

Nutrition Research Series

Volume 2: Issues and Challenges in Conducting Systematic Reviews to Support Development of Nutrient Reference Values: Workshop Summary

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0022

Prepared by:

Tufts Evidence-based Practice Center, Boston, MA

Investigators

Robert Russell, M.D.
Mei Chung, M.P.H.
Ethan M. Balk, M.D., M.P.H.
Stephanie Atkinson, Ph.D.
Edward L. Giovannucci, M.D., Sc.D.
Stanley Ip, M.D.
Alice H. Lichtenstein, Sc.D.
Susan Taylor Mayne, Ph.D.
Gowri Raman, M.D.
A. Catharine Ross, Ph.D.
Thomas Trikalinos, M.D., Ph.D.
Keith P. West, Jr., DrPH
Joseph Lau, M.D.

AHRQ Publication No. 09-0026-2
March 2009

This report is based on research conducted by the Tufts Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0022). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials noted for which further reproduction is prohibited without the specific permission of copyright holders.

Suggested Citation:

Russell R, Chung M, Balk EM, Atkinson S, Giovannucci EL, Ip S, Lichtenstein AH, Taylor Mayne S, Raman G, Ross AC, Trikalinos T, West KP Jr, Lau J. Issues and Challenges in Conducting Systematic Reviews to Support Development of Nutrient Reference Values: Workshop Summary. (Prepared by the Tufts Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 09-0026-2. Rockville, MD: Agency for Healthcare Research and Quality. March 2009.

No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in this report.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Beth A. Collins Sharp, R.N., Ph.D.
EPC Program Director
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Task Order Officer
Agency for Healthcare Research and Quality

Nutritional Systematic Reviews

The medical and clinical communities have effectively used systematic reviews to develop clinical and public health practice guidelines, set research agendas, and develop scientific consensus statements. However, the use of systematic reviews in nutrition applications is more recent and limited. The Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH) has been proactive and developed an evidence-based review program using the EPC Program established by AHRQ, as part of a Congressional mandate to review the current scientific evidence on the efficacy and safety of dietary supplements and identify research needs (http://ods.od.nih.gov/Research/Evidence-Based_Review_Program.aspx). To date, this program has sponsored 17 evidence reports on a range of supplement-related topics including B-vitamins, ephedra, multivitamin/mineral supplements, omega-3 fatty acids, soy, and vitamin D. ODS is currently sponsoring an augmentation of the vitamin D report published in August 2007 to provide relevant information for a pending Institute of Medicine review of the current Dietary Reference Intakes for vitamin D and calcium. The completed ODS-sponsored evidence reports have resulted in numerous associated publications in scientific journals, have formed the basis for an NIH-sponsored state-of-the-science conference, and have been used to assist in setting research agendas.

To facilitate a better understanding of the challenges involved in conducting nutrition-related systematic reviews and in integrating these reviews with nutrition applications for which such reviews have not been previously used, ODS has sponsored the development of a series of technical reports via the EPC Program. The purpose of these reports was to: a) identify the challenges, advantages, and limitations of conducting nutrition-based systematic reviews; b) work with a panel of experts to explore approaches for integrating systematic reviews into processes associated with the derivation of nutrient intake reference values; c) identify the breadth and quality of currently available nutrition-related systematic reviews against generally accepted quality guidelines within the context of the unique needs for nutrition topics; and d) critically explore the consistencies and inconsistencies in results between observational and intervention studies and evaluate how the formulation of research questions may have contributed to these discrepancies.

Paul M. Coates, Ph.D.
Director, Office of Dietary Supplements
National Institutes of Health

Elizabeth A. Yetley, Ph.D.
Senior Nutrition Research Scientist
Office of Dietary Supplements
National Institutes of Health

Abstract

Nutrient reference values have significant public health and policy implications. Given the importance of defining reliable nutrient reference values, there is a need for an explicit, objective, and transparent process to set these values. The Tufts Medical Center Evidence-based Practice Center assembled a group of nutrition experts from academic institutions and federal government agencies, led participants in discussions, conducted exercises in formulating questions and evidence review criteria that would be amenable to systematic reviews of the scientific literature, performed a literature search on the questions to identify potentially relevant publications, and identified challenges and limitations of applying this method to support the development of nutrient reference values, using vitamin A as an example. The workgroup concluded that the systematic review approach could be productively used to inform the development of reference values. Challenges identified in this exercise include prioritizing and defining research questions when the volume of literature is large, relying on intermediate (surrogate) outcomes when few or no studies directly linked nutrient intake with clinical outcomes are available, and determining reliable nutrient biomarkers. Ultimately, an objective, unbiased systematic review of a defined question could be useful; not only in helping to set nutrient reference values, but also for increasing the transparency of the decision making process.

Key words: systematic review, evidence-based, diet, nutrition recommendations, nutrition guidelines.

Contents

Chapter 1. Introduction	1
Organizations conducting systematic reviews in nutrition	2
Impetus for the current report.....	3
Chapter 2. Overview of Systematic Review Methods	5
Key question formulation.....	5
Analytic Framework.....	6
Evidence mapping to inform the state of evidence in a particular topic	6
Critical appraisal	7
Evidence synthesis	8
Potential challenges in applying evidence-based methods to support the setting of nutrient reference values.....	8
Chapter 3. Integrating systematic reviews into a process to establish nutrient reference values ..	11
Generic analytic framework for nutrient reference values.....	11
Decision-making for questions and outcomes of interest / PICO generic	13
Chapter 4. Workgroup Exercise.....	15
Activities surrounding the first meeting.....	15
Activities surrounding the second meeting	16
Analytic framework for vitamin A reference values.....	17
Chapter 5. Summary and Conclusions.....	23
References.....	25
Acronyms/Abbreviations	29
Glossary	31
List of Workshop Participants	33

Tables

Table 1. Number of potentially qualifying studies per exposure and outcome category among 363 abstracts meeting criteria	19
--	----

Figures

Figure 1. An example of a generic analytic framework used by the US Preventive Services Task Force Integrating systematic reviews into a process to establish nutrient reference values	6
Figure 2. Generic analytic framework applicable to assessment of nutrients.....	11
Figure 3. Analytic framework for adequacy of Vitamin A intake.....	17
Figure 4. Analytic framework for Vitamin A excessive intake	18

This report is available electronically at:

<http://www.ahrq.gov/downloads/pub/evidence/pdf/nutrition/nutrtp2.pdf>.

Chapter 1. Introduction

The Office of Dietary Supplements (ODS) requested the Tufts Medical Center Evidence-based Practice Center (EPC) to conduct an exercise to identify the issues and challenges of including evidence-based methods as a component of the process used to develop nutrient reference values (such as the Dietary Reference Intakes [DRI]) issued by the Institute of Medicine (IOM). This work was performed under a task order issued by the Agency for Healthcare Research and Quality (AHRQ) EPC program. The Tufts EPC assembled a group of nutrition experts from academic institutions and relevant federal government agencies, led participants in teleconferences and meetings, conducted exercises in formulating questions that would be amenable to systematic reviews of the scientific literature, and identified the challenges and limitations of applying this method to processes previously used to establish nutrient reference values. This report summarizes the impetus behind this project, approach taken, and the lessons learned.

Nutrient reference values have significant public health and policy implications. This type of dietary guidance is needed for planning diets, assessing the adequacy of diets in individuals and populations, developing nutrition education and guidance, and for setting reference values for nutrition labeling.¹

An example of nutrient reference values is the IOM DRIs developed for healthy US and Canadian populations. The DRI values are established by ad hoc study committees convened by the IOM, National Academies of Science. The DRIs for each nutrient are in fact a set of nutrient reference values that typically include an Estimated Average Requirement (EAR), a Recommended Dietary Allowance (RDA), and a Tolerable Upper Intake Level (UL). When available evidence was considered to be inadequate to establish an EAR, the study committees developed a value known as the Adequate Intake (AI). EAR values reflect the median nutrient requirement for the particular life stage and gender group. The EAR was used to calculate RDA values, defined as the nutrient intake level that is sufficient to meet the nutrient requirements of nearly all (97 to 98 percent) individuals within that group. Available data were used to estimate a UL, defined as the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. AIs, when developed, were defined as “the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake of a group (or groups) of apparently healthy people that are assumed to be adequate”.

The IOM Food and Nutrition Board has issued reports on the DRIs for a wide range of nutrients. Six reports have been published and are organized around groups of nutrients.²⁻⁷ Contents of the reports include a summary of what is known about the nutrient function in the human body, selection of indicators of adequacy of nutrient intakes or nutrient levels (for determining nutrient requirements), factors that may affect how the nutrients are utilized and that affect requirements, and how nutrients may be related to the prevention of chronic disease across age groups. Various study committees were convened to evaluate a body of available scientific evidence for specific nutrients. Primarily human studies were reviewed and selected animal studies were used when human data are absent or conflicting. Available evidence was weighted according to quality, peer review status, biological plausibility, and whether similar estimates would be derived from different indicators.¹

However, the process of establishing DRIs has been variable and has evolved as experience accrued from study committees. Concern has been expressed that in some cases the methods

used to determine DRIs have suffered from a lack of transparency and consistency.⁸ Moreover, differences in the reference values derived by various groups of nutrition experts worldwide have been noted for the same nutrient when all presumably have used the same body of available evidence. For example, three different organizations from the European Union (EU-SCF), UK (EVM), and the US (IOM) performing nutrient risk assessment proposed different upper levels of intake for vitamin A.⁹

Given the importance of defining reliable nutrient reference values, there is a need for an explicit, objective, and transparent process to set these values. Evaluating evidence is a major component of informing the process. Because new studies are constantly being published, it would also be desirable to have a framework that allows efficient updating when new information becomes available. Although the mandate to different committees around the world has previously been different (e.g., prevent nutrient deficiency, decrease chronic disease risk), with the globalization of the food supply and health risks it should be expected that evaluating similar evidence will result in similar recommendations.

Over the past 15 years, the concept of evidence-based medicine (EBM) building upon the foundation of systematic reviews, meta-analyses and related methods as important tools for evidence-based practice, has gained widespread acceptance in the evaluation of medical evidence for healthcare decision-making.¹⁰ The application of this approach to evaluating the nutrition literature could provide for the transparent, comprehensive and objective evaluation of scientific evidence and could provide support for a framework for a consistent approach to establishing nutrient reference values for all dietary components. Systematic reviews offer a clear and detailed description of the method used to ensure completeness in identifying the available scientific evidence, rationale for the selection of studies, and method of analysis and interpretation. Systematic reviews also allow for an unbiased retrospective evaluation and could provide a starting point for updating and revising the reviews. They are particularly helpful in identifying research gaps for use in establishing research funding and priorities.

Organizations Conducting Systematic Reviews in Nutrition

Numerous investigators and organizations have published hundreds of systematic reviews on nutrition topics. Nutrition-related systematic reviews have been used by several organizations to develop clinical practice guidelines or recommendations. For example, in 2003, the United States Preventive Services Task Force concluded that the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease. The conclusion was based on several considerations including the findings of an evidence report produced by the Oregon EPC.¹¹ A National Institutes of Health (NIH) State-of-the-Science Conference Panel on Multivitamin/Mineral Supplements and Chronic Disease Prevention reached similar conclusions, partly based on the results from an updated evidence report produced by the Johns Hopkins EPC.¹² Furthermore, the Centers for Disease Control and Prevention's (CDC) Task Force on Community Preventive Services produced many systematic reviews and evidence-based recommendations for programs and policies to promote population health. Many nutrition-related topics were covered, including the effectiveness of school-based nutrition and physical activity programs, and community- or school-based obesity prevention (www.thecommunityguide.org).

In 2000, the American Dietetic Association (ADA) began carrying out evidence analyses on a wide range of nutrition-related diseases and conditions with the goal of enhancing dietetics practice in these areas. Evidence-based practice guidelines are available for some topics on the ADA evidence analysis library (EAL) (www.adaevidencelibrary.com). These guidelines allow food and nutrition professionals to apply the best research knowledge available to their practice with the goal of improving patient outcomes and practitioner effectiveness.¹³

The Cochrane Collaboration (www.Cochrane.org), established in 1992 and currently consisting of over 10,000 international volunteers, is the best known group worldwide conducting and disseminating systematic reviews of healthcare interventions. While it has about 5,000 systematic reviews completed or in progress in its Cochrane Library, currently there are relatively few nutrition titles. In 2005 a group of researchers proposed to establish a Diet and Nutrition subfield with the main goal of ensuring that the nutrition community is not left behind in the move towards the evidence-based approach.¹⁴ However, as of this writing this has not been implemented.

Impetus for the Current Report

While many concepts and methodologies of EBM could be applied directly to nutrition questions, there are importance differences between evaluations of medical interventions (e.g., drug therapies) and nutrient requirements.¹⁵ One of the aims of this project was to assess the feasibility of applying evidence-based methods to the process of developing nutrient reference values. By leading a workgroup through the systematic review process to formulate questions that a nutrient reference values panel might consider, the intent was to identify unanticipated issues and challenges.

The following sections briefly describe the methods of systematic review and the activities surrounding the two workgroup meetings. The bulk of the discussion is about integrating evidence-based methods to the process for deriving nutrient reference values. We focus on the process of identifying and reviewing evidence, which is only one aspect of setting nutrient reference values. We did not actually review the evidence identified in the literature searches, as this was beyond the scope of the current project. The intent of this exercise was not to make specific recommendations for reference values or propose how an expert panel should integrate the evidence into its decision-making process. Finally, this report does not recommend a specific approach for implementing the evidence-based methods for the development of nutrient reference values.

Chapter 2. Systematic Review Methods

Overview

A systematic review is a protocol driven comprehensive review and synthesis of data focusing on a topic or on related key questions. It is typically performed by experienced methodologists with the input of domain experts.

The first step to conduct a systematic review is to formulate specific key questions. For situations that involve addressing more than a single, simple question, it is often useful to construct an analytic framework (evidence model) depicting the key questions being addressed to help appreciate their relationships. Furthermore, when many questions are being addressed, it may be beneficial to construct an “evidence map”, an exploratory exercise that informs on the amount of evidence potentially relevant to different questions. This information can aid in more detailed planning to allocate resources and ensure a timely completion of the project. Additional essential steps include developing a protocol, refining the questions of interest, conducting a literature search for evidence, selecting studies that meet the inclusion criteria, appraising the studies critically, and synthesizing and interpreting the results.

These steps are briefly described in this section. As mentioned above, systematic reviews should be carried out as a collaborative activity by individuals knowledgeable in the evidence-based methods and those with expertise in the questions of interest. As systematic reviews are increasingly being published on nutrition related topics, the term *systematic review* has been subjected to various modifications to include *evidence-based review*, *systematic evidence-based review*, and *evidence-based systematic review*. In this report, we use the term systematic review, which is the longstanding common usage in medicine and other disciplines.

Key Question Formulation

Overarching questions such as “What should be the upper intake level for vitamin A?” cannot be answered directly from primary data in the literature although the answer may be the ultimate goal of the exercise. The question must be dissected into smaller and more specific questions that individual studies can address. Multiple systematic reviews will then address these individual questions and the results will be synthesized according to a predefined framework. Thus, a vital step in performing a systematic review is formulating clearly stated research questions that would be amenable to literature review. “Key questions” are analogous to the hypotheses of primary research studies; they should be focused and explicitly stated because they define the scope of research the systematic review will address. Key questions are commonly formulated according to the “PICO” method, which defines the Population, the Intervention (or exposure in the case of observation studies), the appropriate Control or Comparator, and the Outcomes of interest.¹⁶ Describing the inclusion criteria for each of the PICO elements clearly provides the investigators the opportunity to understand the specific questions being asked – and equally important, what questions are not being asked – in the systematic review. This step ensures reproducibility and transparency, and it guides the determination of study eligibility, data extraction, analysis, and interpretation of results. The reviewers must also decide which study designs are acceptable to answer specific questions. The choice about the types of evidence to be included is often a balance between what evidence is needed for conclusive answers to the

review questions and the limitations of published studies. While randomized controlled trials may be ideal, these studies are often not practical or feasible, and other sources of evidence may need to be evaluated.

Analytic Framework

To guide assessment of studies that addresses the topic of interest, it is helpful to develop an analytic framework that visually maps the specific linkages associating the populations of interest, exposures, modifying factors, and outcomes of interest (Figure 1).¹⁷ The framework graphically presents the key components of the study questions:

- Who are the participants (i.e., what is the population and setting of interest, including the diseases or conditions of interest)?
- What are the interventions or exposures?
- What are the outcomes of interest (intermediate and clinical outcomes)?
- What study designs provide data that can help answer the question?

Specifically, the analytic framework depicts the chain of logic that evidence must support to link the intervention or exposure to improved health outcomes. This process helps guide the development of key questions. The framework can also provide a basis for interpreting and contextualizing relevant studies, and establishing which links in the chain of logic are answered, inconclusive or not yet addressed.

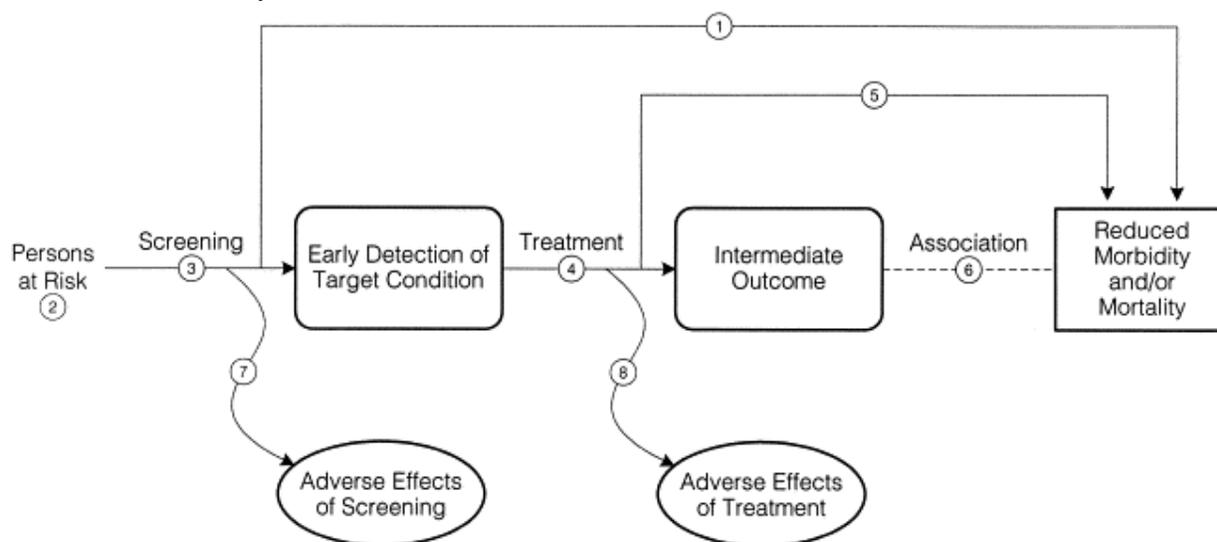


Figure 1. An example of a generic analytic framework used by the U.S. Preventive Services Task Force (USPSTF).¹⁷ Each number represents a specific link or answerable research question. A generic analytic framework for nutrient reference values is shown in Figure 2.

Evidence Mapping to Inform the State of Evidence in a Particular Topic

Evidence mapping is a method to facilitate exploring new ideas and hypotheses. It can be used to direct limited resources to potentially more fruitful areas for systematic review as well as to complement comprehensive systematic reviews on specific key questions. It aims to provide investigators with information about the type and amount of research available, the

characteristics of that research, and the topics where a sufficient amount of evidence has accumulated for synthesis.

Individual systematic reviews are labor intensive activities and might require the evaluation of hundreds of articles before identifying a handful of studies meeting the predetermined eligibility criteria. An evidence map to provide a “bird’s eye” view requires only a fraction of the resources needed to produce a full systematic review, allowing users to appreciate the depth, breadth, and characteristics of research in a particular area before investing valuable resources in a full systematic review. Evidence mapping is a cost-effective method to inform users of the current state of research findings that could be used to generate hypotheses, inform ongoing research, and identify research gaps.

Critical Appraisal

The quality of an individual study has been defined as the “confidence that the trial (study) design, conduct, and analysis has minimized or avoided biases in its treatment (exposure) comparison.”¹⁸ Quality assessment may suggest the extent to which a study’s design and methodology prevented systematic error, and may explain differences in the results among systematic reviews. However, implementing and interpreting the results of quality assessment is not straightforward. Numerous approaches have been proposed to assess the quality of studies and apply these assessments to systematic reviews. Until recently, checklists and quality scales, generally comprised of several to several dozen factors believed to be associated with study quality, were commonly used.

Among the more common quality indicators for intervention trials are adequate concealment of random allocation, accurate reporting of withdrawals, degree of reporting accuracy, appropriateness of statistical analysis, and blinding in the assessment of outcomes. In theory, studies in which these measures are poorly achieved are more likely to result in biased outcomes. For example, compared to double-blinded studies, non-blinded studies may exaggerate the benefit of treatment (e.g. a larger odds ratio, or treatment effect). Of those criteria assessed, only lack of concealment of randomization and double blinding, with limited empirical evidence, have been shown to be related to exaggerated estimates of treatment effects.¹⁹ However, other studies evaluating the importance of these quality measures have differed regarding the extent to which they were related to effect sizes.²⁰⁻²² Furthermore, individual quality measures may not be consistently associated with the magnitude of treatment effect across studies and medical areas.²³ As a result, methods that arbitrarily weight these measures to establish quality scores for studies are no longer deemed appropriate.

Approaches to assessing the quality of observational studies have been proposed;^{24,25} however, there are no empirical data validating any of these methods. The assessment of study quality is limited by the need to rely on author-supplied information and an understanding that there is no true reference standard for quality.²⁶ Critical appraisal of individual studies should be performed as part of a systematic review, but the results should be interpreted cautiously. The primary value may be to explore possible reasons for differences in results among studies. No specific instrument has been proposed to assess the quality of nutrition studies for the purpose of systematic review, although several factors (e.g., methods to assess dietary intake, quality of the statistical models used, independent replication of results from two or more laboratories) have been identified as important to consider based on the theoretical assumption that failure to adhere to the item proposed could lead to biased results.

Evidence Synthesis

A systematic review often identifies several studies addressing the same question. The results of these studies need to be synthesized and interpreted. Synthesis of the findings of different studies can be done qualitatively or quantitatively. It is not necessary for a systematic review to include quantitative analyses of individual study findings; however, when possible, quantitative analyses should be preferred over qualitative-only synthesis. Because quantitative synthesis has strengths and limitations, we briefly describe it below. An authoritative discussion on meta-analysis can be found in the Cochrane Handbook.²⁷

The quantitative synthesis of results obtained from different studies is termed meta-analysis.²⁸ By aggregating information from different studies, meta-analysis can increase statistical power and provide answers that no single study can give (i.e., detect modest associations, or conversely, exclude the presence of clinically important effects). For example, a meta-analysis of 19 clinical trials found a statistically significant increased overall mortality in participants who received “high doses” of vitamin E;²⁹ levels that had previously been considered as well below the upper limit, a finding that was not statistically significant in most of the individual studies. Of equal importance, meta-analysis quantifies between-study heterogeneity (between-study dissimilarity), and provides tools (e.g., meta-regression) to explain it.³⁰ Finally, meta-analysis facilitates the evaluation of systematic errors and biases, and their effect on any given topic.

Meta-analysis has sometimes been criticized as an inappropriate exercise of combining apples and oranges. Deciding when a meta-analysis is appropriate can be a challenge as there are numerous sources of heterogeneity that one needs to consider. If the designs, quality, and results of the studies are deemed to be so heterogeneous, then statistically combining them can yield misleading conclusions. In such cases where meta-analyses are deemed inappropriate, the data should be organized and presented in an analytic framework, and in summary evidence tables. This approach will help clarify the similarities and differences among studies that appear to address similar research question (qualitative synthesis).

Potential Challenges in Applying Evidence-based Methods to Support the Setting of Nutrient Reference Values

While the basic methodologies employed in systematic reviews of medical topics can be adapted to nutrition topics, there are also challenges and unique problems when incorporating the process into approaches to establish nutrient reference values. Many of these potential issues are unique to individual nutrients. Taking these factors into account while formulating the systematic review questions will minimize the risk of generating uninformative or wrong answers. The relative importance of each issue is nutrient specific. This section serves to provide a general discussion of potential issues to consider.

Many nutrients naturally occur in multiple bioactive forms. It is important to determine whether generally accepted nutrient conversion factors are valid in cases of marginal or excess intakes. The background or habitual diet of the study subjects is a critical factor that must be accounted for when extracting data from individual study reports. Response to deletion or supplementation of a nutrient will differ on the basis of this factor. It is important to document the nutrient status of the subjects prior to intervention, the status of body stores, and the potential bioavailability of those stores. It is also important to document body weight changes. Weight loss can result in hormonal changes and subsequent release of certain nutrients (e.g. iron status) not

normally available.^{30,31} Alternatively, weight gain can create nutrient reservoirs (e.g. fat soluble vitamins) that are unavailable in times of nutrient, but not energy, need.^{30,32,33}

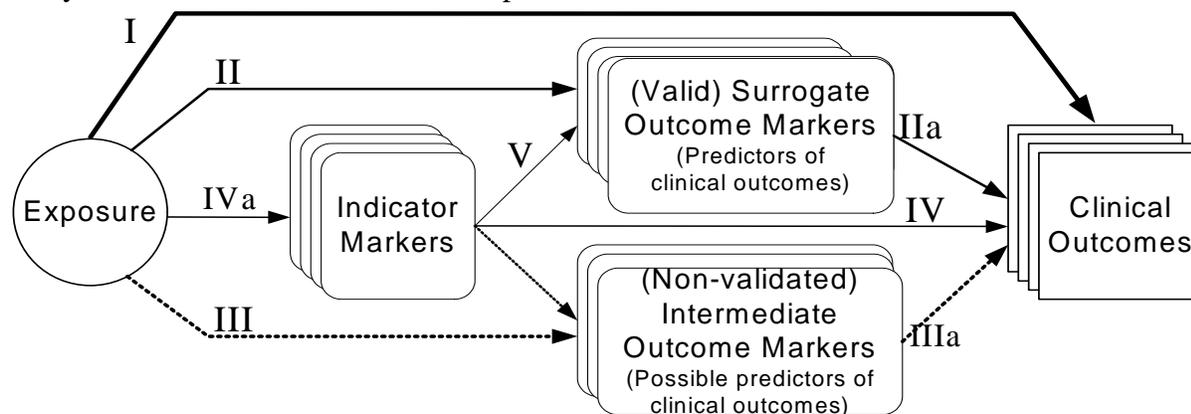
Some factors are particularly important and should be taken into account when data from multiple populations are examined. These include differences in nutrient bioequivalency that depend on the type of natural or fortified foods available to the general population (e.g. heme and nonheme iron); differences in food processing techniques (e.g. lye treated corn and niacin); and differences in whether the major source of the nutrient is limited to naturally occurring forms or whether a synthetic form is commonly added to in the food supply (e.g. folate and enriched grains). The increasingly common practice of supplementing foods with nutrients may also need to be accounted for (e.g. nutrient-fortified soft drinks, calcium-fortified orange juice). Additional factors that are important in cross-cultural comparisons include nutrient bioavailability as altered by coingestion of other foods, supplemental nutrients or drugs, and non-food sources of a nutrient (e.g. sun exposure and vitamin D, gut microflora and vitamin K).

Chapter 3. Integrating Systematic Review Into a Process to Establish Nutrient Reference Values

As mentioned above, an analytic framework is a useful graphical representation of the perceived relationships between the nutrient of interest and the associated health outcome. It provides several advantages to both reviewers and readers of systematic reviews by illustrating linkages among nutrients, other substances of interest, co-morbid conditions, and intermediate endpoints, and their interactions and sequential effects on clinical outcomes. It is a conceptual representation of the plausible underlying biology, simple enough to study and complex enough to capture the most relevant relationships. By depicting the chain of logic that evidence must support to link the nutrient exposures to clinical outcomes, this process helps guide the development of answerable key questions, define study eligibility criteria, and interpret and contextualize relevant studies.

Generic Analytic Framework for Nutrient Reference Values

Figure 2 shows an example of a generic analytic framework. The framework describes the relationships between “exposure” (nutrient intake) and clinical outcome(s) of interest. The components of the generic framework are described below in more detail. Not all components would be considered for all nutrients or all questions for a specific nutrient; therefore, actual analytic framework needs to be developed for each nutrient of interest.



- I. Association of exposure with clinical outcomes of interest
- II. Association of exposure with surrogate outcomes for which there is "good" evidence of a linkage with clinical outcomes
 - IIa. Association between surrogate outcomes and clinical outcomes ("good" evidence for linkage)
- III. Association of exposure with surrogate markers for which the linkage with clinical outcome is uncertain
 - IIIa. Association between surrogate markers and clinical outcomes (uncertain linkage)
- IV. Association of indicator markers to clinical outcomes
 - IVa. Association between exposure and indicator markers
- V. Association of indicator markers to surrogate outcomes (with good or possible evidence for linkage with clinical outcomes)

Figure 2. Generic Analytic Framework applicable to assessment of nutrients. A representation of the putative associations between an exposure (e.g., a nutrient) and indicator markers of intake (e.g., serum or tissue nutrient levels), (non-validated) intermediate outcomes, (valid) surrogate markers, and clinical outcomes. The arrows represent associations among factors. Line thickness represents the relative “directness” of an association, and the strength of the relationship with clinical outcomes. Dotted lines represent associations to surrogate markers for which there is no good evidence of an association with clinical outcomes.

The generic analytic framework can be thought of as a template to be modified to reflect the underlying biological factors associated with a specific nutrient. Furthermore, different generic analytic frameworks will be needed to describe the exposure and clinical outcome, including the intermediate factors, for the different types of nutrient reference values because the criteria for exposure and clinical outcomes will be different. For example, developing reference values for a reference value for a *nutrient level that meets the needs of ~50 percent of the population*, versus a reference value for an *excessive intake level*.

Clinical Outcomes

Clinical outcomes can be perceived by a study subject, and their improvement (or not worsening) is preferable to outcomes that cannot be perceived by a study subject, for examples bone fractures, depression, chronic fatigue, quality of life, or angina pectoris due to atherosclerotic coronary disease. For the purposes of this discussion “anemia” is not considered a clinical outcome. “Fatigue” would be the corresponding clinical outcome. Adverse events would also be considered as clinical outcomes.

An additional caveat pertains to the distinction between “hard” and “soft” clinical outcomes. Hard outcomes, such as mortality, stroke, myocardial infarction, or fractures can be objectively assessed. Soft outcomes, such as feeling depressed, chronic fatigue, or quality of life are subjective and their evaluation or measurement may be more susceptible to the interplay of systematic errors and biases compared to hard outcomes.

Valid Surrogate Outcome Markers

Because most often there are few or no studies that directly link specific nutrient intakes with clinical outcomes, intermediate (surrogate) outcomes need be considered. Typically, we would consider only *validated surrogates* of the clinical outcome. These are outcomes that are strongly correlated with the clinical outcome (e.g., bone mineral density is a valid surrogate for fractures), and changes in their status reflect corresponding changes in the risk for the clinical outcome (e.g., changes in bone mineral density generally reflect changes in fracture risk). In contrast, homocysteine levels are not a valid surrogate endpoint for cardiovascular disease risk: intervention-induced changes in homocysteine levels (e.g., by increasing folate consumption) do not correspond to changes in the risk for cardiovascular disease.

Non-validated Intermediate Outcome Markers

Non-validated intermediate markers are possible predictors of clinical outcomes that have not been proven to fulfill the criteria for a *validated surrogate outcome*. However, in the absence of validated surrogate outcomes, one might consider such intermediates as the next best available evidence. An example would be absence of anemia as an intermediate marker for the absence of disease (well-being), or serum osteocalcin (a bone turnover index) as an intermediate marker for fractures. When considering non-validated intermediate markers the implicit assumption is that they would have the properties of a *validated surrogate outcome*. Not only should this assumption be made explicit, but the uncertainties involved in applying this assumption should also be identified and discussed. To emphasize this, the corresponding links in the generic framework in Figure 2 are indicated with dashed lines.

Indicator Markers (of Nutrient Intake)

Although the ultimate goal is to provide nutrient reference values for all essential nutrients, it may be preferable to associate clinical outcomes with an indicator (or biomarker) for the corresponding nutrient when reliable indicator (or biomarker) are available. A reliable indicator (or biomarker) fulfills the classical assessment model (i.e. linear, dose-response model) with an error that is independent of that for (self-reported) nutrient consumption estimates. Using a reliable indicator of dietary intake (e.g., serum levels for vitamin C) can enhance objectivity because estimates of intake are not affected by subjects' memory or ability to accurately report food intake, or the accuracy of the database used to estimate nutrient intake from food intake data. However, readily available indicators of nutrient exposure, more frequently blood and urine, are often under homeostatic control and do not represent good markers of nutrient status. Moreover, like the error and variation associated with dietary intake measures, the magnitude and impact of both biological (preanalytical) and laboratory (analytical) variability need to be considered when using biomarkers.³⁴

Using a biomarker to evaluate the strength of downstream associations requires that the biomarker levels be back-translated into levels of nutrient intake. Thus, if an association is found between a given biomarker level and risk of a clinical outcome, an estimate of the nutrient intake level that corresponded with the clinical outcome would likewise be necessary. This step has proven to be challenging.

Decision-making for Questions and Outcomes of Interest

An important aspect of the decision-making is which questions should be addressed by systematic reviews and which questions will either not be addressed or will be addressed by other methods. For systematic reviews, answerable research questions need to be formulated. After organization of general topics and questions based on the linkages in the analytic framework, detailed determinations are needed to define the parameters of the systematic review(s).

Following the PICO format, first the population of interest is defined. Nutrient reference values are needed for specific categories (based on age, gender and pregnancy status) of generally healthy Americans. However, to operationalize this in reviewing studies, it is necessary to make judgments about what health conditions and nutritional status are of interest, are allowable, and should be excluded. These decisions can be quite complex and need to be made in light of what is known about how the nutrient affects or is affected by conditions such as cancer, infections and malnutrition. Other considerations that contribute to heterogeneity of populations across studies include varied study designs (differences in patient or participant sampling), background diets, and studies conducted in different environments.

The interventions or exposures of interest need to be defined. In contrast with pharmaceuticals, for nutrients it is common that there is a range of substances (that may not yet be fully elucidated) that are active and interact with each other, such as the different forms of vitamins A and D, or multiple minerals altering gut bioavailability. Furthermore, the principal source of nutrients is food or dietary supplements, which are consumed against background levels of exposure, in contrast to precisely dosed pharmaceuticals that generally are the only exposure source. Thus, decisions are needed regarding which forms of the nutrient are of interest and what methods for measuring their intake are appropriate, taking into account the strengths

and limitations of the dietary assessment methods and of the quality of the food composition database. For many nutrients acceptable measurements of intake are not readily available. In this case, alternative to a “subjective” decision-making process to choose which measurements of intake to be evaluated would be desirable. An “objective” evidence map to capture and present the information on what dietary assessment method and which food composition database was used, and how well the statistical model dealt with the measurement error inherent in the dietary intake assessment (and in any biomarkers) in all studies will help a transparent decision-making process.

The possible comparators of interest are generally related to the study designs that will be included. Many nutrition studies are observational studies (whether cross-sectional or longitudinal) that estimate and analyze nutrient intake as a continuous variable across a range of intakes or create quantiles or other categories to describe intake. The appropriateness of these approaches and of the threshold used to categorize the intake need to be defined. In nutrition studies it may also be necessary to account for the co-varying of multiple nutrients in the diet. For example, any reduction of one macronutrient (e.g., saturated fat or animal protein) must be accompanied by an increase in other macronutrients (e.g. carbohydrate) to maintain weight. It may thus be difficult to ascertain whether potential outcomes are related to changing the macronutrient of interest (e.g., soy protein) or to what replaced that macronutrient (e.g., milk protein). Similarly, the possibility that differences in intake of the micronutrient of interest may be correlated with other dietary differences (e.g. changes in vitamin E intake with changes in the fatty acid profile of the diet).

Clearly defining the outcomes of interest is critical to focusing the systematic review questions to those topics that are relevant to determining nutrient reference values. The types of outcomes are different depending on the analytic framework linkage being addressed. These may include human tissue (e.g., serum, liver, erythrocyte) levels, surrogate or intermediate markers of disease (e.g., lipoproteins, blood pressure, inflammatory markers), or clinical outcomes (e.g., cancer, cardiovascular disease, death). In general, the ultimate question of interest is what levels of intake (whether too little or too much) are associated with poor clinical outcomes. However, studies that directly address this question are relatively rare. Judgments need to be made about how reliably surrogate outcomes or disease markers predict clinical outcomes.

Prior to conducting literature searches and analyzing the data the study designs of interest (e.g., randomized controlled trials, other comparative trials, prospective or retrospective analyses, cross-sectional or longitudinal studies, adjusted or unadjusted analyses) need to be established. In addition, the year that studies were conducted should be part of the inclusion criteria because for many topics the earliest studies may no longer be relevant. One needs to take into consideration how the science (e.g., measurement tools for exposures and outcomes) may have changed or possibly how dietary, exercise, or other health-related factors have changed. It is also necessary to determine the minimum number of subjects that should be included and, depending on the study design, the minimum duration of follow-up. These decisions may be somewhat arbitrary but they balance the need to focus the review on the studies most likely to provide useful results with the need to often incorporate sparse data. Very small studies (e.g., case series) may provide useful lists of potential adverse events but are unlikely to provide precise estimates of effect sizes. Studies of “too” short a duration may be inadequate to estimate outcomes of interest (e.g., change in lipoprotein level or cancer incidence).

Chapter 4. Workgroup Exercise

The purpose of this project was to conduct an exercise to explore the feasibility of integrating systematic reviews into decision-making processes for deriving nutrient reference values, as well as to identify unanticipated issues and challenges. The EPC led an interactive process with a workgroup comprised of: 1) a panel of scientific experts that include scientists knowledgeable about establishing nutrient reference values such as those used to establish DRIs, 2) ODS-designated liaisons (including representatives from AHRQ, DHHS, FDA, FNB/IOM, ODS, and USDA/CNPP), and 3) EPC staff. Specifically, the aims of this project were to:

- Identify the types of sequential questions that need to be informed by science in the process of making decisions relative to derivation of nutrient reference intakes.
- Identify how these questions interact with the decision-making process and which questions lend themselves to systematic review approaches.
- Identify options, with appropriate modifications, for incorporating systematic reviews and evidence-based methods into the nutrient reference intake decision-making process.
- Describe pros and cons and appropriate and inappropriate applications of systematic reviews for nutrient reference intake decision-making processes.

The activities for the workgroup consisted of teleconferences, e-mail discussions, and two 1-day meetings. ODS-designated liaisons helped plan the activities and participated as observers and resources to the scientific panel meetings. The EPC staff and ODS-designated liaisons held teleconferences to select the case study nutrient, identified scientific experts to serve on the workgroup, and formulated the agenda for the meetings. Vitamin A was selected as the case study nutrient by ODS with input from the EPC and other ODS-designated liaisons prior to selection of scientific experts. Vitamin A was selected because it encompasses many of the challenges that are anticipated to arise in the process for revising the current DRIs.

Eight scientific experts from various academic institutions were invited to participate in the workgroup. They included vitamin A researchers, experts with a good understanding of the issues in setting nutrient reference values, and people with expertise in other nutrients in order to consider issues that may be encountered in nutrition topics other than vitamin A. Due to scheduling conflicts, two individuals who initially accepted the invitation were unable to participate in the workgroup teleconferences and meetings.

The workgroup exercise focused on the process of identifying and reviewing evidence to address specific questions. The workgroup did not make specific recommendations on nutrient values or how an expert panel should integrate the evidence into its decision-making process because these topics were outside the scope of the current project. While the workgroup carried out the exercise of formulating research questions for systematic reviews, building analytic frameworks, and screening a sample of potentially relevant abstracts, actual systematic reviews of the questions were not conducted.

Activities Surrounding the First Meeting

The first workgroup meeting was held on June 20, 2007. It focused on the nature of the questions related to systematic reviews and the process for interfacing with the decision-making paradigms associated with establishing nutrient reference values (the meeting agenda is

presented in Appendix A). Prior to the meeting, ODS in conjunction with its designated liaisons and the EPC staff, drafted potential science-based generic questions that were thought likely to arise during deliberations on establishing nutrient reference values. The EPC then convened two teleconferences with the entire workgroup to review and revise the generic questions. The agreed upon preliminary questions guided the EPC staff to prepare a draft analytic framework and to conduct preliminary literature searches in preparation for the first meeting.

The meeting began with a discussion of the potentials and limitations of evidence-based methods, and the experiences of several groups (including AHRQ and the USPSTF) that have applied these tools. Workgroup members involved in the last vitamin A DRI panel also presented their experience. The EPC staff presented a draft analytic framework and preliminary questions derived from it. The workgroup discussed issues related to identifying indicators or outcomes that would be needed to determine nutrient reference values and how the standard systematic review process might usefully interface with the decisions-making process for establishing these values.

The EPC staff presented methodological approaches for selecting studies, critically appraising them, and summarizing evidence for systematic reviews. This was followed by a workgroup discussion of the relevance of these issues to the process of establishing nutrient reference values. The workgroup completed the session by specifying the PICO criteria for agreed upon key questions. An example of a key question that was formulated as a result of the discussion and upon which an evidence map was produced was “What level of plasma retinol and/or beta-carotene is associated with greater risk of morbidity, mortality, xerophthalmia, immune dysfunction or compromise, and poor growth status in children?”

Following the workgroup meeting, the EPC incorporated workgroup suggestions and:

- Refined the analytic framework (see Figure 2)
- Refined the research questions for systematic reviews
- Refined the review criteria (PICO)
- Refined and implemented the MEDLINE® search strategies (Appendix B)
- Screened abstracts obtained from the literature search and estimated the amount of literature available to address questions
- Developed a data extraction form and performed data extraction on a few full-text articles as prototypes
- Developed generic evidence and summary tables (Appendix C)
- Generated evidence maps for questions to be addressed by systematic review

Activities Surrounding the Second Meeting

The second workgroup meeting was held on August 13, 2007. Workgroup members reviewed the refined analytic framework and an evidence map on one of the key questions, discussed an analytic framework for deriving upper intake limits, and provided feedback on the usefulness of integrating evidence-based methods to the process of developing nutrient reference values.

An important activity of this meeting was an abstract evaluation exercise led by the EPC staff (Appendix D). The purpose of this exercise was to provide workgroup members with the experience of evaluating abstracts obtained from literature search guided by the key questions. The goal was to gain an appreciation of the issues and challenges of an unbiased review of the literature. Prior to the second meeting, EPC staff selected 20 abstracts representative of different

issues in applying eligibility criteria. At the meeting, workgroup members discussed the relevance of the article for the question of interest. The exercise highlighted disagreements among experts in evaluating potential evidence and revealed some of the fundamental problems in expert workgroups convening without an explicit analytic framework for assessing evidence. This exercise was instructive and much appreciated by the workgroup members. The success of this abstract exercise was reflected by the voluntary request from workgroup members for a similar exercise via a teleconference on questions related to upper tolerable limits. This was conducted on October 1, 2007, on 20 abstracts selected from a literature search on potential harms of vitamin A (Appendix E).

Analytic Framework for Vitamin A Reference Value

Discussed in this section are two specific analytic frameworks resulting from the workgroup meetings. These frameworks could be used to guide systematic reviews of the key questions.

Specific Example – Vitamin A Requirement

Figure 3 shows an example of a general analytic framework to establish adequate levels of vitamin A intake (e.g., when identifying means such as an EAR). Here, clinical outcomes considered were death, xerophthalmia, night blindness and immune dysfunction. These clinical outcomes need be more clearly defined in an actual systematic review, as discussed earlier in the Systematic Review Methods section.

Because of the buffering effect of liver stores of vitamin A on plasma concentrations the relationship between plasma retinol and dietary vitamin A intake reaches a plateau after a certain level of intake has been achieved (excess is stored in the liver). However, when liver vitamin A concentrations drop below a critical level (e.g., 20 $\mu\text{g}/\text{mg}$) serum vitamin A levels also decrease, resulting in a number of clinical and surrogate outcomes.

There are no validated surrogate outcomes for each one of the aforementioned clinical endpoints.

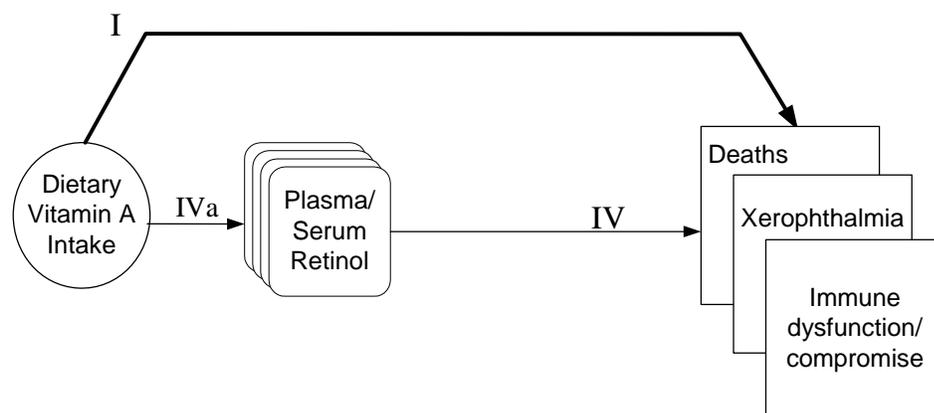


Figure 3. Analytic Framework for adequacy of Vitamin A intake. Note that in the figure “Immune dysfunction/compromise” serves as a placeholder for a clinical outcome that has not yet been defined by the workgroup.

Specific Example – Vitamin A Excessive Intake

Figure 4 describes a general analytic framework that could be considered for the estimation of upper level of intake (e.g., when identifying a UL). The clinical endpoints are different from those considered for establishing requirements or adequate intake levels. Again, a separate analytic framework would be considered for each outcome.

Note that because bone mineral density is a valid surrogate for fractures we opted to consider it as a surrogate endpoint. A different biomarker of intake (plasma retinyl ester rather than serum retinol) is considered when focusing on excess intake. Circulating retinyl esters levels rise once the hepatic capacity to store vitamin A has been exceeded.

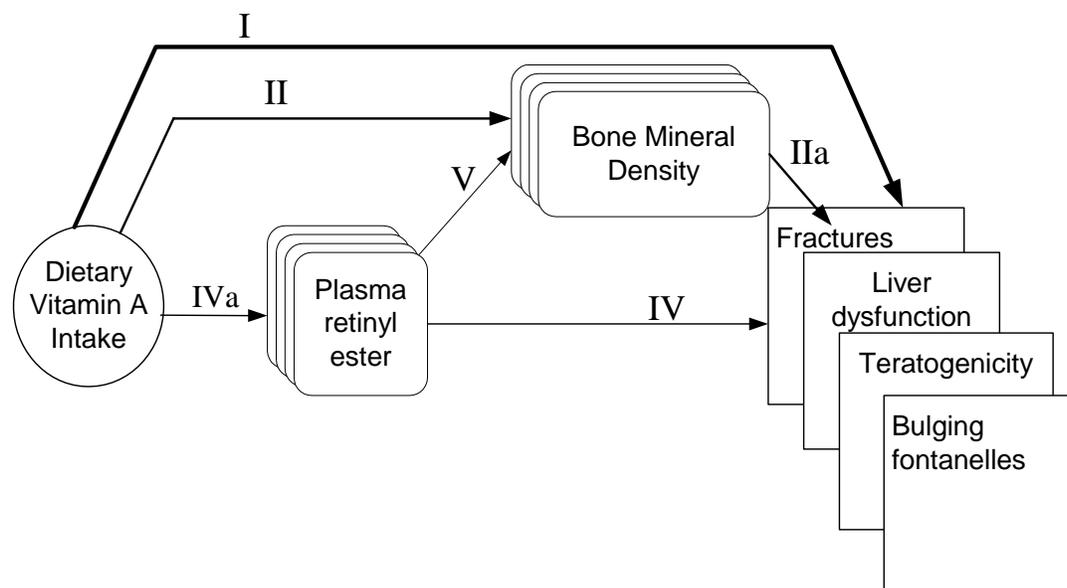


Figure 4. Analytic Framework for Vitamin A Excessive Intake

Evidence Map for Key Questions on Vitamin A Reference Values

The aim of the evidence map presented here is to provide an indication of the potential number of studies that might be available to address the relationships between vitamin A and/or beta-carotene and the risk of morbidity and mortality, xerophthalmia, immune dysfunction or compromise in adults, and the risk of poor growth in children. In practice, only a fraction (5 to 30 percent, dependent on the topic) of abstracts identified as potentially relevant will be found acceptable upon full text evaluation.

After extensive consultation with workgroup members, the EPC staff searched MEDLINE® from 1950 to July 2007 using key words for serum or plasma vitamin A, retinol, retinyl ester, pro-vitamin A, and beta-carotene, and exploring various MSH heading for outcomes of interests (e.g., mortality, xerophthalmia, dark adaptation, infection, failure to thrive). We limited the abstracts to English language and human studies. We excluded case reports and review articles. The completed search strategy is described in Appendix B.

The MEDLINE® search yielded a total of 3,170 abstracts. We screened all of these abstracts using the following eligibility criteria. These criteria were developed with input of the workgroup members based on the key question.

- Inclusion criteria:
 - Population: all human studies
 - For growth outcome – children only
 - Exposure: blood vitamin A measurements (e.g., plasma retinol, retinoic acids, retinal, retinyl ester); blood beta-carotene, a vitamin A, or beta-carotene intervention, or the presence of “vitamin A deficiency”, or “vitamin A status” was measured
 - Comparator: different levels or concentrations in individual or population
 - Outcomes: as mentioned above according to the exposure
 - Study designs: any design
 - For mother-and-infant pair study – the exposure and outcome can be measured in either mother or infant, or both
- Exclusion criteria:
 - Non-human
 - Study designs: in vitro¹, ex vivo² (or cell level outcomes only)
 - For outcomes of immune dysfunction or compromise outcome (including cancer outcomes) – cross-sectional design
 - Exposure: All-trans retinoic acid therapy
 - Diseases or conditions at baseline (in the whole study population):
 - Kidney diseases, liver disease, kidney, or liver transplantation, HIV-AIDS, diseases or conditions requiring medications that may interfere with lipid or protein metabolism, acute infectious diseases (e.g., malaria, meningococcal meningitis, trichuriasis)
 - For plasma retinyl ester only – hyperlipidemia

A total of 363 (11 percent) out of 3,170 abstracts were screened in by applying the above eligibility criteria. Table 1 shows the breakdown of the potentially qualifying abstracts per exposure and outcome category. It should be noted that the purpose of this project was not to actually review potentially relevant articles identified through the literature search.

Table 1. Number of potentially qualifying studies per exposure and outcome category among 363 abstracts meeting criteria †

	Mortality	Vision	Immune	Growth (children only)	Total
Serum or plasma retinol	19	82	71	48	248
Serum or plasma beta-carotene	21	2	33	2	65
Both	15	5	25	4	50
Total	55	89	129	54	363

† Cells across the same row are not mutually exclusive.

¹ In vitro experimentation means manipulating the living tissues directly (e.g., incubate the pigs’ hepatocytes in vitamin A enriched solution, then measure the enzymes of interest).

² Ex vivo experimentation means isolating the living tissues of interest after manipulating the whole organism in some experimental way (e.g., feed the pigs extra loads of vitamin A, then isolate the pigs’ hepatocytes for analysis)

Operationalizing the Model of Using Systematic Reviews to Inform the Development of Nutrient Reference Values

The model posits the formation of a workgroup composed of experts in the field of the nutrient of interest (domain experts) who are charged with drafting the recommendations concerning that nutrient, supported by a team of methodologists who are charged with reviewing (or assisting the review of) the evidence. Members may overlap between the two groups depending on the individual expertise and interest. Regardless, it is important for workgroup members to be familiar with the evidence-based review process so that the findings and limitations of the review are appropriately understood and utilized. Similarly, it is important for methodologists to understand the nuances and limitations of the scientific evidence base concerning the specific nutrient under review.

For those experts in nutrition who are unfamiliar with the process of systematic review, training in evidence-based process could be introduced at the beginning of the deliberations or on an ad hoc basis, as needed. Similarly, workgroup members who are experts in the field of nutrition could also serve as consultants to the methodologists, explaining the science concerning the specific nutrients.

The following are the potential responsibilities of the methodologists:

- Conduct preliminary literature searches
- Facilitate the first workgroup meeting where domain experts will be familiarized with the systematic review process, including formulation of the analytic framework and the key questions; study eligibility criteria; quality and applicability grading, and grading strength of evidence; how study results will be synthesized and presented
- Continue workgroup training by either teleconferences and/or email
- Perform literature review with further input from the workgroup
- Create evidence tables for publication and use by the workgroup
- Facilitate additional workgroup meetings as needed

The following are the potential responsibilities of the domain expert workgroup members:

- Become familiar with the evidence-review process
- Be available to the methodologists as domain experts in the evidence-review process
- Help formulate literature search strategy
- Help determine what data need to be extracted from studies and summarized in evidence tables
- Suggest criteria for critical appraisal (quality assessment) of the primary studies
- Review the content of evidence tables for accuracy and completeness
- Discuss with the methodologists on how the systematically-gathered evidence may or may not be helpful in crafting the recommendations; and how the review process could be refined
- Identify missing key studies

Numerous sequential and overlapping methods could be used for training of domain expert members of the workgroup. The entire workgroup can be introduced to the concepts and process

of systematic review at an introductory face-to-face meeting. This process includes the important step of ensuring acceptance of the methodologies by the workgroup members, along with individualization of the process to the needs of both the specific nutrient of interest and the workgroup members. At this meeting, discussions would center on the analytic framework, formulation of the key questions, the rationale for specific inclusion and exclusion criteria, important factors for data extraction, and quality and applicability assessment of the evidence. Didactic presentations, group discussions, and hands-on exercises could be used at these workgroup meetings. Training in evidence-based methods could continue, in an iterative fashion, through e-mail, multiple teleconferences, subsequent written materials, individualized consultations regarding specific issues, and at subsequent workgroup meetings.

Chapter 5. Summary

In this exercise, the EPC staff began by reviewing the literature cited for the vitamin A section in the DRI publication. A simple analytical framework was created as an approach to the process of systematic review to derive reference values for vitamin A. This “straw man” model was introduced to the workgroup members during a series of teleconferences. Based on the domain experts’ input, the EPC staff refined the analytical framework for the systematic review process. A preliminary search of the literature was conducted and it yielded several thousand potentially relevant abstracts. EPC staff provided introductory training to the workgroup members in the methodology of conducting the systematic review during teleconferences and at the first workgroup meeting. This included familiarizing them with the systematic search strategy - drafting well focused key questions and establishing the PICO criteria, explicit descriptions of the population, interventions (or exposures), comparators, and outcomes. The expert panel created a set of key questions and systematically worked through the biological roles of vitamin A in the body. An abstract screening session led by EPC staff was conducted at the second meeting. All workgroup members participated in this exercise. A sample of 20 abstracts was selected using the PICO criteria. Through an iterative process, the PICO criteria were further refined and finalized by the workgroup members.

This short training exercise raised the workgroup members’ awareness and appreciation of the methodological rigor and the transparency involved in the systematic review process. The need for systematic appraisal of the literature was apparent in their discussions and there was willingness to incorporate the systematic review methodology into future efforts to review and potentially revise nutrient reference values.

Conclusions

The published literature on vitamin A is large and its extent is likely similar to that of most other nutrients for which reference values have been or have yet to be established. The lesson learned from this exercise, focused on vitamin A, suggests that evidence-based methods, including systematic reviews, are applicable to the development of nutrient reference values, with appropriate nutrient specific modifications. When the volume of literature is large, rational and well-defined eligibility criteria must be applied in conducting a systematic review to manage the workload. Appropriate questions must be formulated so that the answers to those questions can be used to inform the derivation of a set of reference values and help to ensure transparency and reproducibility, and form the foundation for future updates as new data emerge.

In the past, the process to derive a set of reference values for a particular nutrient has been, to a large degree, dependent on the make up of the expert panel. Using this new approach, it would be not only important that the members of the expert panel represent a balanced range of scientific views but that they also are familiarized with the process of conducting a systematic review and interpreting its results.

It became apparent from this exercise that it would be desirable if nutrient reference values could be linked to specific health outcome(s). Although this issue presents challenges it should be considered in the future. The process in selecting specific health outcomes and intermediate outcomes (e.g., biomarkers, indicators) when specific health outcomes are not available for deriving of a reference value should be defined prior to starting systematic reviews.

Some of the issues in the existing literature that will need to be addressed directly when applying systematic reviews to the process of establishing nutrient reference values include: generalizability of well-controlled experiments but with few subjects (e.g., <10) or subjects selected from limited spectrum of the general population; applicability of findings of animal studies to humans; generalizability of early studies that employed methodologies that are not state of the art or directly comparable to contemporaneous data; and appropriate interpretation and integration of scientific evidence from observational studies. Contemporary issues such as the role of genomics, and en masse nutrient fortification will also need to be factored in when undertaking this process.

References

- (1) Institute of Medicine. Dietary Reference Intakes. The Essential Guide to Nutrient Requirements. National Academy of Sciences; 2006.
- (2) Institute of Medicine. Dietary Reference Intakes. Calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy of Sciences; 1997.
- (3) Institute of Medicine. Dietary Reference Intakes. Thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. National Academy of Science; 1998.
- (4) Institute of Medicine. Dietary Reference Intakes. Vitamin C, vitamin E, selenium, and carotenoids. National Academy of Science; 2000.
- (5) Institute of Medicine. Dietary Reference Intakes. Vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. National Academy of Sciences; 2001.
- (6) Institute of Medicine. Dietary Reference Intakes. Energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. National Academy of Sciences; 2005.
- (7) Institute of Medicine. Dietary Reference Intakes. Water, potassium, sodium, chloride, and sulfate. National Academy of Sciences; 2005.
- (8) Institute of Medicine. The development of DRIs 1994-2004: Lessons learned and new challenges—workshop summary. National Academy of Sciences; 2008.
- (9) A model for establishing upper levels of intake for nutrients and related substances: report of a Joint FAO/WHO technical Workshop on Food Nutrient Risk Assessment. WHO Headquarters; May 2005.
- (10) Users' guides to the medical literature. A manual for evidence-based clinical practice. AMA Press; 2002.
- (11) Morris CD, Carson S. Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2003; **139**: 56-70.
- (12) National Institutes of Health State-of-the-science conference statement: multivitamin/mineral supplements and chronic disease prevention. *Ann Intern Med* 2006; **145**: 364-71.
- (13) Blumberg-Kason S, Lipscomb R. Evidence-based nutrition practice guidelines: A valuable resource in the evidence analysis library. *J Am Diet Assoc* 2006; **106**: 1935-6.

- (14) Becker LA, van Binsbergen JJ. How can a proposed Cochrane diet and nutrition field work effectively? *Eur J Clin Nutr* 2005; **59 Suppl 1**: S167-S171.
- (15) De LM, Salen P. Fish and N-3 fatty acids for the prevention and treatment of coronary heart disease: nutrition is not pharmacology. *Am J Med* 2002; **112**: 316-9.
- (16) Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Ann Intern Med* 1997; **127**: 380-7.
- (17) Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001; **20**: 21-35.
- (18) Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials* 1995; **16**: 62-73.
- (19) Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273**: 408-12.
- (20) Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* 2001; **135**: 982-9.
- (21) Linde K, Scholz M, Ramirez G, Clausius N, Melchart D, Jonas WB. Impact of study quality on outcome in placebo-controlled trials of homeopathy. *J Clin Epidemiol* 1999; **52**: 631-6.
- (22) Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; **352**: 609-13.
- (23) Balk EM, Bonis PA, Moskowitz H, Schmid CH, Ioannidis JP, Wang C et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* 2002; **287**: 2973-82.
- (24) Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; **52**: 377-84.
- (25) Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007; **36**: 666-76.
- (26) Verhagen AP, de Vet HC, de Bie RA, Boers M, van den Brandt PA. The art of quality assessment of RCTs included in systematic reviews. *J Clin Epidemiol* 2001; **54**: 651-4.

- (27) The Cochrane Collaboration. The Cochrane Handbook. <http://www.cochrane.org/resources/handbook/index.htm>.
- (28) Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; **127**: 820-6.
- (29) Miller ER, III, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; **142**: 37-46.
- (30) Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet* 1998; **351**: 123-7.
- (31) Beard J, Borel M, Peterson FJ. Changes in iron status during weight loss with very-low-energy diets. *Am J Clin Nutr* 1997; **66**: 104-10.
- (32) Rock CL, Vasantharajan S. Vitamin status of eating disorder patients: relationship to clinical indices and effect of treatment. *Int J Eat Disord* 1995; **18**: 257-62.
- (33) Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000; **72**: 690-3.
- (34) Blanck HM, Bowman BA, Cooper GR, Myers GL, Miller DT. Laboratory issues: use of nutritional biomarkers. *J Nutr* 2003; **133 Suppl 3**: 888S-94S.

Acronyms

ADA:	American Dietetic Association
AHRQ:	Agency for Healthcare Research and Quality
AI:	Adequate Intake
CDC:	Centers for Disease Control
DHHS:	Department of Health and Human Services (US)
DRI:	Dietary Reference Intakes
EAR:	Estimated Average Requirement
EBM:	Evidence-based Medicine
EPC:	Evidence-based Practice Center
EU-SCF:	European Union – Scientific Committee on Food
EVM:	Expert Group on Vitamins and Minerals (UK)
FDA:	Food and Drug Administration
FNB [IOM]:	Food and Nutrition Board
IOM:	Institutes of Medicine (US)
NIH:	National Institutes of Health
ODS:	Office for Dietary Supplements
PICO:	Population, Intervention (or exposure), Comparator, Outcome
UL:	Tolerable Upper Intake Level.
USDA/CNPP:	United States Department of Agriculture, Center for Nutrition Policy and Promotion
USPSTF:	United States Preventive Services Task Force

Glossary

Biomarkers of intake are measurements of the nutrient itself or a metabolite of the substance in biological samples (e.g., serum selenium) that have been validated to confirm that they reflect the level of intake of that nutrient.

Clinical outcome is a measure of how a patient (or study subject) feels, functions, or survives; or a clinical measurement of the incidence or severity of a disease (e.g., diagnosis of disease).

Essential nutrient is a nutrient required for normal body functioning that cannot be synthesized by the body and must be obtained from a dietary source.

Indicator markers (of nutrient intakes) are measures correlated with dietary intake levels of a nutrient, such as biomarkers of intake, nutritional status, or markers of nutritional status.

Marker of nutritional status is a laboratory measurement or a physical sign that is thought to reflect the early stage of an abnormality (either deficiency or toxicity) of a nutrient intake. Changes induced by a nutritional intervention on the marker of nutritional status are expected to reflect the correction of the abnormality.

Nutritional status is the state of a person's health in terms of the nutrients in his or her diet. Nutritional status is a global term that encompasses a number of specific components from nutritional assessments.

Nutritional assessment is a comprehensive approach to define nutritional status using medical, nutrition, and medication histories, physical examination, anthropometric measurement, and laboratory data.

Surrogate outcome marker is a laboratory measurement or a physical sign used as a substitute for a clinical outcome. Changes induced by a therapy on a surrogate outcome marker are expected to reflect changes in a clinical outcome.

Vitamin A Examples:

- Plasma retinol is a biomarker of inadequate intake
- Bone mineral density is a surrogate outcome marker of osteoporosis
- Mortality, xerophthalmia and poor growth status in children are clinical outcomes
- Dark adaptation test is a marker of nutritional status
- Vitamin A deficiency is a nutritional status, which is a global term. There are various markers of vitamin A deficiency including an abnormal dark adaptation test (a marker of nutritional status), low plasma retinol (a biomarker of intake), and xerophthalmia (a clinical outcome).

Workshop Participants

Academic Institutions

Stephanie Atkinson, Ph.D.; McMaster University
Edward L. Giovannucci, M.D., Sc.D.; Brigham and Women's Hospital
Susan Taylor Mayne, Ph.D.; Yale University School of Medicine
A. Catharine Ross, Ph.D.; Penn State University
Robert Russell, M.D.; Jean Mayer USDA HNRCA
Keith West, Ph.D.; Johns Hopkins University School of Public Health

Federal Government Agencies/IOM*

Stephanie Chang, M.D., M.P.H.; AHRQ
Joan M.G. Lyon, M.S., R.D., L.D.; USDA/CNPP
Kathryn Y. McMurry, M.S.; DHHS
Mary Frances Picciano, Ph.D.; ODS, NIH
Christine Taylor, Ph.D.; IOM
Ann Thurn, Ph.D.; ODS, NIH
Paula R. Trumbo, Ph.D.; FDA
Dorothea K. Vafiadis, M.S.; USDA/CNPP
Elizabeth A. Yetley, Ph.D.; ODS, NIH

Tufts EPC

Joseph Lau, M.D.
Ethan M. Balk, M.D., M.P.H.
Mei Chung, M.P.H.
Deirdre Devine, M.Litt.
Stanley Ip, M.D.
Gowri Raman, M.D.
Thomas Trikalinos, M.D., Ph.D.
Alice H. Lichtenstein, Sc.D.

* Members in this category are participants of the workshop but not authors of this report.