A planning meeting entitled “Framework for Dietary Reference Intake Development – Chronic Disease Indicators” was held by the Food and Nutrition Board of the Institute of Medicine on July 6-7, 2009. The meeting was held in Washington, DC.

The objective of the 1.5-day meeting was to consider what is known and what needs to be addressed in order to facilitate the development of nutrient reference values in cases where the most appropriate indicator is a measure of chronic disease.

Ten invited attendees, two Canadian government sponsors and two U.S. government observers were present for discussion of the issue. A roster of participants is attached as Appendix 1. The meeting Co-Chairs, Stephanie Atkinson and Elizabeth Yetley, developed a list of key topics and questions to guide the discussions. The discussions focused on the steps and considerations most useful to clarifying approaches for incorporating chronic disease indicators into the DRI development process. The meeting agenda is attached as Appendix 2.

The primary suggestions and discussion points resulting from the planning meeting are summarized below.

**Discussion: Utility of the threshold model for reference value development, as is required for the Estimated Average Requirement**

- A new, specific model or approach is likely needed for chronic disease indicators.
  - The model currently employed to establish Dietary Reference Intakes (DRI) based on the term “Estimated Average Requirement (EAR)” is likely not applicable for use with chronic disease indicators. For example, chronic disease data are not readily compatible with establishing a threshold effect of benefit that is applicable to almost all persons as is used for setting the EAR.
  - To incorporate chronic disease indicators into the DRI development process will likely require development of a new model that includes assessment of benefit/risk (beneficial to health/not harmful) and may provide opportunities to use multiple indicators as opposed to selecting just one indicator, as is typical in the EAR threshold model.
- The goal of the chronic disease indicator model would be to identify the optimal intake via a distribution curve that would include intake-response information for both benefit and risk.
  - Chronic disease indicators may require obtaining a distribution for effect by examining intake distributions relative to a number of disease outcomes.
(as opposed to use of a single outcome measure of nutritional status (e.g., s blood levels) or a single functional measure of nutrient adequacy (e.g., enzyme activity).

- If multiple (or a composite of) chronic disease indicators are used:
  
  o Criteria are likely needed to practically determine how many diseases can be meaningfully considered or how to prioritize disease outcomes if they yield quite different intake-response curves.
  
  o A limitation of the multiple indicators approach is that it might lead to a range of intake values since the amount of nutrient varies widely between individuals to achieve the same risk reduction. If the outcome is expressed as a range rather than a single number there might be problems in application of the recommendation:
    
    ▪ Policy makers will not know what number to use if a range is specified.
    
    ▪ Interpretation of “being outside the range” is unclear.
  
  o One possible approach in the case of a range of values is to use the chronic disease indicator for which the nutrient intake value is highest, provided that there is no evidence of increased risk for other diseases.
    
    ▪ The potential for increased risk could be determined by randomized clinical trials that have adequately evaluated the potential for adverse effects at the determined nutrient level and found no harm or from observational data that have examined the determined nutrient level and found no increased mortality.

- The model may need to better define the target population(s).
  
  o While it is clear that reference values are not intended for individuals already experiencing disease, it is less clear as to whether reference values should be targeted at healthy populations versus the general population, which may not be healthy (e.g., populations who are obese).
  
  o Application of the model for children should be examined.

- If a model is developed, reference value terminology should be carefully considered.
  
  o While there may be differences in the approach used to develop a DRI value based on a non-chronic disease indicator as compared to one using chronic disease indicators, multiple terminologies for the actual reference values that reflect model differences may create unnecessary confusion for users. Thus, careful consideration should be given to user needs in selecting reference value names.

- It is anticipated that the development of a chronic disease model may reduce reliance on use of Adequate Intake (AIs) values. That said, it was pointed out that AIs were also developed for reasons other than challenges associated with chronic disease indicators such as for recommended intakes for infants, for whom the AI remains a reasonable approach.
Discussion: Criteria for selecting critical indicators in the case of chronic disease indicators, given the possibility of using multiple indicators rather than one indicator?

- In using multiple indicators, the basic question may be “what is the totality of the evidence?”
  - For statistical purposes, separate plots may have to be generated; there may be a need to explore combining all into one plot. It is important to employ a statistical approach that determines the relative contribution of each indicator.
- Criteria may appropriately specify a direct link to a disease risk reduction through intake although not all intermediate indicators have a 1:1 relationship to the end disease of interest.
  - The need for intermediate nutritional status and outcome indicators may be eliminated.
  - Also, given the recent evidentiary history of nutrient-chronic disease relationships where preliminary data were initially promising but did not survive more rigorous scientific testing, a chronic disease model that precludes intermediate indicators offers promise for more reliable and sustainable conclusions.
- Specific criteria are needed for the consideration of observational data in the case of the development of nutrient reference values based on chronic disease endpoints.

Discussion: Substantiation criteria for selecting chronic disease indicators

- Substantiation should include evidence from randomized clinical trials if the decision being made relates to whether or not a specific nutrient or food-substance has an independent and causal relationship to reducing the risk of a chronic disease.
  - DRI development requires intervention and corresponding data establishing a causal link between intakes and disease risk reduction.
  - A question to be explored is whether there is a different evidentiary standard for using observational data in deciding to develop a DRI for a specific nutrient/disease risk reduction relationship as compared to using observational data for other purposes (e.g., relating dietary patterns to dietary guidelines based on foods and food groupings).
    - The logical division between dietary guidelines and DRI reference values may be that dietary guidelines address recommendations regarding foods and dietary patterns, while reference values focus on individual nutrient or food-substance effects.
- Developing reference values likely requires accuracy (an “absolute value”) in quantifying the intakes associated with health outcomes as opposed to the relative differences often reported in research studies.
  - Basing reference values on ascertainment of current intake data as an assumption of adequacy can be problematic; it is best to have clinical or biological measures directly linked to intake data.
• Intake-response curves present special challenges for nutrients; these issues should be explored.
  o The assumption is often made that nutrient relationships are linear, but many are non-linear.
  o Statistical methods for allowing the data to describe the curve should be pursued.
• “Generalizability” – which may be more appropriately expressed as “Applicability” – is an important component of selecting and weighing substantiation studies for the purposes of developing a DRI value.
• Uncertainty can be a key consideration in reference value development and should be addressed by a priori developing guidelines for dealing with uncertainty, including built-in flexibility to allow committees to deal with specific situations. Sensitivity analysis can assess uncertainty in a single study.
• Reporting a “single number” to signal the relative uncertainty surrounding a reference value would be extremely challenging, but it may be possible to discuss categories of uncertainty surrounding a reference value.

Discussion: Handling confounders
• Committees developing reference values should develop a list of specific confounders and effect modifiers to be taken into account for each chronic disease outcome being evaluated. Confounders should relate to both the exposure and the outcome.
• Confounders to be considered may fall into four categories:
  o Measured confounders
  o Known confounders with little or no data available
  o Highly correlated confounders
  o Unknown (and therefore unmeasured) confounders
• Confounders are very problematic for observational data, and as such limit the use of observational data in the absence of collaborating clinical trial data for setting reference values

Discussion: Extrapolation to unstudied groups
• Applicability to unstudied groups should be accounted for in developing reference intakes. Such groups include racial diversity, social class, infants and children for whom few primary data are available.
• Simple extrapolation is often inappropriate.
• Criteria should be established to determine when extrapolation should be used, the best approaches for making extrapolations, and to give guidance when extrapolation is not possible.

Next Steps
• While a conference or workshop could be useful, the approach most likely to support the development of a chronic disease model – along with activities to address its application – would be a standing committee, working group,
roundtable or forum as appropriate. Key issues could include but are not limited to:

- Developing a model for use within the DRI development process that is better matched to the key questions and types of data associated with chronic disease indicators.
  - This may include: considering multiple indicators; concurrently taking into account risk/benefit, confounders and uncertainty; and providing an easy-to-use, single number reference value.
- Clarifying the scope of the model including definition of chronic disease, other terminology, and specification of target population(s).
- Developing criteria for type and quality of data to be used.
- Developing criteria for making extrapolations for groups for which few data exist (children, minorities, etc.).
- Testing the resulting model and criteria using several nutrients with varied amounts of available data from which to set new reference values.
- In developing the process, consideration should be given to collaborative and integrative, but possibly separate discussions (or subcommittees or working groups), with one focused on the model development and the second focused on the users’ perspectives and needs.

**Research Needs and Wish List Items**

- Researchers should validate approaches, and develop guidelines, for evaluating the quality of nutrition-based studies and for preparing meta-analyses with relevance to nutrient-disease relationships.
- Researchers and journal editors should be encouraged to include in their publications results on the reduction in chronic disease risk associated with specified intakes both before and after adjusting for confounders.
- Researchers should be encouraged to bank biological specimens from current studies for future research, especially from large longitudinal cohort studies currently under development, so that future nutrient/disease hypotheses can be evaluated as warranted by evolving science.
- Researchers should explore and test approaches for improving the quality of dietary intake data and to try to validate it by comparison with appropriate biomarkers where possible.
- Basic safety studies and total mortality data are lacking for many nutrients and researchers should be encouraged to address these issues in future studies.
- Funders of research should consider supporting more studies that track dietary nutrient exposure with biomarkers.

[Attachments: Participants Roster; Meeting Agenda]
IOM DRI Chronic Disease Indicators Planning Meeting  
ROSTER OF PARTICIPANTS

**Stephanie A. Atkinson, Ph.D. (Co-Chair)**  
Professor and Associate Chair, Research  
Department of Pediatrics  
Associate Member, Dept. Biochemistry and Biomedical Sciences  
Faculty of Health Sciences, HSC 3A42  
McMaster University

**Joanne R. Lupton, Ph.D.**  
Distinguished Professor  
Regents Professor and University Faculty Fellow  
William W. Allen Endowed Chair in Nutrition  
Texas A&M University

**Elizabeth A. Yetley, Ph.D. (Co-Chair)**  
Retired, Former Senior Nutrition Research Scientist  
National Institutes of Health

**Demetrius Albanes, M.D.**  
Senior Investigator, Nutritional Epidemiology Branch  
National Cancer Institute  
National Institutes of Health

**Ralph B. D'Agostino, Sr., Ph.D.**  
Chair  
Mathematics and Statistics Department  
Professor of Mathematics/Statistics and Public Health  
Director, Statistics and Consulting Unit  
Boston University

**Valerie Tarasuk, Ph.D.**  
Professor  
Department of Nutritional Sciences  
Dalla Lana School of Public Health  
University of Toronto

**Sponsor Representatives and Observers**

**Dr. William R. Harlan, Jr., M.D.**  
Retired (NIH)

**Dr. Joseph Lau, M.D.**  
Professor of Medicine  
Institute for Clinical Research and Health Policy Studies  
Tufts Medical Center

**Linda Greene-Finestone**  
Public Health Agency of Canada

**Steve Brooks**  
Health Canada

**Kathryn McMurry**  
U.S. Health and Human Services

**Paula Trumbo**  
U.S. Food and Drug Administration
FRAMEWORK FOR DIETARY REFERENCE INTAKES DEVELOPMENT:
PLANNING MEETING – CHRONIC DISEASE INDICATORS

July 6-7, 2009
The Keck Center of the National Academies
500 Fifth Street NW
Washington, DC

AGENDA

Monday, July 6, 2009: Day 1

Keck Room 101

5:00 pm Welcome and Introductions

5:30 Background to the Current DRIs

What are the DRIs? Their purpose, the conceptual models and assumptions applied in the first set of DRI recommendations – EAR, RDA, AI and UL; population coverage

Stephanie Atkinson, PhD, Co-Chair

Consideration of nutrient-chronic disease relationships in previous DRIs

Elizabeth Yetley, PhD, Co-Chair

Discussion and questions – What worked? What were the challenges? What were the gaps in knowledge? What were the barriers to application?

6:30 Working Dinner

7:00 Organizing the Evidence for Evaluating Nutrient-Chronic Disease Relationships

The analytic framework developed for the systematic reviews – Vitamin A and Vitamin D examples

Joseph Lau, MD

Discussion and questions
8:00 Discussion: Future Challenges of Definitions and Conceptual Model Development for the DRIs

8:30 Adjourn

Tuesday, July 7, 2009: Day 2

Keck Room 101

7:30 am Continental Breakfast in Meeting Room (Keck 101)

8:00 Summary of Discussions from Day 1

Stephanie Atkinson, PhD, Co-Chair
Beth Yetley, PhD, Co-Chair

GROUP DISCUSSIONS

OBJECTIVE: To identify issues related to using chronic disease as endpoints for setting DRIs

8:15 1. Key Questions and Methodologies for Incorporating Chronic Disease Indicators into DRI Development

8:15 Does a threshold model such as is required for EARs and ULs work for chronic disease endpoints?

- If so, how?
- If not, what options are available as alternative?

9:15 Selection of indicators as critical endpoints

- What criteria should be followed in selecting indicators of chronic disease as the critical endpoint; or not selecting it as the critical endpoint?
- How do these relate to or differ from traditional indicators of nutritional status?

10:15 Break

10:30 Continued Group Discussion on Key Questions and Methodologies

10:30 Use of substantiation criteria

- What substantiation criteria are needed for selecting chronic disease endpoints?
  - For causality and attribution to the target nutrient?
  - For dose-response?
  - For extrapolation to unstudied groups?
• How are uncertainties identified and described?
• How useful are different types of studies for each of these substantiation questions?

11:30 What options are available for estimating intake-response curves for chronic disease endpoints when dose-response curves are not part of the study design or adequately delineated in the available evidence? What are the pros and cons of the different options?

12:00 Lunch

12:30 Continued Group Discussion on Key Questions and Methodologies

12:30 How should issues of confounders be handled (non-nutrient factors contributing to the chronic disease of interest (such as smoking, sedentary lifestyle), etc?

1:30 How and when should a nutrient-chronic disease relationship used to develop a DRI in adults be extrapolated to children and other non-studied groups?

• Macronutrients
• Micronutrients

2:30 Break

2:45 2. Summary and integration of discussions – What factors in the current conceptual model, definitions, use of available evidence, and decision-making are barriers to including chronic disease endpoints in deriving DRIs? What options can be considered in addressing these barriers?

3:30 3. Discussion of other topics raised by the group and discussion of options for resolving identified challenges

4:00 4. Future Directions and Next Steps

4:30 Adjourn