Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease

Highlights of the Consensus Report
Sponsors

Agricultural Research Service, USDA
Health Canada
National Cancer Institute, NIH, HHS
National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Office of Dietary Supplements, NIH
Office of Disease Prevention and Health Promotion, HHS
Centers for Disease Control and Prevention, HHS
Food and Drug Administration, HHS
Study Focus

• Potential organizational process for developing dietary reference intakes (DRIs) based on effects of nutrients or other food substances (NOFS) on chronic diseases

• Guiding principles and recommendations for addressing conceptual and methodological challenges
The Committee

- Shiriki K. Kumanyika (Chair), Drexel University
- Cheryl A. M. Anderson, University of California-San Diego
- Susan I. Barr, University of British Columbia
- Kathryn G. Dewey, University of California-Davis
- Gordon Guyatt, McMaster University
- Janet C. King, Children’s Hospital Oakland Research Institute
- Marian L. Neuhouser, Fred Hutchinson Cancer Research Center
- Ross L. Prentice, Fred Hutchinson Cancer Research Center
- Joseph Rodrigs, Ramboll Environ Inc.
- Patrick J. Stover, Cornell University
- Katherine L. Tucker, University of Massachusetts
- Robert B. Wallace, The University of Iowa

- Consultant: Weihsueh A. Chiu, Texas A&M University
Background and Approach

Chapters 1 to 3
• What are Dietary Reference Intakes?
• How are they used?
• How would a process focused on chronic diseases be different from what has been done previously?
What are Dietary Reference Intakes?
Examples of DRIs Uses

Population Level
- Food labeling
- Food fortification
- Federal supplemental food program planning
- Military DRIs
- Nutrition surveillance

Individual Level
- Dietary Guidance for the U.S. Population
- Clinical assessment
# Traditional DRIs vs. DRIs for Chronic Disease

<table>
<thead>
<tr>
<th>Traditional DRIs</th>
<th>Chronic Disease DRIs</th>
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<tbody>
<tr>
<td>DRIs for essential nutrients are needed because deficiencies:</td>
<td>Are not warranted unless sufficient evidence exists because:</td>
</tr>
<tr>
<td>a) will affect everyone, if intake is inadequate</td>
<td>a) risk to acquire CDs varies by individual</td>
</tr>
<tr>
<td>b) are caused by one nutrient</td>
<td>b) chronic diseases are often related to many risk factors (genetic, environmental)</td>
</tr>
<tr>
<td>c) are prevented by nutritional interventions</td>
<td>c) nutritional interventions will only partly ameliorate the risk of CD</td>
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**The National Academies of Sciences Engineering Medicine**
Statement of Task: Options Report

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


Core Questions in Options Report

(1) What are acceptable levels of confidence that the relationship between a NOFS and a chronic disease is causal?

(2) If a causal relationship exists, what are acceptable levels of confidence in the data to establish an intake-response relationship and what are approaches for identifying and characterizing the intake-response relationship and, if appropriate, to recommend DRIs?

(3) What should be the organizational process for recommending chronic disease DRIs?
Statement of Task

Methodological guidance to future DRI committees

• Assess options presented in the Options Report

• Determine guiding principles for the inclusion of chronic disease endpoints for food substances that will be used by future National Academies committees in establishing Dietary Reference Intakes (DRIs)

• Provide justification for the selection (and non-selection) of options that served as the basis for the guiding principles, including additions not considered in the Options Report
DRI Process

See Figure 1-2 in report
Approach of the Committee

- Initial clarifications
- Review *Options Report*
- Examine relevant challenges in past DRIs
- Review current methods of conducting systematic reviews and rating quality of evidence, with particular attention to evidence relevant to NOFS and chronic diseases
- Review current methods of characterizing intake-response relationships
Initial Clarifications

• Population of interest

• NOFS definition: nutrients that are essential or conditionally essential, energy nutrients, or other naturally occurring bioactive food components (e.g., phytoestrogens)

• NOFS in foods vs. supplements

• Limited experience in making quantitative associations between NOFSs and chronic disease up to date
Requirements to develop a DRI

1) Evidence that intake of a NOFS is casually related to risk of a chronic disease (with a specified level of certainty)

2) Quantitative data on the relationship between NOFS intake and risk of chronic disease (with a specified level of certainty)

3) Specification of the range of intakes over which chronic disease risk is reduced (based on the above analyses and specified public health goals)
Main Challenges for DRI Committees

• Variations in health effects depending on the chemical form of a nutrient, and how an individual digests and makes a nutrient available

• The need to determine nutrient intake with accuracy

• How to identify the contribution of a single nutrient (or a group of nutrients) to chronic disease when many other variables (genetic, environmental, and behavioral) also affect chronic diseases

• Strengths and limitations of randomized controlled trials and observational study designs for evaluation NOFS-chronic disease associations
Recommendations
Measuring Dietary Intake and Chronic Disease

Chapters 4 and 5
How should dietary intake measures be evaluated?

Recommendation 1. Until better intake assessment methodologies are developed and applied widely, DRI committees should strive to ensure that random and systematic errors and biases of nutrient or other food substance (NOFS) exposure assessment methodologies are considered in their evidence review. In the long term, research agendas should include accelerated efforts to improve NOFS exposure assessments for application in studies of chronic disease risk.
Recommendation 2. The ideal outcome used to establish chronic disease DRIs should be the chronic disease of interest, as defined by accepted diagnostic criteria, including composite endpoints, when applicable. Surrogate markers could be considered with the goal of using the findings as supporting information of results based on the chronic disease of interest. To be considered, surrogate markers should meet the qualification criteria for their purpose.
Confidence about the Causal Relationship between a NOFS and Chronic Disease

Chapter 6
What are acceptable levels of confidence that the relation is causal?

Recommendation 3. DRI committees should use GRADE* in assessing the certainty of the evidence related to the causal association between nutrient or other food substances and chronic diseases. Using GRADE, the committee recommends that a decision to proceed with development of chronic disease DRIs be based on at least moderate certainty that a causal relationship exists and on the existence of an intake-response 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/](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 with a high rating, observational studies with a low rating.

<table>
<thead>
<tr>
<th>Rating is then modified downward:</th>
<th>Rating is then modified upward:</th>
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<tbody>
<tr>
<td>✓ Study limitations</td>
<td>✓ Large magnitude of effect</td>
</tr>
<tr>
<td>✓ Imprecision</td>
<td>✓ Dose response is observed</td>
</tr>
<tr>
<td>✓ Inconsistency of results</td>
<td>✓ Confounders likely minimize the effect</td>
</tr>
<tr>
<td>✓ Publication bias likely</td>
<td></td>
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Final rating for each outcome is ‘high’, ‘moderate’, or ‘low’

**NOTE:** The criteria for modifying a rating downward or upward are specified in detail in the GRADE handbook.
Rationale for recommending use of GRADE

• Meets criteria for an appropriate evidence review tool

• Is in wide use and applicable to nutrition policy questions

• Has criteria for assessing strength of recommendations
Characterizing the Intake-Response Relationship and Developing Chronic Disease DRIs

Chapter 7
Recommendation 4. The committee recommends the use of a single outcome indicator on the causal pathway. However, when a single food substance reduces the risk of more than one chronic disease, reference values could be developed for each chronic disease.
When should intake–response data be extrapolated?

**Recommendation 5.** The committee recommends extrapolation of intake-response data for chronic disease Dietary Reference Intakes only to populations that are similar to studied populations in the underlying factors related to the chronic disease of interest.
Recommendation 6. DRIs for chronic disease risk should take the form of a range, rather than a single number.

- Relationships should be defined as different ranges of the intake-response relationship where risk is at minimum, is decreasing, and/or is increasing (i.e., slope = 0, negative, or positive).

- When a nutrient or other food substance reduces the risk of more than one chronic disease, DRIs could be developed for each chronic disease, even if the confidence levels for each chronic disease are different.
What should be the different types of DRIs associated with reduction in chronic disease risk?

Recommendation 7. The committee recommends retaining ULs based on traditional toxicity endpoints.

- In addition, if increased intake of a substance has been shown to increase the risk of a chronic disease, such a relationship should be characterized as the range where a decreased intake is beneficial.

- If the increase in risk only occurs at intakes greater than the traditional UL, no chronic disease DRI would be required, because avoiding intakes greater than the UL will avoid the chronic disease risk.
Recommendation 8. To develop a chronic disease DRI, the level of certainty in the intake-response relationship should generally be the same as the level of certainty for a determination of causality, that is, at least “moderate,” using GRADE.

- However, in some cases, for example when a food substance increases chronic disease risk, the level of certainty considered acceptable might be lower.
- In all cases, a thorough description of the scientific uncertainties is essential in describing quantitative intake-response relationships.

What are acceptable levels of confidence in the Intake-response data?
Recommendation 9. If possible, health risk/benefit analyses should be conducted and the method to characterize and decide on the balance be made explicit and transparent.

• Such a decision needs to consider the certainty of evidence for harms and benefits of changing intake and be based on clearly articulated public health goals.

• If DRI committees do not perform such risk/benefit analyses, it is still necessary to describe the disease outcomes and their severities, the magnitudes of risk increases and decreases over various ranges of intakes, and other factors that would allow users to make informed decisions.
Integrating Chronic Disease DRIs in the Current Process

Chapter 8
Recommendation 10. Because of the need for close coordination and exchange of ideas when setting DRIs based on indicators of adequacy, toxicity, and chronic disease, one single National Academies of Sciences, Engineering, and Medicine parent committee should develop DRIs for the prevention of nutrient deficiencies and toxicities and for reducing the risk of chronic disease.
What should be the starting point of chronic disease DRIs?

Recommendation 11. When sufficient evidence exists to develop chronic disease DRIs for one or more nutrient or other food substances (NOFSs) that are interrelated in their causal relationships with one or more chronic diseases, a committee should be convened to review the evidence of their association with all selected diseases.
Guiding Principles
Guiding Principles

Related to Systematic Review

1. Well structured and established protocols
2. Guidance from technical expert panel
3. SR inclusive of all study designs
4. Protocols inclusive of various dietary assessments but consideration of quality
5. Protocols inclusive of health outcomes and surrogates but consideration of quality
6. Defensible instruments and analytical methods to assess evidence
7. Clear presentation of results from SR
Guiding Principles

Related to Review of the Totality of Evidence

8. Managing conflict of interests in DRI committee and interactions with other actors in DRI process
9. Expertise of DRI committee
10. Comprehensive review of the evidence and anticipation of scientific issues
11. Completeness, clarity, and transparency in evidence review process
12. Importance of peer review process
13. Addressing apparent discrepancies
14. Description of scientific uncertainties
Staff

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• Ann L. Yaktine, Director, Food and Nutrition Board
Download the report and highlights at nationalacademies.org/DRIchronicdisease

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