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Establishing the Chronic Disease Risk Reduction Value

https://www.wellnessworksdetroit.com/preventing-and-managing-chronic-disease/

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Disclosures

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Speakers Bureau	None
Stock Shareholder	Mutual funds, Public Service of Canada pension
Employer	Texas A&M AgriLife Research
Other	American Society for Nutrition – Associate Editor, AJCN

Outline

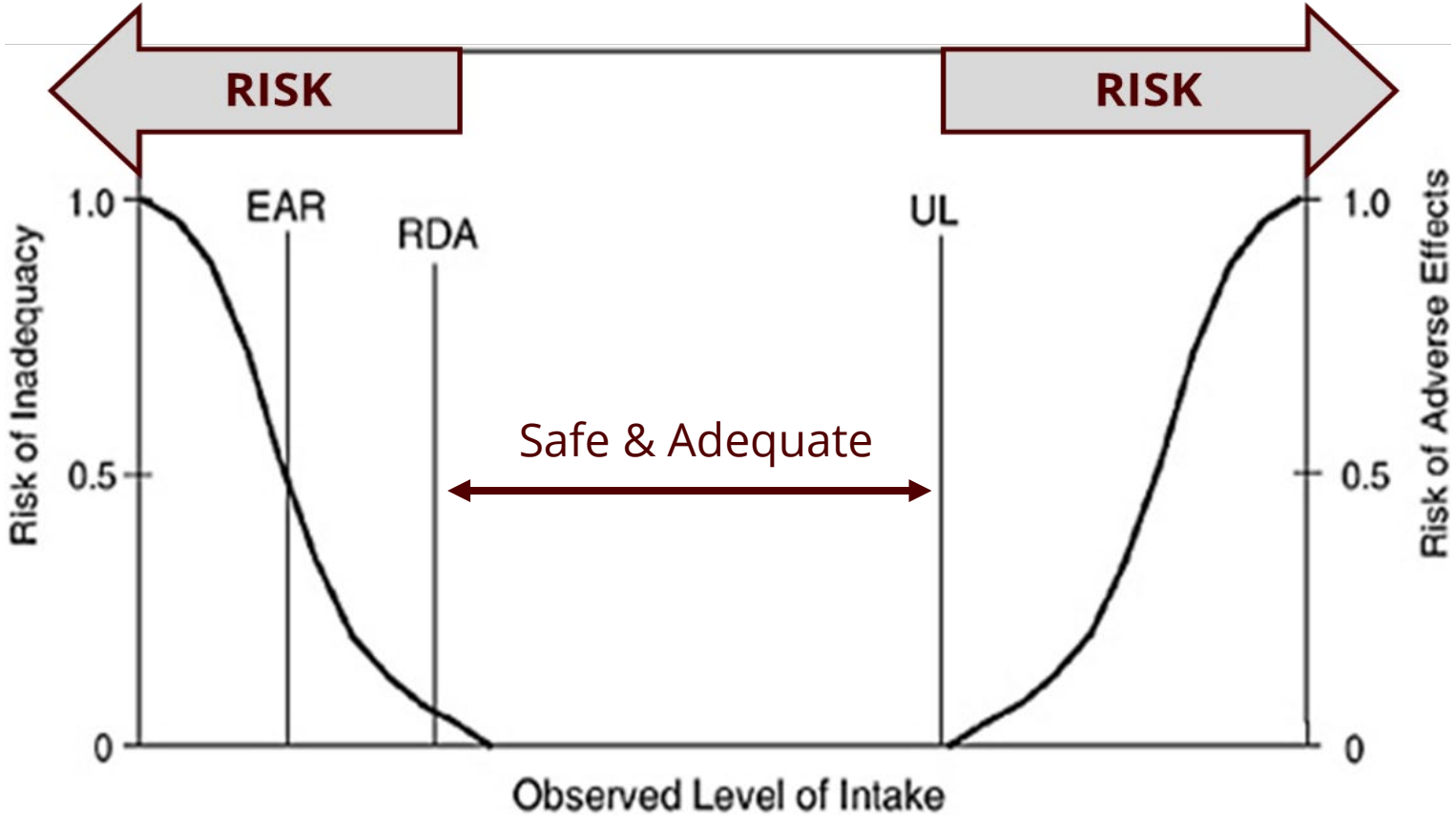
- Scientific and evidentiary issues related to the use of chronic disease endpoints for basing DRIs in the past
- Guiding principles for the application of Chronic Disease Risk Reduction (CDRR) values
- Application of the CDRR values to sodium
- Integration of CDRR values when estimating Acceptable Macronutrient Distribution Range (AMDRs)

Dietary Reference Intakes Framework

- DRI values based on:
  - Relationships between nutrient intakes and indicators of:
    - Adequacy
    - Adverse effects
  - Data from *apparently healthy populations*
  - **Chronic disease (CD) risk reduction *where sufficient data for efficacy and safety exist***

Institute of Medicine (US) Food and Nutrition Board. How Should the Recommended Dietary Allowances Be Revised? Washington (DC): National Academies Press (US); 1994.

U-SHAPED RISK CURVE



EAR: Estimate Average Requirement; RDA: Recommended Dietary Allowance; UL: Tolerable Upper Intake Level

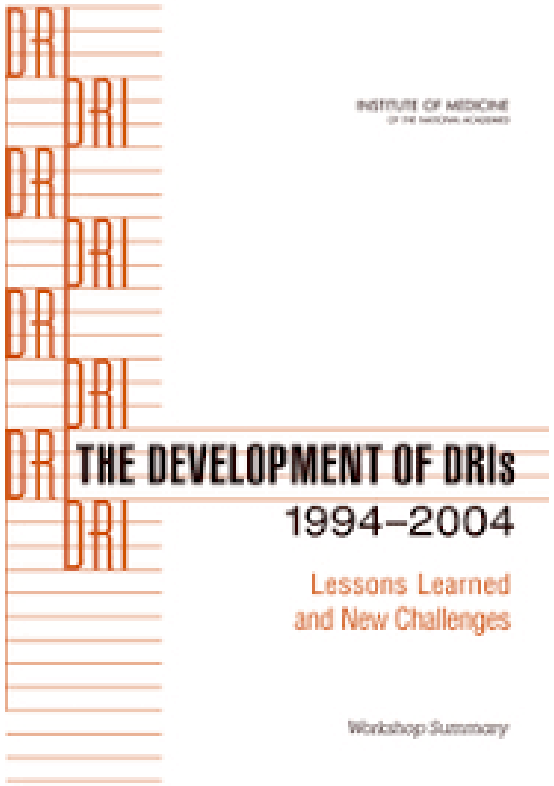
IOM. 1994. How Should the Recommended Dietary Allowances Be Revised? Food and Nutrition Board. Washington, DC: National Academy Press

Assumptions of the EAR/UL approach

- "Essentiality" of the substance
- Evidence of causality and dose response
- Biomarkers on causal pathway
- Threshold for adequacy and adverse effects
- Relevant population
- Absolute nature of the risk

- These don't always apply to ***food substance***-chronic disease (CD) relationships
- DRI values 1997-2005: When a CD endpoint used, Adequate Intake (AI) set due to a limitation of the "classic" DRI approach
  - Fluoride, fiber, potassium (AI 2019), calcium (EAR/RDA 2009), vitamin D (EAR/RDA 2009)

SCIENTIFIC AND EVIDENTIARY DIFFERENCES WHEN ESTIMATING REQUIREMENTS VS CHRONIC DISEASE RISK REDUCTION



Identified limitations when using CD endpoints for setting DRIs

Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group[1–3]

Elizabeth A Yetley,[4] Amanda J MacFarlane,[5] Linda S Greene-Finestone,[5] Cutberto Garza,[6–8] Jamy D Ard,[9] Stephanie A Atkinson,[10] Dennis M Bier,[11] Alicia L Carriquiry,[12] William R Harlan,[13] Dale Hattis,[14] Janet C King,[15–17] Daniel Krewski,[18] Deborah L O'Connor,[19,20] Ross L Prentice,[21,22] Joseph V Rodricks,[23] and George A Wells[24]*

- Evaluated key scientific issues in using CD endpoints for setting DRIs
- Provided *options* (with strengths and weaknesses) for whether and/or how CD endpoints can be used in the setting of DRI values
- **Not** a consensus report and **not** recommendations

- Institute of Medicine. 2008. The Development of DRIs 1994-2004: Lessons Learned and New Challenges: Workshop Summary. Washington, DC: The National Academies Press.
- Yetley et al. Am J Clin Nutr January 2017 vol. 105 no. 1 249S-285S

Scientific and evidentiary differences when assessing requirements vs chronic disease risk reduction

Consideration	Nutrient requirement	Chronic disease risk
Indicators/outcome	Disease of deficiency Validated surrogate indicator - responds to nutrient intake and on the causal pathway	Chronic disease Validated surrogate endpoint – may respond to nutrient intake and be predictive of outcome
Population affected by inadequate intake	100% of the population will develop disease of deficiency	<100% (usually much less) will develop the CD, highly variable, CD-dependent
Population prevented with adequate intake	100%	<100%, highly variable, risk reduction (vs. prevention)
Variables that affect indicator	Specific essential nutrient Other unmodifiable factors (age, sex, genetics, etc) may play a role	Nutrient is only one of many variables that can include physical activity, body weight, environmental factors, age, sex, genetics, etc.
Time course	Relatively short depending on severity of limited intake	Very long (years, decades, lifespan)

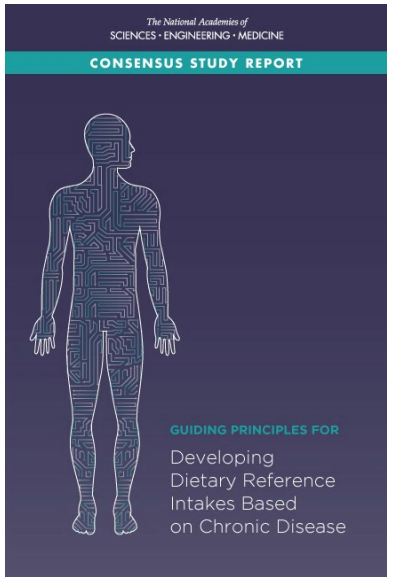
Scientific and evidentiary differences when assessing requirements vs chronic disease risk reduction

Consideration	Nutrient requirement	Chronic disease risk
Type of available evidence	RCT, intervention studies, balance studies etc	Possibly RCTs and intervention studies but usually with surrogate endpoints Observational studies
Relationship between intake and indicator	Inadequate intake impairs function	Relationship between nutrient and disease risk may vary (linear, nonlinear, multimodal) A different relationship with different chronic diseases Different nutrients will have different relationships with a single chronic disease
Intake assessment	Measured or established/validated indicators of intake	Self-reported – inherent systematic bias and random errors

National Academies of Sciences, Engineering, and Medicine. 2017. Guiding principles for developing Dietary Reference Intakes based on chronic disease. Washington, DC: The National Academies Press.
Yetley E.A., A.J. MacFarlane, L.S. Green-Finestone, B.G. Garza, et al. Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: Report from a Joint US/Canadian-sponsored working group. *Am J Clin Nutr* 105(1): 249S-285S. 2017.

NASEM Guiding Principles for using CD Endpoints Released August 2017

- *Options Report* was the foundation for developing principles for basing DRIs on chronic disease endpoints
- 11 recommendations



National Academies of Sciences, Engineering, and Medicine. 2017. Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease. Washington, DC: The National Academies Press.

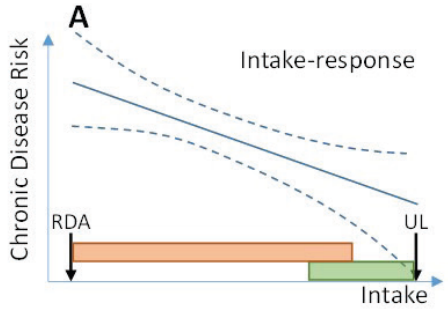
Chronic Disease Risk Reduction (CDRR) Value

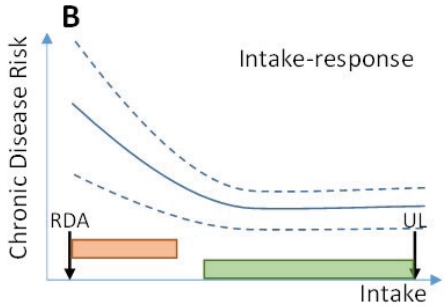
- Use chronic disease/qualified surrogate markers as endpoints
- ≥ Moderate level of evidence (GRADE) for BOTH causality and intake-response
- Range of beneficial intakes
  - Cut-off above/below which risk of the CD increases
- Extrapolation only to populations similar to those studied in underlying factors related to the CD
- Differentiated from ULs – ULs based on acute adverse reactions/toxicity endpoints only, and the CDRR value, even when risk for CD is decreasing with increasing intake, cannot be higher than the UL
- When risk overlaps
  - Health risk/benefit analyses to be conducted and the method to characterize and decide on the balance must be transparent

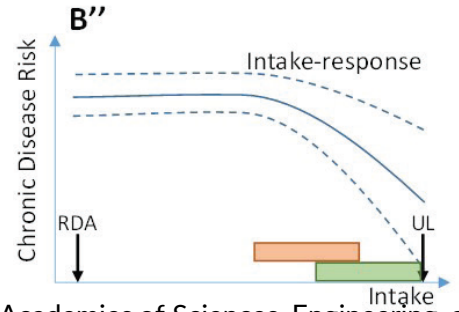
National Academies of Sciences, Engineering, and Medicine. 2017. *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease*. Washington, DC: The National Academies Press.

CDRR ranges will depend on the level of evidence and shape of relationship

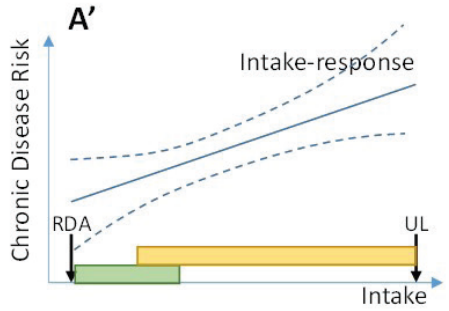
CD risk decreases with increasing intake

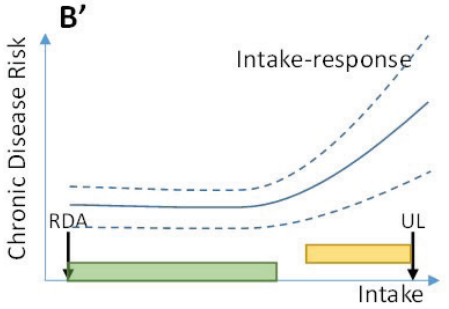


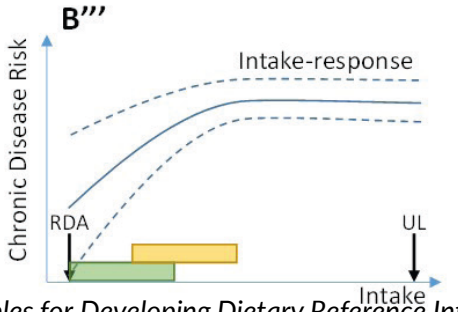




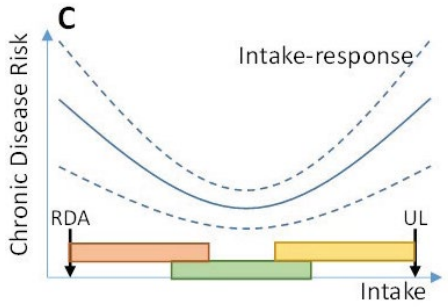
CD risk increases with increasing intake







U-shaped CD risk with increasing intake



Possible Dietary Reference Intake Ranges for a Single Chronic Disease

= Acceptable Range of Intakes

= Range of Beneficial Decreased Intakes

= Range of Beneficial Increased Intakes

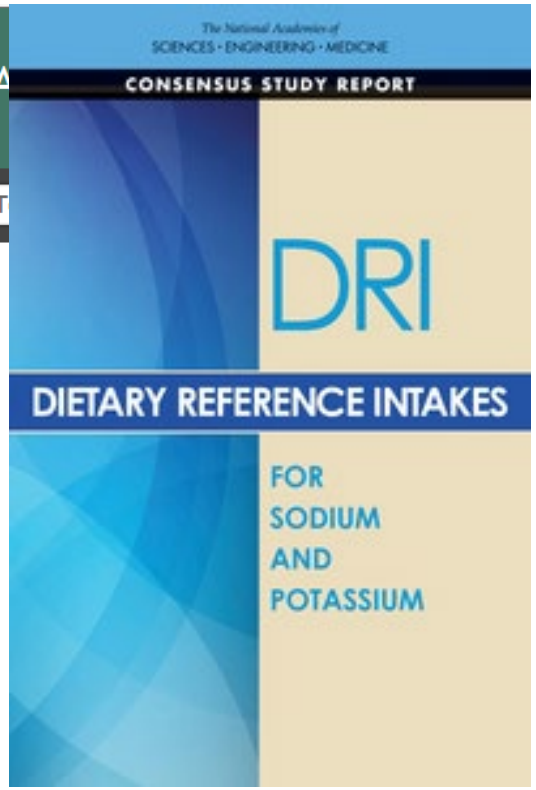
For multiple chronic diseases, the overlaps between different ranges with different slopes would need to be compared.

National Academies of Sciences, Engineering, and Medicine. 2017. *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease*. Washington, DC: The National Academies Press.

APPLICATION OF THE CDRR

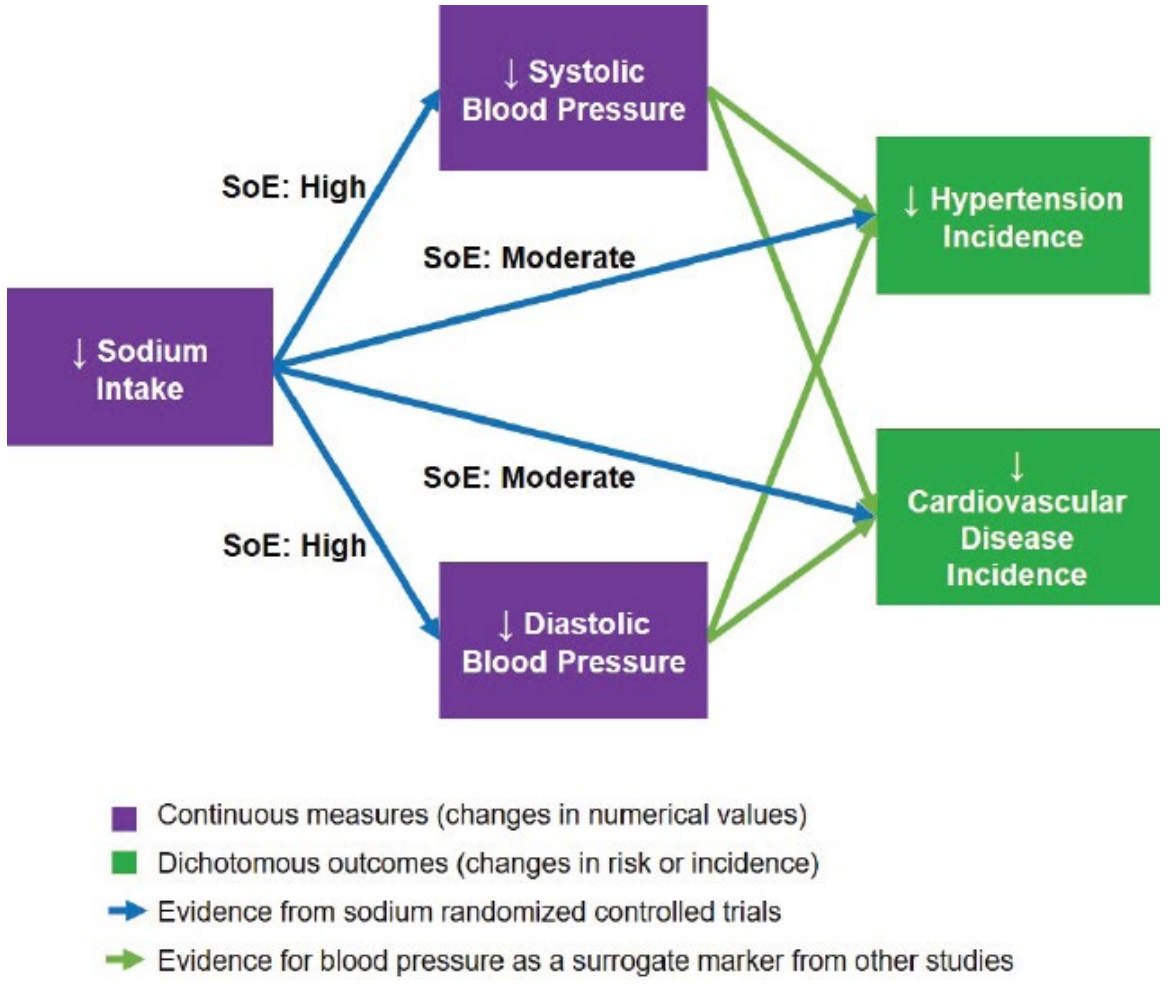
Sodium/potassium review – March 2019

- First DRI review to apply the new Guiding Principles



National Academies of Sciences, Engineering, and Medicine. 2019. Dietary Reference Intakes for Sodium and Potassium. Washington, DC: The National Academies Press.

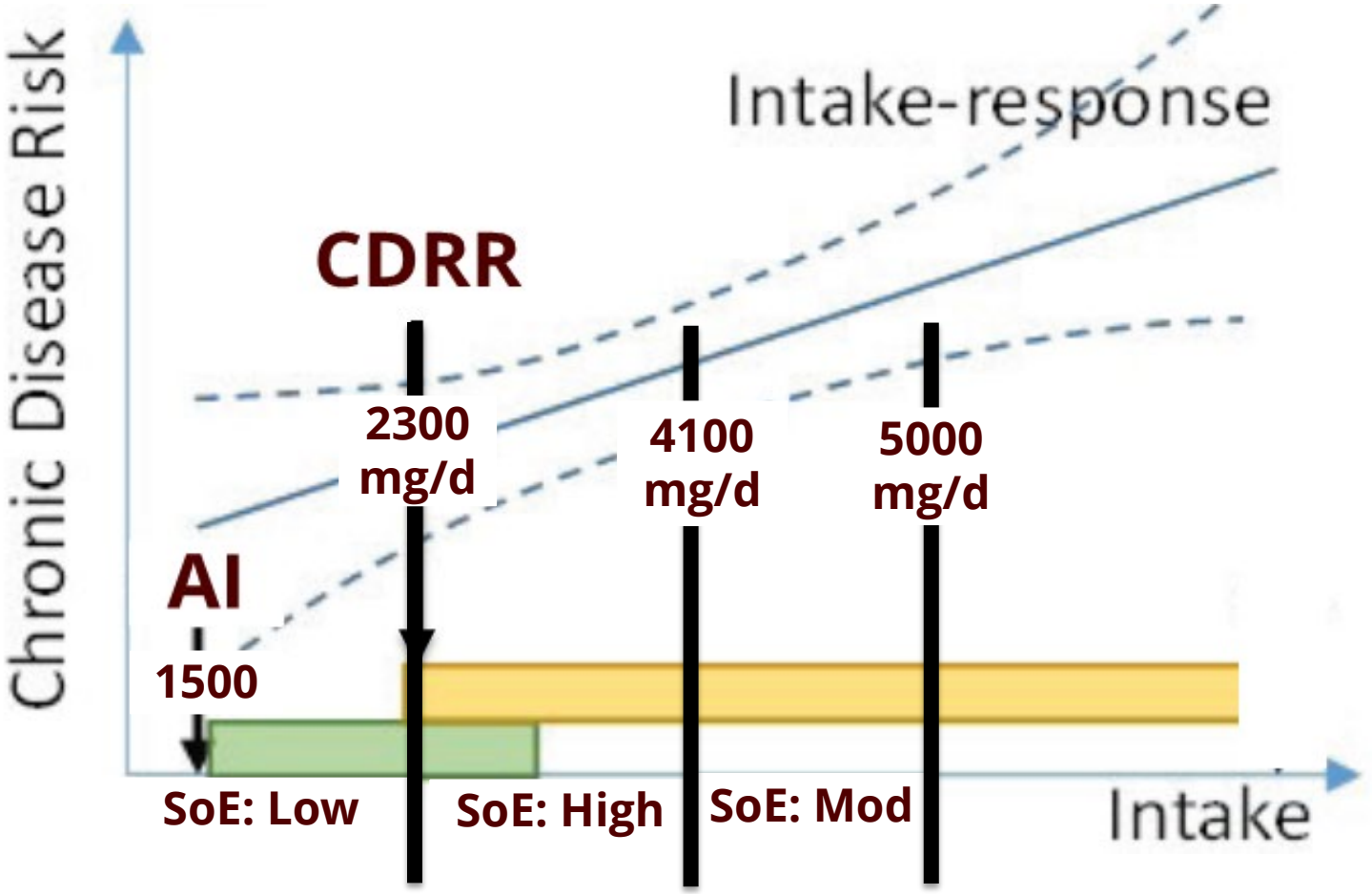
ANALYTIC FRAMEWORK FOR SODIUM CDRR



Approach allowed for the consideration and integration of 4 indicators of CVD risk

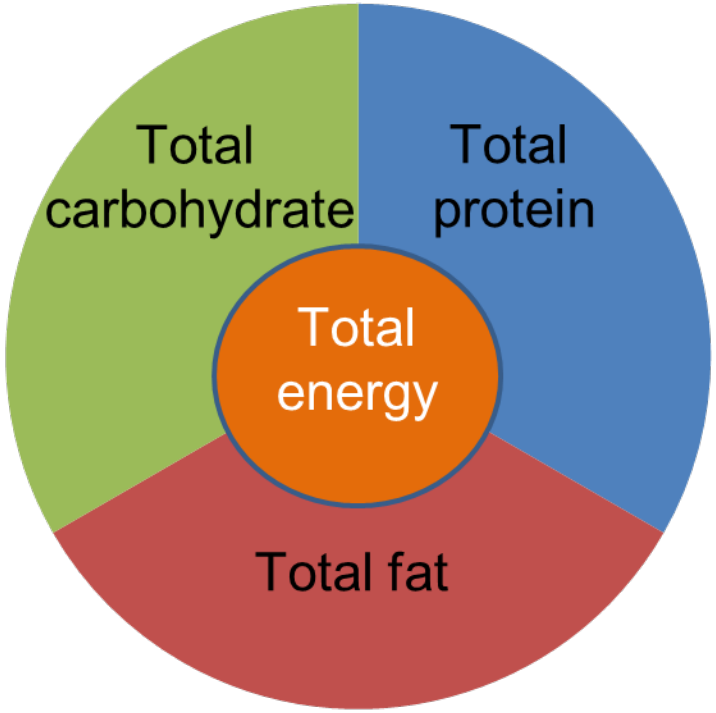
National Academies of Sciences, Engineering, and Medicine. 2019. *Dietary Reference Intakes for Sodium and Potassium*. Washington, DC: The National Academies Press.

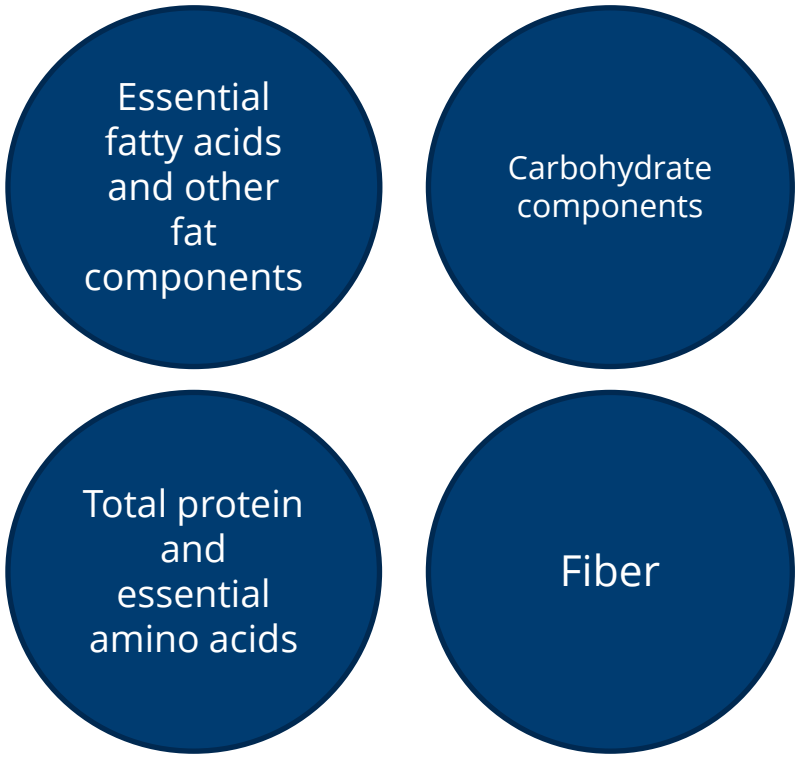
CDRR: The intake above which intake reduction is expected to reduce CD risk



INTEGRATION OF CDRR VALUES IN THE ASSESSMENT OF CD RISK FOR DETERMINING AMDRS

Comparing the CDRR and AMDR approaches





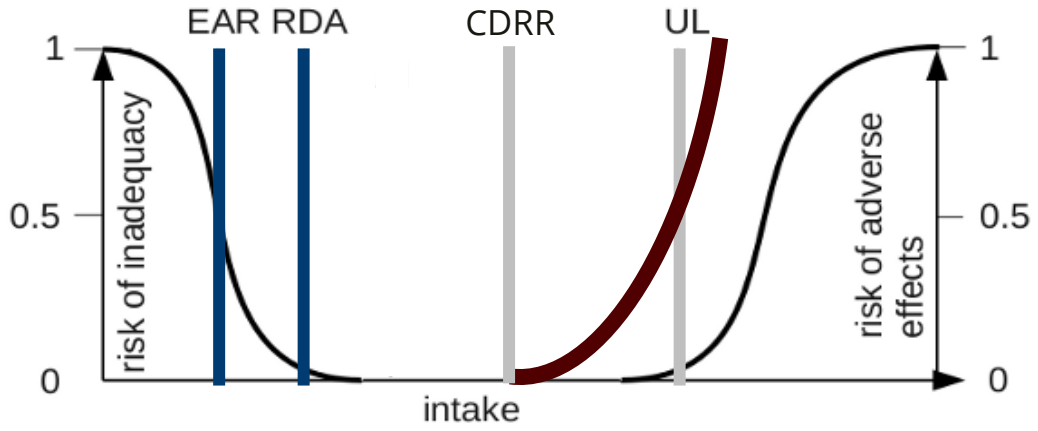
- Acceptable Macronutrient Distribution *Range*
- Purpose: Reduced chronic disease risk while providing adequate intakes of essential nutrients
- Intake for an energy source (protein, fat, or carbohydrate), expressed as % total energy
- Includes concept of energy balance

- Flexible
  - Different shapes and directions of associations
  - Ranges and/or cut-points for intakes
- Set independently of other DRI values (ie, EAR/RDA, UL)
- Standard of evidence – moderate for causality and D-R
- Could apply to total protein and other macronutrient components, where there is sufficient evidence

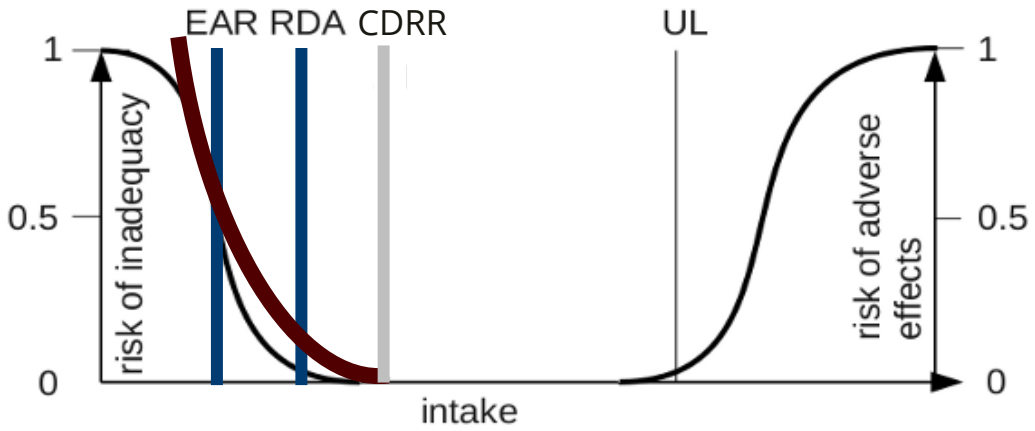
Establishing macronutrient ranges through an order of operation and the U-Shaped Risk curve

1. **Estimated energy requirements** need to be established
    1. Usual intakes of the macronutrients assessed
2. **Set EAR/RDA, UL, CDRR values** based on the available evidence and where the standard of evidence is achieved for each macronutrient and component
3. **If setting ranges to achieve energy balance**, **the order in which the macronutrients are addressed is key** - needs to be based on the available evidence for requirements (1), adverse effects (2) and CD risk reduction (3). Which means,
    1. Protein and essential amino acids
    2. Essential fatty acids and other fats
    3. Carbohydrate, fiber, sugars
4. **Options for building ranges**:
    a. An AMDR could be developed for each macronutrient based on the "safe and adequate" range of intakes considering the integration of the evidence for EAR, UL and CDRR values related to that macronutrient in ORDER of priority macronutrients (ie, protein first), and constrained by total energy
        a. Note: Often insufficient evidence to estimate quantitative reference values that would inform AMDR boundaries

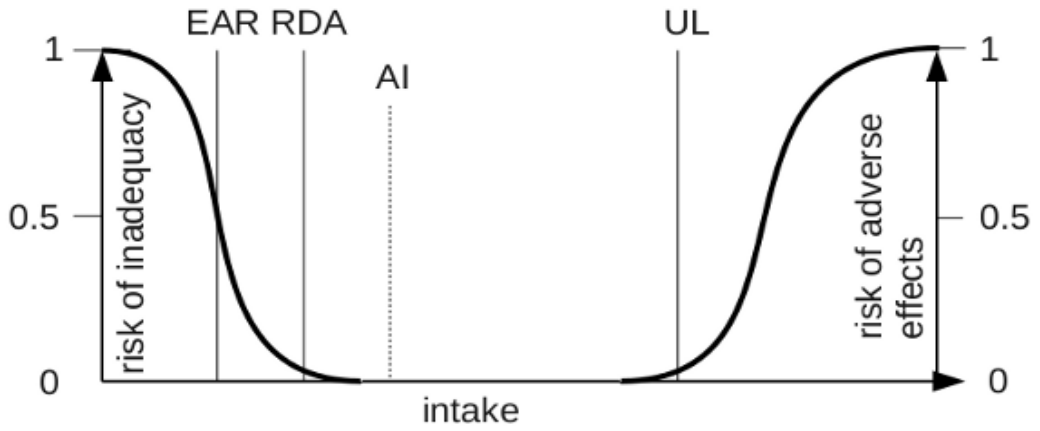
1. Total Protein and Essential Amino Acids



2. Essential FAs



3. Carbohydrate



Energy **COULD** be the final constraint for combining macronutrient intakes to ranges that provide energy balance

OR Leave the application of energy to development of dietary patterns/guidance.

Option B: Better yet, don't build AMDRs

Dietary planning, when incorporating the suite of EAR/RDA, UL, CDRR values will automatically result in patterns within specific ranges to achieve the health outcomes associated with each of macronutrients/components.

Avoids the need for qualifying statements, avoids blurring the lines between DRIs and dietary guidance, and avoids use of AMDR ranges for fats and carbohydrates as targets for intake

In summary…

- "Classic" DRI approach works well for estimating adequate intakes/adverse effects for essential nutrients
- It has not worked well for CD endpoints
  - Assumptions made for EAR/UL do not always apply
  - Available evidence differs significantly from that available for establishing essentiality/toxicity
- The Guiding Principles for using chronic disease endpoints established a framework for setting DRIs based on CD endpoints including the establishment of a *standard of evidence*
- Sodium CDRR was the first application of the CDRR approach
- The Guiding Principles should be applied to all nutrients and food substances moving forward, including the macronutrients
- An opportunity to clarify the role of the DRIs in dietary planning

Acknowledgements

Canadian Interdepartmental/Interagency DRI Steering Committee

US DRI Subcommittee

Canadian-US Joint DRI WG (during CDRR development)

- Samantha Adas (NIH)
- Janet de Jesus (HHS)
- Krista Esslinger (HC)
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- Chris Lynch (NIH)
- Amanda MacFarlane (HC)
- Matthew Parrot (HC)
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- Pam Starke-Reed (USDA)
- Eve Stoody (USDA)
- Essie Yamini (FDA)

DRI-Chronic Disease Workshop Panel

- Beth Yetley (NIH)
- Amanda MacFarlane (HC)
- Linda Greene-Finestone (HC)
- Cutberto Garza (Chair)
- Jamy Ard
- Stephanie Atkinson
- Dennis Bier
- Alicia Carriquiry
- Janet King
- Daniel Krewski
- George Wells
- William Harlan
- Dale Hattis
- Deborah O'Connor
- Ross L. Prentice
- Joseph V. Rodricks

NASEM Committee on the Development of Guiding Principles for the Inclusion of Chronic Disease Endpoints in Future Dietary Reference Intakes

NASEM Committee to Review the Dietary Reference Intakes for Sodium and Potassium

References

- Institute of Medicine (US) Food and Nutrition Board. How Should the Recommended Dietary Allowances Be Revised? Washington (DC): National Academies Press (US); 1994.
- Institute of Medicine. 2008. The Development of DRIs 1994-2004: Lessons Learned and New Challenges: Workshop Summary. Washington, DC: The National Academies Press.
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- MacFarlane, A.J., M.E. Cogswell, J. de Jesus, L. Greene-Finestone, et al. A report of activities related to the Dietary Reference Intakes from the Joint Canada-US Dietary Reference Intakes Working Group. *Am J Clin Nutr* 109: 1-9. 2019.
- National Academies of Sciences, Engineering, and Medicine. 2017. Guiding principles for developing Dietary Reference Intakes based on chronic disease. Washington, DC: The National Academies Press.
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QUESTIONS?

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