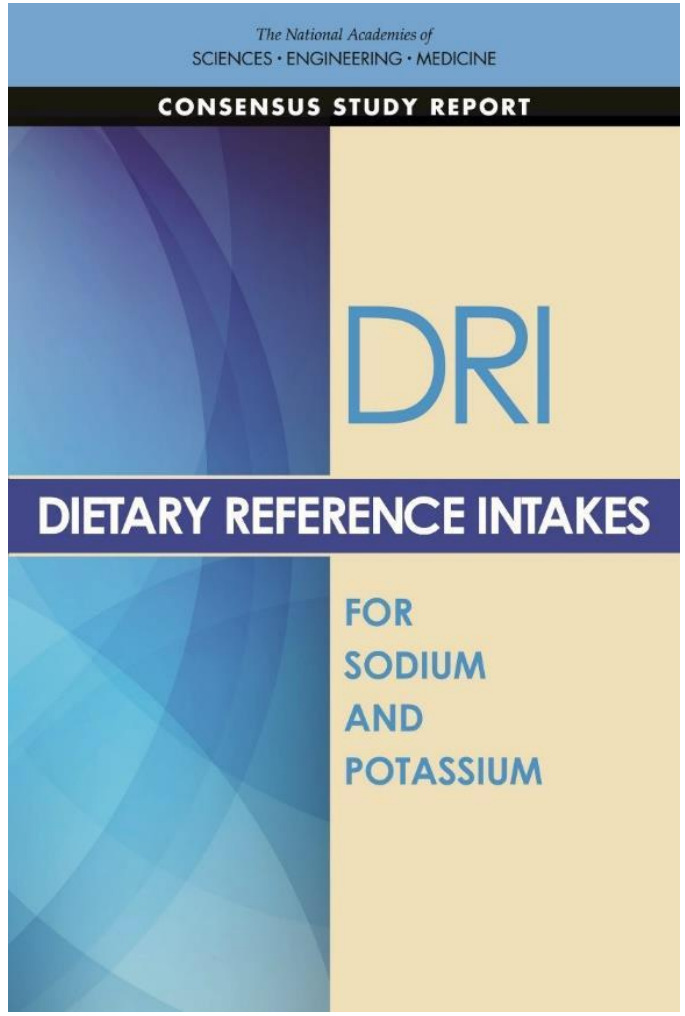
OR

Decreasing intakes

} will reduce disease risk

Committees may also select intakes associated with maximum observed risk reductions as DRIs.

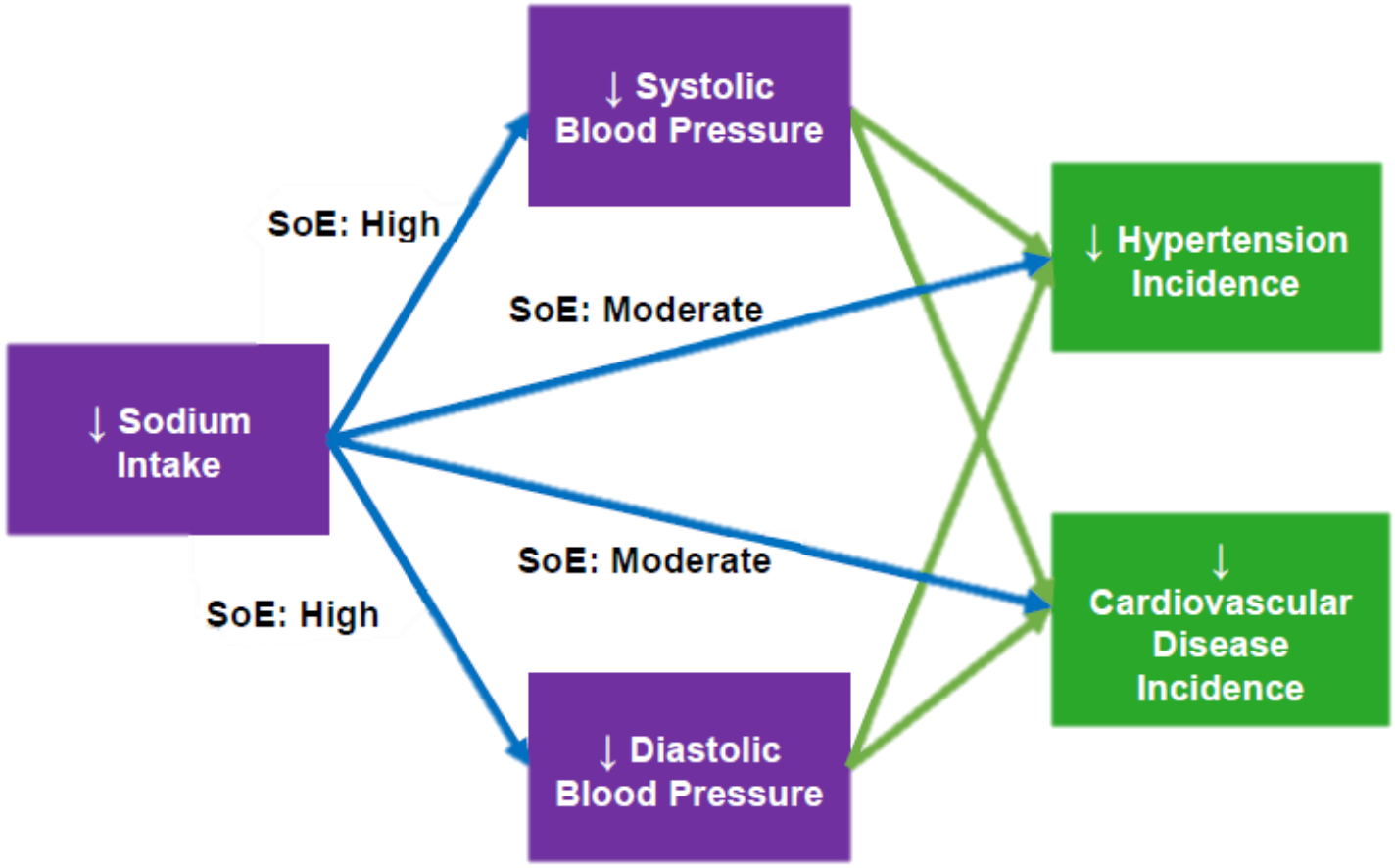
Dietary Reference Intakes for Sodium and Potassium



SODIUM DRI BASED ON CHRONIC DISEASE

- **Strength of Evidence for Causal Relationship with Reductions in Sodium Intake**
  - Insufficient
    - Cardiovascular mortality
    - Myocardial infarction
    - Left ventricular mass
    - Stroke
    - Osteoporosis
    - Kidney disease
  - Moderate
    - All-cause mortality
    - Cardiovascular disease incidence
    - Hypertension incidence
  - High
    - Systolic blood pressure
    - Diastolic blood pressure

RELATIONSHIP BETWEEN INDICATORS



Continuous measures (changes in numerical values)

Dichotomous Outcomes (changes in risk or incidence)

Evidence from sodium randomized controlled trials

Evidence for blood pressure as a surrogate marker from other studies

SODIUM DRI BASED ON CHRONIC DISEASE

Intake Range (mg/d)	Strength of Evidence for Intake-Response Relationship Between Reduction in Sodium Intake and Chronic Disease Risk
> 4,100	Moderate up to 5,000 mg/d
2,300-4,100	High
< 2,300	Low down to 1,000 mg/d

SODIUM CHRONIC DISEASE RISK REDUCTION INTAKE (CDRR)

- **Conclusions**
  - There is moderate to high strength of evidence for both a causal relationship and an intake–response relationship between sodium and several interrelated chronic disease indicators: **cardiovascular disease**, **hypertension**, **systolic blood pressure**, and **diastolic blood pressure**
  - For sodium, the CDRR is the intake above which intake reduction is expected to reduce chronic disease risk, within an apparently healthy population.

CDRR = 2,300 mg/day (adults)

SODIUM UL (2019)

Following the NASEM Guidelines

- UL should not be based on risk of chronic disease
- UL should be based on risk of toxicity
  - No UL established in 2019 Report
- CDRR is used to describe risk of chronic disease and risk reduction target

TWO FRAMEWORKS FOR EXAMINING RISKS OF NUTRIENT EXCESS