The DRI Process: Considerations for Assessing Omega-3 Fatty Acids and Cardiovascular Disease in the DRI Framework of Chronic Disease Risk

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Conflict of Interest

• Member, DRI Committee for Calcium and Vitamin D
• Member, DRI Committee for Sodium and Potassium
Objectives

• Understand how the Expanded Dietary Reference Intakes include CDRR and chronic disease outcomes

• Relate what is needed for the nature and strength of evidence to consider a chronic disease outcome
  – Causality of Relationship
  – Intake-Response Relationship

• Consider implications for omega 3 fatty acids
Assumptions of DRI Framework: Adequacy

• Meets needs of ‘apparently healthy population’
  – Includes a diverse population
    • Many vary in their health conditions (obesity, etc.)
    • Many are at risk for one or more chronic diseases
  – Excludes those who
    • Have chronic disease that requires management with medical foods and medical nutrition therapy
    • Are malnourished or undernourished
    • Have diseases resulting in malabsorption or requiring dialysis
    • Have altered energy needs due to disability or altered mobility

• Need varies, generally normally distributed across population
Expanded Dietary Reference Intakes with CDRR and Chronic Disease Outcomes

Risk of Inadequacy

Risk of Toxicity

INTAKE
Expanded DRI Framework Resulted in Change for UL for Sodium in 2019

<table>
<thead>
<tr>
<th>UL for Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2005</strong></td>
</tr>
<tr>
<td>2300 mg/d based on sodium-blood pressure relationship (a chronic disease indicator outcome)</td>
</tr>
<tr>
<td><strong>2019</strong></td>
</tr>
<tr>
<td>Not determined due to lack of toxicologic indicator</td>
</tr>
</tbody>
</table>
Expanded Dietary Reference Intakes with Chronic Disease Risk Reduction (CDRR) and Chronic Disease Outcomes
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DRI and Possible Intake Relationships for Increased Risk with Increased Intakes

Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease Outcomes. 2017, National Academies Press
### Distinctions Between DRI for Adequacy/Toxicity and Chronic Disease

<table>
<thead>
<tr>
<th>DRI for Adequacy/Toxicity</th>
<th>DRI for Chronic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needed because of deficiency (essential) or toxicity of a nutrient:</td>
<td>Not warranted unless sufficient evidence exists for nutrient or naturally-occurring food substance (NOFS) because risk of chronic disease:</td>
</tr>
<tr>
<td>• Affects everyone if intake is inadequate or excessive</td>
<td>• Varies by individual, age and lifestage</td>
</tr>
<tr>
<td>• Is caused by single nutrient</td>
<td>• Is relative and can be small</td>
</tr>
<tr>
<td>• Is prevented by nutritional interventions</td>
<td>• Related often to many factors (individual and environmental)</td>
</tr>
<tr>
<td></td>
<td>• Is only partly ameliorated by nutritional intervention</td>
</tr>
</tbody>
</table>

Adapted from *Dietary Reference Intakes for Sodium and Potassium. 2019*, National Academies Press.
DRI Decision-Making Steps: A Systematic Framework

1. Health Outcome (Hazard) Identification & Selection
   (Causal Relationship Based on Systematic Review & Evaluation of Evidence)

2. Dose-Response Assessment
   (Hazard Characterization)

3. Intake Assessment
   (Prevalence of Intakes Outside DRI)

4. Risk Characterization
   (Public Health Implications)

*Based on nutrient risk assessment models (WHO, 2006)
Evidence for Selection of Adequacy/Toxicity Outcomes

- Indicator of status (biomarkers), on the causal pathway for disease of deficiency
Evidence for Selection of Adequacy/Toxicity Outcomes

• Indicator of status (biomarkers), on the causal pathway for disease of deficiency or adverse effect
direct evidence of disease of deficiency or depletion/repletion studies

• High certainty of causal & intake-response relationships (RCT, metabolic/balance, depletion/repletion studies)

Insufficient Evidence to Support Selection of Adequacy Indicator for Sodium or Potassium: Approach to AI Differed

**Potassium**

Median intakes of healthy US/CN populations appropriate for AI (No CDRR)

- 2005 AI 19+ 4000 mg/d
- 2019 AI (mg/d)
  - M 19+ 3400
  - F 19+ 2600

**Sodium**

Median sodium intakes > CDRR so median intake of ‘healthy’ US/CN population not appropriate for AI

- Committee concluded lowest levels of sodium intake evaluated in best designed RCT and evidence from best designed balance studies (limited in number) congruent in adults and used to set AI.
- Extrapolated to children 1-18 yr based on sedentary EER.
- AI for 19+ yr 1500 mg/d

**FIGURE 4-2** Median usual potassium intake of U.S. and Canadian normotensive adults 19 years of age and older.
At least moderate strength of evidence (GRADE) for causal association of nutrient or NOFS with chronic disease outcomes

- Assess strength of evidence for single chronic disease outcome (IDEAL) or single qualified surrogate outcome individually (no aggregate of outcomes)
- Nature of evidence may vary from that for adequacy
  - More evidence may be from observational studies than RCTs
  - Lower certainty of causal relation
    - Inherently higher risk of bias
      - Selection, confounding, etc.
      - Methodologic (intake assessment, exposure-disease continuum across lifespan, outcome assessment)
    - More use of qualified surrogate outcomes
    - Publication
Evidence for Selection of Chronic Disease Outcomes: Qualifying a Surrogate Outcome

For reproducible, analytically-validated surrogate outcomes, evidentiary process requires that the surrogate outcome:

- Is on causal pathway (observational and small intervention studies)
- Is concordant with changes in health outcome with specific nutritional intervention (rigorous clinical trials)
  - Explains a clinically significant proportion of response to nutritional intervention
- Predicts accurately (prognostic value) effect of nutritional intervention on clinical outcome (rigorous clinical trials)

Adapted from Russell et al. Opportunities and challenges in conducting systematic reviews to support the development of nutrient reference values: vitamin A as an example. American Journal of Clinical Nutrition. 2009; 89:728–33

Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease Outcomes. 2017, National Academies Press
Use GRADE to Evaluate Strength of the Evidence

GRADE = Grading of Recommendations: Assessment, Development and Evaluation

Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease Outcomes. 2017, National Academies Press
Evidence for Selection of Chronic Disease Outcome

• **Moderate** strength of evidence (GRADE) for **intake does-response** of nutrient or NOFS with chronic disease outcomes

Potassium – a case study

- Moderate evidence for causal relationship of potassium supplementation with reductions in blood pressure (a qualified surrogate outcome)
- Lack of evidence for intake-response relationship
  - Heterogeneity across studies
  - Lack of supportive evidence for benefit of potassium on CVD prevention
- No CDRR specified
<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Na and CVD Incidence</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCYP I (rev), 2007</td>
<td>0.48 [0.25, 0.92]</td>
<td></td>
</tr>
<tr>
<td>TCYP II (rev), 2007</td>
<td>0.79 [0.67, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Appel (TONE), 2001</td>
<td>0.78 [0.52, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Chang (rev), 2006</td>
<td>0.59 [0.37, 0.95]</td>
<td></td>
</tr>
<tr>
<td>China SSS, 2007</td>
<td>1.58 [0.62, 4.79]</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 10-1** Random-effects meta-analysis of trials of effects of sodium reduction on cardiovascular disease incidence.
### Sodium: Summary of Evidence for Causal Association with Chronic Disease

**TABLE 10-8 GRADE Summary of Findings Used to Determine the Causal Relationship Between Reduction in Sodium Intake and Chronic Disease Risk**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Duration of Study or Follow-Up</th>
<th>Study Results and Measurements</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease event incidence</td>
<td>2.5 to 12 years</td>
<td>Relative risk: 0.74 [95% CI: 0.58, 0.93]</td>
<td>Moderate, due to imprecision</td>
</tr>
<tr>
<td>Hypertension incidence</td>
<td>2.5 to 4 years</td>
<td>Relative risk: 0.79 [95% CI: 0.67, 0.93]</td>
<td>Moderate, due to imprecision</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>4 weeks to 4 years</td>
<td>See Table 10-6</td>
<td>High</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>4 weeks to 4 years</td>
<td>See Table 10-7</td>
<td>High</td>
</tr>
</tbody>
</table>
Analytic Framework for the Relationship of Sodium Intake and Chronic Disease and Qualified Surrogate Outcomes (Fig. 10-13)
## Sodium: Summary of Evidence for Intake-Response and Reduction of Chronic Disease Risk

<table>
<thead>
<tr>
<th>Sodium Intake Range (mg/d)</th>
<th>Chronic Disease Indicator</th>
<th>Nature of Evidence</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;8000</td>
<td>CVD, HTN, SBP, DBP</td>
<td>No RCT/low risk bias observational studies</td>
<td>Insufficient</td>
</tr>
<tr>
<td>5000-8000</td>
<td>CVD, HTN, SBP, DBP</td>
<td>No RCT/1 low risk bias CVD observational study</td>
<td>Insufficient</td>
</tr>
<tr>
<td>4100-5000</td>
<td>CVD, HTN SBP, DBP</td>
<td>No RCT/1 low risk bias CVD observational study 11(SBP)-10(DBP) RCT</td>
<td>Moderate (indirectness)</td>
</tr>
<tr>
<td>2300-4100</td>
<td>CVD, HTN SBP, DBP</td>
<td>3 RCT/1 low risk bias CVD observational study 21 RCT</td>
<td>High</td>
</tr>
<tr>
<td>1000-2300</td>
<td>CVD, HTN SBP, DBP</td>
<td>No RCT/1 low risk bias CVD observational study 19 RCT</td>
<td>Low, (inconsistency &amp; indirectness)</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>CVD, HTN, SBP, DB_</td>
<td>No RCT or low risk bias observational studies</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
Specifying Sodium CDRR Evidence for Causal and Intake Response Relationship for Reduction of Chronic Disease Risk

CDRR set at lowest sodium intake level 2300 mg/d in range of 2300-5000 mg/d, with high to moderate evidence of reduction of cardiovascular disease based on several interrelated indicators.

Benefit of reducing intakes above 2300 up to 5000 mg/d

FIGURE 10-27 Spline plot of the hazard ratio for cardiovascular disease by mean sodium excretion from observational follow-up of Trials of Hypertension Prevention studies.
Implications for Omega 3 FA and Chronic Disease

• Is there at least moderate evidence for **causal association AND intake response** needed for CDRR?
  – What is the analytic framework for intake of omega 3 FA and chronic disease?
  – Are surrogate markers qualified?
  – Is there sufficient intake-response data to determine the nature of the relationship
### Recent Meta-Analyses & Evidence Summaries Relative to Evidence Requirements for CDRR

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Relevant Population</td>
<td>Includes in some studies those with prior history of CHD, stroke, diabetes</td>
<td>Includes in some studies those with prior history CHD/CVD, diabetes,</td>
</tr>
<tr>
<td>Relevant intervention</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Multiple outcomes each analyzed individually</td>
<td>Y (except aggregate major vascular events)</td>
<td>Y (except some composite endpoints)</td>
</tr>
<tr>
<td>Indicators on causal pathway (analytic framework)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Surrogate markers qualified</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>GRADE used to evaluate strength of evidence</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Moderate to High evidence for causal relationship</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Moderate to High evidence for intake-response relationship</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Sufficient evidence to determine nature of intake-response relationship</td>
<td>Y (if moderate to high strength evidence)</td>
<td>Y?</td>
</tr>
</tbody>
</table>
Implications for Omega 3 FA and Chronic Disease

• Is there at least moderate evidence for causal association AND intake response needed for CDRR?
  – Unclear as evidence has not been evaluated with GRADE

• What is level of evidence for primary prevention in those who are apparently healthy with no prior history of CVD, CHD or relevant outcomes?
  – Will need to address question of inclusion of diabetes given its medical nutrition therapy and recognizing the increased risk for CVD?

Included populations for AHRQ Systematic Review of Sodium and Potassium Intake: Effects on Chronic Disease Outcomes (Newberry et al., 2018)
Implications for Omega 3 FA and Chronic Disease:

- Is there at least moderate evidence for **causal association AND intake response** needed for CDRR?
  - Unclear as evidence has not been evaluated with GRADE

- **What is level of evidence for primary prevention in those who are apparently healthy with no prior history of CVD, CHD or relevant outcomes?**
  - Will need to address question of inclusion of diabetes given its medical nutrition therapy and recognizing the increased risk for CVD?

- What is the analytic framework for intake of omega 3 FA and chronic disease?
  - Unclear

- Is there sufficient intake-response data to determine the nature of the relationship
  - Likely based on metaanalyses (Hu et al.) if strength of evidence is moderate to high
Summary

• Expanded Dietary Reference Intakes include CDRR and chronic disease outcomes
• Moderate to high strength of evidence (GRADE) needed for nutrient/NOFS intake for chronic disease for both
  – Causality of Relationship
  – Intake-Response Relationship
• Key Implications for Omega 3 Fatty Acids
  – Strength of evidence using GRADE
  – Relevance of inclusion in some studies of participants with existing CVD/CHD decreases in some studies to apparently healthy population needed for DRI