Framework for DRI Development

Components "Known" and Components "To Be Explored"

BACKGROUND PAPER

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ACRONYMS

AI	Adequate Intake
AMDR	Acceptable Macronutrient Distribution Range
BW	body weight
DRI	Dietary Reference Intake
EAR	Estimated Average Requirement
EER	Estimated Energy Requirement
FACA	Federal Advisory Committee Act
FAO	Food and Agriculture Organization of the United Nations
FNB	Food and Nutrition Board
IOM	Institute of Medicine
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
RDA	Recommended Dietary Allowance
RNI	Recommended Nutrient Intake
SEBR	systematic evidence-based review
UL	tolerable upper intake level
WHO	World Health Organization

ACRONYMS IN APPENDICES

α-EALT	erythrocyte alanine aminotransferase
α-EAST	erythrocyte aspartate aminotransferase
CHO	carbohydrates
BMC	bone mineral content
BMD	bone mineral density
DNA	deoxyribonucleic acid
EGR	erythrocyte glutathione reductase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
NAD	nicotinamide adenine dinucleotide
NHANES III	Third National Health and Nutrition Examination Survey
PIVKA	proteins induced by vitamin K absence

1. INTRODUCTION

1.1 Scope of Work
1.2 Background
1.3 Acronyms and Terminology
1.4 Organization of Topics

1.1 Scope of Work

This background paper outlines the general *knowns* as well as the components *to be explored* (or perhaps the *unknowns*) regarding development of the Dietary Reference Intakes (DRIs). The general "bare bones" framework for DRI development is described. The paper describes the current general state of understanding relevant to DRI development as acquired by the experiences since DRIs were first introduced, as well as those of the more than 50 preceding years of reference value development. It also highlights the gaps in knowledge and issues to be explored to point the way to needed next steps and refinements.

The paper draws heavily from the discussions that took place in September 2007 during a workshop—hereafter referred to as Workshop2007—convened by the Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) and sponsored by the U.S. and Canadian governments. Workshop2007 was designed to explore emerging challenges and lessons learned from the new approach to creating nutrient reference values put in place by the IOM/FNB in 1994. The goal was to identify those aspects of the process that could be enhanced, as well as to acknowledge components that had been successful. Information about the workshop including its summary[2] can be found on the IOM website at http://www.iom.edu/driworkshop2007.

Following Workshop2007, Health Canada entered into a contract with the IOM/FNB to develop this paper. Responsibility for the content of this paper rests with the author and does not necessarily represent the views of the IOM or its committees and convening bodies. The scope of work for the paper was specified in cooperation with representatives from the U.S. Federal DRI Steering Committee. The paper is intended to outline the general framework for the development of DRIs. To this end, it is to specify the major steps and considerations for the process, specifically discussing (a) existing conceptual underpinnings and key components of the DRIs; (b) initial steps of problem formulation and sponsor/stakeholder input activities; and (c) possible decision-making tasks for future study committees including the available criteria for doing so, and the tasks of report development and risk characterization.

[2] IOM (2008).

Further, the paper is to identify gaps in the understandings, guidance, criteria or methodological knowledge base relevant to the general approach for DRI development. These appear as "Issues/Gaps" sections within the paper and may help target future studies or collaborative work to enhance the approach for DRI development. Some of the "Issues/Gaps" require scientific considerations and others focus on decisions concerning common understandings or conceptual underpinnings.

Finally, the scope of work indicated that the framework outlined in this paper is to (a) allow for enhanced transparency and documentation of decision making, (b) incorporate the risk assessment approach, (c) incorporate systematic evidence-based reviews (SEBRs) or related methodologies, (d) include consideration of the complexity and multifactorial nature of chronic disease indicators, as data allow and as strategies are developed, and (e) ensure a specific risk characterization component.

In drawing on the discussions from Workshop2007, efforts were made to reorganize and integrate the discussions as they relate to components of a DRI framework and to the major questions and issues that have arisen. Other available documents identified during the planning stage of Workshop2007 or noted during the workshop were also used. A comprehensive search for relevant literature was outside the scope of this paper. Undoubtedly other useful resources exist, and their failure to be included is not a judgment of their relevance or worth.

► 1.2 Background

Reference values known in the United States as Recommended Dietary Allowances (RDAs) and in Canada as Recommended Nutrient Intakes (RNIs) were used through the 1990s. They were established primarily to assist federal agencies in developing nutrition policy, and have also been used by an array of scientists and public health professionals. In 1994, in response to important changes in the nutrition field as well as the recognition that for many nutrients the single RDA or RNI values did not meet the expanding needs for nutrient reference values, the IOM began an initiative to develop a new, broader set of values known as the DRIs. The U.S. and Canadian governments supported this initiative.

In brief, the DRIs reflect an expansion as compared to RDAs and RNIs and:

- Includes estimated average requirements and upper levels of intake, where appropriate, so as to specifically highlight concepts of probility and risk for defining nutrient reference values;
- incorporates consideration of reference values germane to the reductionof chronic disease risk, as data allow; and
- includes review of "nonclassical" nutrients such as fiber and carotenoids;

In short, the DRIs were foreshadowed as a set of values that would include more than an RDA, specifically additions that became known as the Estimated Average Requirement

(EAR) and the tolerable upper intake level (UL). Activities in 1997 and beyond added other components to the DRIs as well as publications to guide application of the DRIs in planning and assessing diets.

The values that comprise the DRIs are shown in Table 1-1.

Table 1-1: Components of the Dietary Reference Intakes, 1994–2004

DRI component	Description
Estimated Average Requirement (EAR)	Reflects the estimated median requirement and is particularly appropriate for applications related to planning and assessing intakes for groups of persons.
Recommended Dietary Allowance (RDA)	Derived from the EAR and intended to cover the requirements for 97–98 percent of the population.
Tolerable Upper Intake Level (UL)	Highest average intake that is likely to pose no risk.
Adequate Intake (AI)	Used when an EAR/RDA cannot be developed; average intake level based on observed or experimental intakes.
Acceptable Macronutrient Distribution Range (AMDR)	An intake range for an energy source associated with reduced risk of chronic disease.
Estimated Energy Requirement (EER)	Average dietary energy intake predicted to maintain energy balance in a healthy adult of defined age, gender, weight, height and level of physical activity that is consistent with good health.

These reference values, along with descriptive text, are contained in six volumes published by the IOM between 1997 and 2005 (http://www.iom.edu/CMS/3708.aspx). To help users understand the DRIs, given the expansion of both the nutrient reference value approach and the types of reference values issued, two publications were created to provide general guidance for users. One is focused on uses related to planning[3] and the other on uses for assessment.[4] In 2006, the IOM issued *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*,[5] which is available in English and French. It provides an overall summary of the DRIs.

The committees associated with the 1994–2004 DRI development process are illustrated in Figure 1-1 below. The groupings of nutrients addressed by the six study committees are also shown.

[3] IOM (2003).
[4] IOM (2000).
[5] IOM (2006).

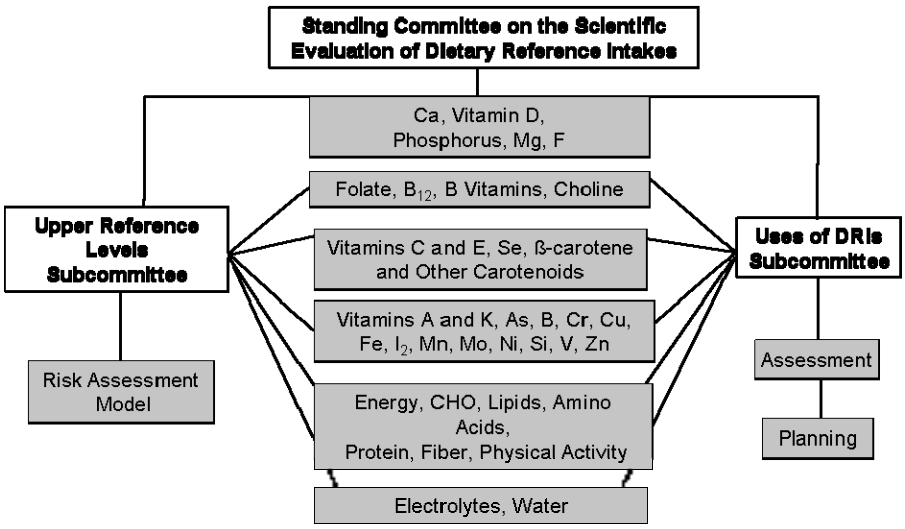


Figure 1-1: Dietary Reference Intake Development, 1994–2004: Committees and Topic Areas

► 1.3 Acronyms and Terminology

Discussions about DRIs are characterized by acronyms, special terms and a parlance that can be challenging and at times conflicting. The acronyms used in this paper are included in the list that follows the table of contents.

Three documents are referred to frequently in the paper, and a special abbreviated version of their titles is used. One is **Workshop2007**, which is used without a specific reference citing but is included in the reference listing at the end of the paper.[6] It refers to the workshop summary mentioned earlier reflecting the discussions held in September 2007 that explored the lessons learned and new challenges that have emerged as a result of the 10-year experience of developing DRIs. As appropriate, references to the discussions that took place during the workshop are footnoted in this paper. Reference may be made to a presentation by a specific "presenter" in a specific session of the workshop, remarks made by a designated "discussant" or comments from unspecified "participants" who may be unidentified presenters, discussants or members of the audience.

Additionally, reference is made to the **1994 DRI Plan**. This is an IOM/FNB document describing the revisions to the RDA development process that resulted in the DRIs. It is found in the reference listing as well.[7] Also, a report from a workshop jointly convened by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), and charged with considering the model for establishing upper levels of intake for nutrient substances, contains much background material useful for this paper. Relevant discussions from this report are included as appropriate, and for

[6] IOM (2008).
[7] IOM (1994).

simplicity the report is referred to as the **FAO/WHO Report**. It also can be located in the reference list.[8]

Although care was taken to use terms consistently in this report, some terms warrant special attention. Readers will note the term *indicator*, which appears in place of all terms that commonly refer to the measures that serve (or have been considered) as the basis for establishing DRI values. The term therefore encompasses what are variously referred to as *endpoints*, *surrogates*, *biomarkers* or *risk factors*. Clearly, not all indicators are of a similar nature, and the DRI indicators are quite varied, as shown in Appendix 1. Additionally, the term *clinical outcome* (sometimes referred to as *health outcome*) is used to refer to the ultimate measurable effect of interest for nutrients. Other measures preceding the occurrence of a clinical outcome are presumably reflective of an undesirable outcome[9] or predictive of the clinical outcome itself, although this is not necessarily the case and they must be validated before this can be assumed. A clinical outcome is also an indicator. Figure 1-2 illustrates the general nature and sequencing of indicators as discussed in this paper.

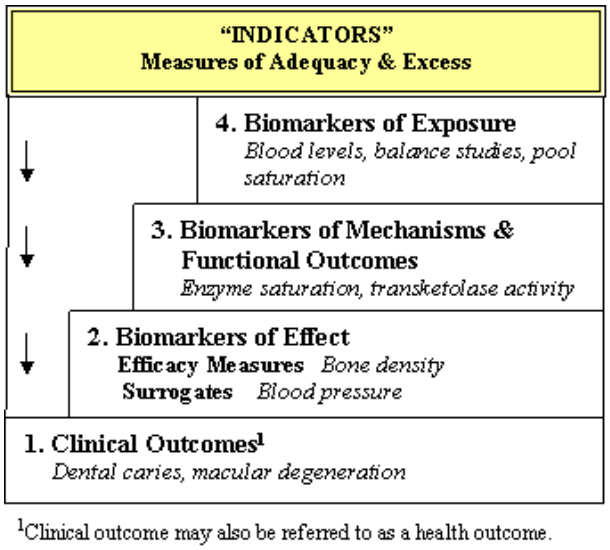


Figure 1-2: Measures Reflective of "Indicators" for Nutrient Substances.
NOTE: Numbering and arrows reflect hierarchical proximity to the clinical outcome of interest.

Further, confusion can occur regarding the use of the term *intake* synonymously with *dose* and *exposure*. Many of the organizing components for the DRI process evolved from nonnutrient fields where terms such as dose and exposure are commonly used and appropriate. Many in the nutrition field prefer the use of the term *intake* as more relevant for a substance that is essential to the body and less akin to drugs or contaminants, as might be suggested by the terms *dose* and *exposure*. This paper uses the term *intake* to refer to both *dose* and *exposure*, and at times the terms are used interchangeably.

[8] FAO/WHO (2006).
[9] Or conversely a presumably desirable outcome, such as tissue saturation.

► 1.4 Organization of Topics

Finally, the organization of the topics germane to the framework for DRI development is challenging. An effort was made to introduce the overall topic generally and to follow this with more detail in subsequent sections. The sections that follow in the paper are organized as follows:

- *Section 2*: Provides a broad-brush consideration of the framework, focusing on the nature of its general activities, its overarching principles and statistical foundation, and its link to risk analysis. Two topics that serve as "Issues/Gaps" are identified.
- *Section 3*: Begins more in-depth discussion about the conceptual underpinnings of the DRI framework, focusing on the purpose of DRIs within the context of general purpose and target populations. Two topics reflecting "Issues/Gaps" are identified.
- *Section 4*: Continues the discussion concerning conceptual underpinnings and scientific models by reviewing the values to be expressed, the general nature of appropriate indicators for DRI development and substances appropriate for DRI development. Four "Issues/Gaps" are included.
- *Section 5*: Focuses on the activities of the DRI development through the incorporation of the risk assessment scheme. Nine topics serve as "Issues/Gaps."
- *Section 6*: Highlights issues related to guidance for the general application of DRIs in assessing and planning diets for groups and individuals. Two "Issues/Gaps" are identified.
- *Section 7*: Provides a brief summary of the framework in a schematic and compiles the "Issues/Gaps" to be explored in the future.
- References and appendices are included.

2. THE DIETARY REFERENCE INTAKE FRAMEWORK

2.1 Activities Surrounding DRI Development
- 2.1.1 Activities "Inside" the Framework
- 2.1.2 Activities "Outside" the Framework
  - *Issues/Gaps 2-1: Criteria for Revisiting Existing DRI Values*

2.2 What Must a DRI Framework Accomplish?
- 2.2.1 Ensuring Transparency
- 2.2.2 Making Decisions with Limited Data: Scientific Judgment versus "No Decision"

2.3 Linking the DRI Framework to Risk Analysis
- 2.3.1 Roles within Risk Analysis
- 2.3.2 Assumptions of Risk Analysis
- 2.3.3 Probability, Prevalence, Risk and Distributions
- 2.3.4 Relevance to Federal Advisory Committee Act (FACA)
  - *Issues/Gaps 2-2: Interface between Sponsors and Study Committees during Initiation of DRI Activities*

2.4 International Collaboration

A framework is intended to be—in the words of Webster's Dictionary[10]—*a skeletal support used as the basis in an object being constructed*. The important question in the current context is how a framework manifests itself with regard to developing nutrient reference values, the quantitative levels of nutrient intake intended to assist federal agencies in establishing national nutrition policy and serve as a tool for all in planning/assessing diets of apparently healthy populations in Canada and the United States.

A framework embodies the concept of a process—*a system of operations in producing something*.[11] It must also serve to describe and focus the general goals, the key principles and the conceptual underpinnings. In the case of DRI development, the framework has to ensure that the process it provides is designed to respond to the users' needs based on a science-based, objective consideration of the available data. Given that data are often limited for the purposes of elucidating nutrient requirements and the effects of excess intake, the needed framework must provide structure and transparency for the task of scientific judgment.

This section broadly outlines basic topics related to the DRI framework. More detail and specifics about many topics introduced here are included in later sections.

[10] Soukhanov (1988).
[11] Ibid.

► 2.1 Activities Surrounding DRI Development

The many activities that surround the development of DRIs are shown in Figure 2-1. As illustrated, some activities related to the DRIs are "outside" the framework. Identifying activities as "inside" or "outside" the framework helps to organize discussions for this paper.

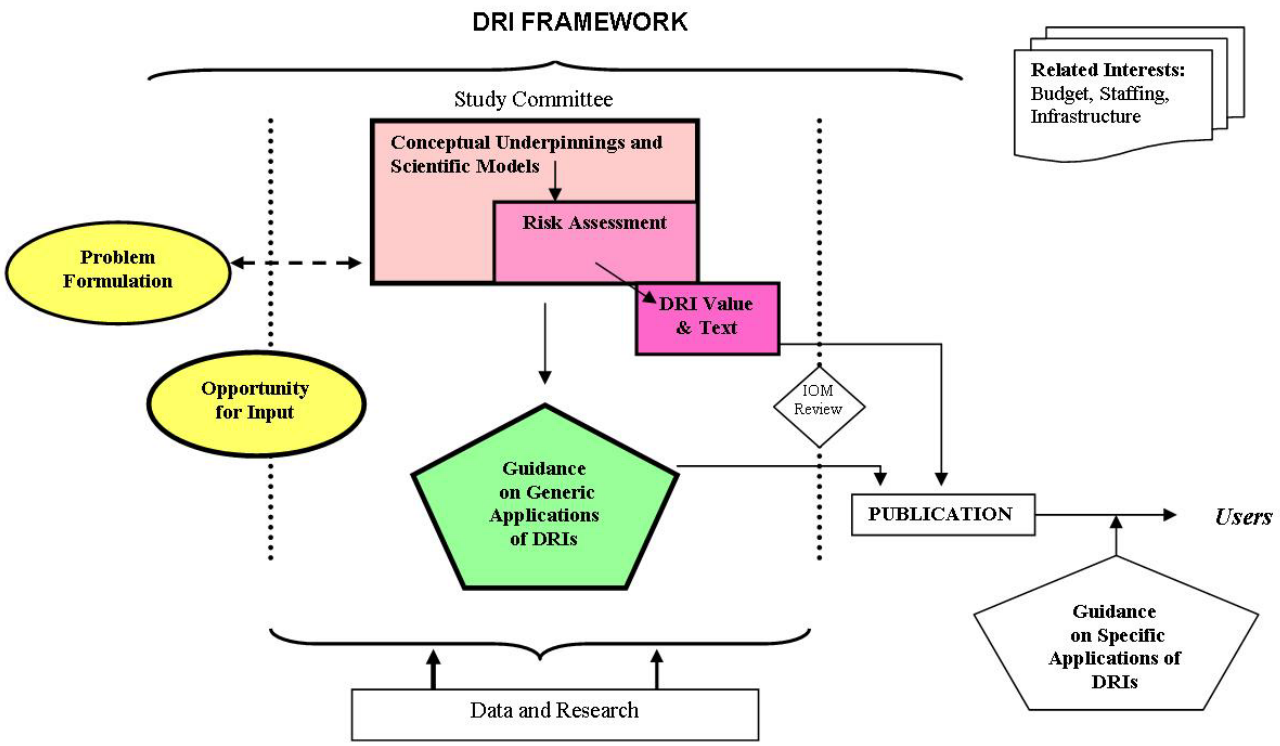


Figure 2-1: Activities Associated with DRI Development

2.1.1 Activities "Inside" the Framework

The DRI framework components are represented as colored geometric shapes under the large bracket at the top of Figure 2-1. These are the primary focus of this paper. Activities outside the framework are shown as white geometric shapes.

The framework activities initiate with a problem formulation step. The work of the study committees is shown within the vertical dotted lines and is based on a common understanding of the conceptual underpinnings and available scientific models. The existing conceptual underpinnings focus on the broad purpose of the DRIs and their basic setup. Conceptual underpinnings and scientific models include the steps of risk assessment, a component of risk analysis, which is shown as nestled within the

conceptual underpinnings and scientific models box above. As appropriate, guidance on the generic applications of the DRIs is part of the framework.

Stakeholders have opportunities for input through such activities as identifying possible committee members, taking part in public information-gathering meetings, participating in special committee-sponsored workshops, suggesting possible reviewers and serving as reviewers. Such input must be consistent with the Federal Advisory Committee Act (FACA), which applies to the work of the IOM (see Section 2.3.4), and should not undermine the scientific integrity of the study committees.

2.1.2 Activities "Outside" the Framework

An important component outside the DRI process per se is the availability of data and current research to inform the study committee deliberations. Data are central to DRI development, but activities to generate basic data about nutrients are generally outside the framework. The text accompanying DRI values highlights research needs with the hope that the listings may help to drive research agendas and enhance funding. This is further described in a summary of a workshop held in 2006.[12]

The reference values and their explanatory text, when published, are intended for use by federal policy makers as well as nutrition scientists, public health officials, dietetic practitioners, other health-related professionals and researchers in government, academia and industry. However, once the study committee reports are issued, some stakeholders may find that they have specific needs relative to their unique applications. They may, in turn, pursue targeted IOM studies to address those needs. Such studies are outside the framework. Examples of these separate studies are work to elucidate the application of DRIs for nutrition labeling or applications for specifying food packages for the U.S. Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants and Children.

Additionally, there is an array of interests for DRI development that focus on the surrounding infrastructure and tasks. These include funding and staffing, among other considerations. They are taken into account when sponsors enter into an agreement with the IOM for a DRI study. Moreover, an activity of emerging interest is the approach and criteria related to signaling when review of a nutrient is warranted. This is a different issue from that in Section 4.3 regarding the nature of "new" substances appropriate for inclusion in the DRI review process. Here the question is, "How do nutrients with existing DRIs become candidates for review and possibly modification?" During the initiation of the DRI process in the mid-1990s, it was considered unlikely that periodic, routine updates of all nutrients could be sustained. Instead, the vision was that the DRIs would exist conceptually, and perhaps in reality, as loose-leaf notebooks. The notebook section for a particular nutrient could be reviewed, updated and reinserted as needed. This activity is now of interest. Strictly speaking, issues related to the approach for determining and ensuring timely reviews of existing DRI values are not within the

[12] IOM (2007).

domain of DRI study committees. They were, however, the topic of discussion during Workshop2007.

Issues/Gaps 2-1:

Criteria for Revisiting Existing DRI Values

Given the prospect that DRI development in the future will not include periodic, across-the-board updates for nutrients as were carried out in the past, relevant criteria and processes should be identified to facilitate specific nutrient updating and allow these updates to take place in a timely, transparent, appropriate and accountable fashion.

The nature of the factors that "trigger" a DRI review for an existing nutrient is of interest to (a) DRI sponsors, who must monitor the research and its public health impact in order to make decisions about funding DRI studies; (b) those who oversee the general process of DRI development, such as the IOM, so that they can ensure that the work of study committees is relevant, timely, efficient and impactful; and (c) all stakeholders who rely on the DRIs to provide appropriate nutrient reference values.

Discussions[13] held during Workshop2007 included the topic of how the need for reviews in the future will be recognized, including the important task of specifying a new public health issue. A question raised relates to determining the characteristics of "significant new" data relative to undertaking a review. Examples of efforts to define significant data in the nutrition field do exist[14] and may be helpful in this regard. Other sources and approaches may also be identified or developed.

The process for instituting a specific review was also discussed during Workshop2007. Suggestions[15] ranged from petitions from stakeholders to the formation of a standing committee. The DRI sponsors play a significant role in this decision-making process and are pivotal in specifying the public health need for DRI review. Exploration of the various options and opportunities for collaboration in this respect would be useful.

► 2.2 What Must a DRI Framework Accomplish?

A complete answer to this question is lengthy, and the topic is addressed throughout this paper. It is important to recognize at the outset that there are two major goals for any framework for objective and scientifically rigorous DRI development. The first is that the framework should ensure and foster transparency of the decision-making process. The second goal is that the framework anticipates the need to make decisions in the face of limited data and, in turn, offers options for making scientific judgments. Scientific judgment in the face of limited data is important, given the interest in protecting public health and the reality that "no decision is not an option"—that is, a science-based judgment is more useful than no recommendation at all.

[13] Suttie, Session 4.
[14] For example: U.S. Food and Drug Administration Guidance for Industry; Significant Scientific Agreement, http://www.cfsan.fda.gov/~dms/ssaguide.html.
[15] Participants, Session 1, Panel Discussion / Suttie, Session 4.

2.2.1 Ensuring Transparency

Transparency in DRI development usually refers to the documentation of the key decisions made so that those outside the study committees are provided a clear and well-justified explanation of the evaluations carried out and the scientific judgments made.

The documentation and hence transparency of the decision-making process for nutrient reference values have evolved over time. In the 1940s and 1950s, the National Research Council (NRC) in the United States commonly issued the reference values with little explanatory text. More explanation was added over the next 50 years as the evidence base grew. The 1994–2004 DRI process resulted in six volumes of text. However, Workshop2007 participants[16] suggested that at times the text was inadequate or not appropriately focused to clarify and explain the decisions made. This can result in the appearance of inconsistency (whether or not it exists) and perceived lack of objectivity.

One Workshop2007 presenter[17] specifically tasked with discussing transparency for DRI development concluded that there were several points in the DRI process where efforts to make decisions more transparent would have helped with the clarity of the outcomes and with acceptance of the inevitable scientific judgments needed. He added that more information about the decision-making process could have mitigated concerns that study committees did not consider or review certain data or options, when, in fact, these may well have been considered even though there was no discussion in the text. Examples of information to improve transparency include specific criteria for literature inclusion/exclusion, criteria for weighing evidence and explanations of uncertainty factors.

In short, transparency is less a matter of the number of pages provided and more a matter of offering an orderly set of documenting discussions that build to the final conclusions. An agreed-upon general organizing scheme for these decisions facilitates a systematic approach to decision making as well as recognition of the decision points that need explanation and justification. Risk analysis as a discipline fosters transparency in decision making.

2.2.2 Making Decisions with Limited Data: Scientific Judgment versus "No Decision"

Data available for DRI development are often limited. As a result, study committees at times make decisions about reference values in the face of uncertainty and gaps in data. The effort to make a decision using available data is encouraged because, from the perspective of protecting public health, a study committee's educated if imperfect input about an appropriate reference value—by way of scientific judgment—is preferable to deferring a decision until the database is more robust. As one presenter[18] pointed out, a

[16] Panel Discussions, Sessions 1, 3 and 4.
[17] Russell, Session 4.
[18] Yetley, Session 1.

failure to offer a value based on scientific judgment results in no scientific guidance at all for those who must make public health decisions. Another participant[19] suggested that the absence of a reference value would suggest that nothing is known about the requirement for the nutrient substance or that the substance may be safely consumed at high levels of intake.

The task of providing reference values in the face of limited data has been described as "no decision is not an option." Although it is clear that no decision can be made if there are really no data, it is often the case that there are limited data. While not ideal, observational data and animal studies may provide a basis for scientific judgment in order to offer a reference value for use by those who must manage nutrient risk and cannot delay action while they wait for more data. Two factors are important. One is that the uncertainty associated with such values must be made clear to users. The second is that the organizing scheme for the development of such values should be sufficiently flexible to allow for scientific judgments and should foster an orderly process for making and documenting such decisions. The prescribed steps of the risk assessment component of risk analysis (Section 5.2) offer this possibility.

► 2.3 Linking the DRI Framework to Risk Analysis

The framework that has evolved for DRI development is increasingly recognized as akin to that developed in other fields and referred to as *risk analysis*. Risk analysis is a process for managing situations where public health monitoring and interventions are expected or needed. In short, it analyzes and controls the "risks" that may be experienced by a population of interest. In the case of DRI development, the "risk" is nutrient intakes that are too low or too high.

While the terminology associated with the discipline of risk analysis may at times be unfamiliar to those in the nutrition field, the discipline's structure and application are a good match for DRI development. Consideration can be given to adapting the terminology as well as some of the decision-making steps so that they fit any unique nutritional modalities.

Risk analysis, as considered generically for all fields of study, has several components. These are often illustrated as overlapping or connected, as in Figure 2-2 below. The component known as *risk assessment* has received attention as an organizing scheme for the study committee review process. It is introduced in this section and is considered in more detail in Section 5. Another component of risk analysis, *risk management*, also plays a role in the DRI development process. The interface between nutritional risk management and nutritional risk assessment is a theme throughout DRI development considerations. Classic risk analysis also includes consideration of *risk communication*.

[19] Miller, Session 4, Panel Discussion.

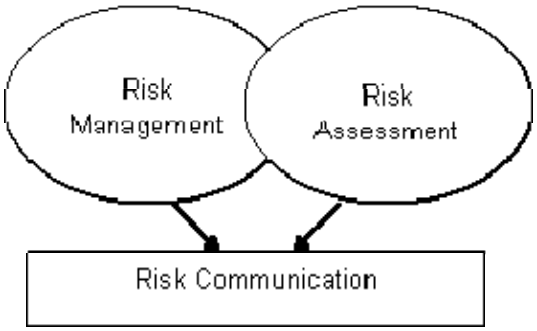


Figure 2-2: Components of Risk Analysis

2.3.1 Roles within Risk Analysis

Risk analysis, as a set of activities intended to both meet the needs of users and maintain scientific integrity of the risk assessment process, includes an articulation of roles and responsibilities of those involved in the overall process. Those who typically request a risk assessment— nutrient reference values, in the case of DRI development—are referred to as "risk managers." They often sponsor the assessment. Those who apply the outcomes of the assessment are also risk managers. Those who carry out the risk assessment are "risk assessors" or, for DRIs, study committees. This is illustrated in Figure 2-3.

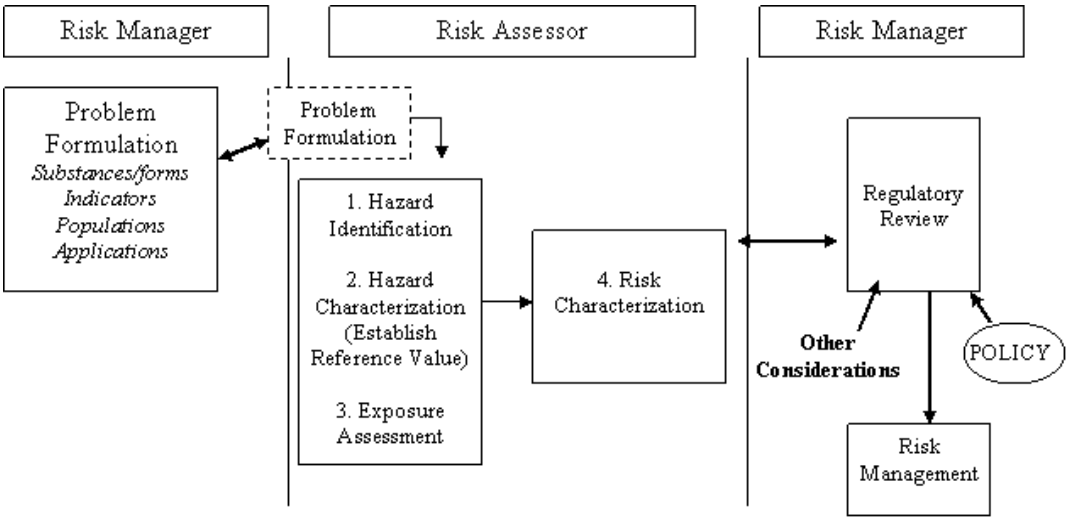


Figure 2-3: Tasks of Risk Managers versus Risk Assessors

The risk managers or sponsors are responsible for setting the stage for the assessment and specifying the nature of the problem (left-hand side of Figure 2-3). This problem formulation activity is illustrated as a back-and-forth set of discussions (double-headed

arrow) during which the risk assessors may help to clarify or finesse the questions to be addressed (dashed-line box). The goal is for the risk assessor to understand the needs and interests of the risk manager or study sponsor. Discussions about problem formulation as it relates to DRI development are included in Section 5.2.2.

While problem formulation is an important communication process for initiating the assessment, the assessment itself is "closed" in order to ensure its scientific integrity and objectivity. During this process, the scientific issues germane to the purposes of the assessment are evaluated and scientific judgment takes place as appropriate, as shown in the middle section of Figure 2-3. The four general steps of risk assessment are shown in Figure 2-3 but are specifically discussed in Section 5. Note that there is interest in ensuring that the results of the assessment are presented in a manner that enhances their usefulness to sponsors and other users—specifically, in an assessment step labeled as "risk characterization."

Once the assessment is complete and fully characterized, the information can be used by the risk manager to carry out his/her responsibilities, which may include policy development, intervention, research or education. Not all of the needed information for risk management purposes is obtained from the risk assessment. Rather, the risk manager must usually combine the risk assessment outcomes with other considerations and data and then work to "manage the risk" based on these combined considerations as appropriate. The FAO/WHO Report, based on an international workshop, attempted to clarify the nature of this interface. Generic examples of these activities developed from the FAO/WHO Report can be found in Appendix 2. While the activities outlined here for risk managers are set primarily in the context of public health promotion and protection, other applications of DRIs (such as research activities) should also be acknowledged.

2.3.2 Assumptions of Risk Analysis

The basic assumptions underlying risk analysis are relevant to DRI development. At its most basic, risk analysis is predicated on the assumption that *scientific deliberations should be organized in a manner that meets user/sponsor needs while maintaining the scientific integrity of the assessment.*[20] This principle manifests itself in a combination of prescribed and documented decision steps commingled with specific delineation of roles and communication channels. These allow input into the process as appropriate but ensure that the scientific decision making is not influenced by groups or individuals with specific agendas or biases. Further, this organization and process enhances the transparency of the process and the decisions made.

As pointed out by a presenter[21] during Workshop2007, the following general assumptions of risk analysis relate directly to the overall development of DRIs, particularly as it relates to making scientific judgments in the face of limited data:

[20] NRC (1983).
[21] Yetley, Session 1.

- *No decision or recommendation about a level of intake (or exposure) is often not a viable option from the perspective of protecting public health*. It is better to offer those operating in the public health arena an informed decision based on the best available scientific expertise and judgment, even if not perfect or very precise, than to offer no information, which by default provides no guidance for evaluating or dealing with the current situation.
- *Available datasets are often incomplete*, and scientific uncertainties must be dealt with through use of scientific judgment and judicious, transparent documentation.
- Meeting the scientific needs of users/sponsors requires a framework for ensuring *understanding of the needs* and a *useful presentation* of the scientific assessments, as well as the *independence* of the scientific evaluations and protection of the scientific reviewers from undue stakeholder influence.

2.3.3 Probability, Prevalence, Risk and Distributions

As a discipline, risk analysis is based on statistical foundations central to identifying and describing risk, specifically as it relates to public health concerns focused on the exposure to substances in the environment. These statistical foundations match those used to develop and apply DRIs. As experience in developing nutrient reference values has accumulated, probability and risk have been increasingly recognized as explicitly underpinning the derivation of the reference values. This understanding is pivotal to users' application of the DRIs and forms the basis for much of DRI development.

The concepts of probability and risk are tied to the fact that the DRIs and their applications are based on the statistical construct of a distribution. The distribution is an arrangement of data values showing their frequency of occurrence throughout the range of possible values. More specifically, for DRIs, a relevant distribution would be the frequency of an occurrence of an event of interest—for example, a symptom of deficiency—as plotted against the various levels of intake at which the symptom occurs. A discussion about probability, prevalence, risk and distributions can be found in Part I of *The Essential Guide to Nutrient Requirements.*[22] It includes illustrations of the types of distributions associated with the DRIs.

Developing DRIs based on distributions offers the opportunity to improve the accuracy of dietary assessment, because it allows calculation of the *prevalence of inadequacy within a group* and the *probability of inadequacy for an individual*. In each case, the issue is the *risk* of inadequacy. While the probability model is as applicable to upper levels of intake as it is to levels of intake to ensure adequacy, the distributions needed for ULs have not yet been developed due to insufficient data. Currently, ULs are derived using other measures, known as no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) (see Section 5.2.4.2). Therefore, a probabilistic approach is not relevant to ULs at this time in the way it is for EARs. Considerable research in this area is needed in order to elucidate such distributions.

[22] IOM (2006).

The impact of the distribution-based DRI development can readily be seen in the approaches that have been developed to assist users of the DRIs. The strategies to determine prevalence estimates for groups and probability estimates for individuals were the subject of the work of the Subcommittee on Interpretation and Uses of Dietary Reference Intakes. This guidance is the subject of Section 6 below.

2.3.4 Relevance to Federal Advisory Committee Act (FACA)

The provisions of FACA (Public Law 105-153) mesh with risk analysis principles as they relate to DRI development. This law applies to the IOM in its role as the developer of scientific advice to the government, including the provision of DRIs. The IOM is part of the National Academies, along with the National Academy of Sciences, the National Academy of Engineering and the NRC.

The National Academies as a group serve as independent advisors to the U.S. government. The government approaches the National Academies for consensus advice that is not influenced by any particular group, including the government. In developing this advice, the National Academies are expected to draw on the best minds and to make proper arrangements for their deliberations to ensure independence.
The 1997 amendments to FACA include certain requirements, referred to as Section 15[23] and intended to ensure the integrity of the National Academies process for providing scientific advice. The IOM, as part of the National Academies, must adhere to these requirements in order for a federal agency to rely on the IOM's advice or recommendations, in this case the DRI values. Section 15 clarifies requirements for public disclosure, while keeping the activities of the National Academies independent from government and governmental control. It also ensures public input into study committee activities and provides opportunities for transparency in the decision-making process. These opportunities for input as well as the maintenance of independent deliberations are consistent with the risk analysis approach and can be outlined as follows:

- *IOM studies include problem formulation.* This is a time for working closely, usually with the sponsor, to define the task statement. Once an ad hoc study committee is formed, members generally take part in orienting discussions with sponsors in order to be fully informed about the needs and interests of the sponsor, to seek clarifications about the study's purpose and to suggest refinements.
- *Related activities.* During establishment of a study committee, nominations for individuals to serve on the study committee are sought. Once a provisional study committee is appointed, biographical sketches of committee members are posted on the website, and there is an additional opportunity for comment.

[23] Information at http://www.nasonline.org/site/PageServer?pagename=ABOUT_FACA.

• *IOM study committee meetings reflect risk assessment steps.* The IOM study committees deliberate in closed sessions to allow the committee members to debate ideas freely and without fear of outside influence and to change their minds as they consider evidence, which is all part of the process. Written materials given to the committee from the outside are placed in a public access file to allow transparency. Data gathering is an important part of the process. IOM study committee meetings often include sessions open to all in order to gather scientific information, carry out discussions with sponsors to ensure understanding of the statement of task and provide the opportunity for interested parties to offer comments. These efforts can also include a technical public workshop. Finally, akin to the general approach for risk assessment, the study committee carries its activities through to the point of issuing a report, which would include the components of risk characterization.

• *Specific review.* Consistent with the interests of scientific rigor and objectivity, a specific review process for study committee reports is an integral part of the IOM process. The report review process is carried out by individual experts separate from the study committee members and is closed. The reviewers are asked to keep the reviews and draft report contents confidential. Once the review comments have been addressed, the report is then released to the public, and dissemination and dissemination planning are activities that are intended to be done collaboratively with the sponsors and stakeholders. Reviewers are listed in the final report.

Given FACA requirements, DRI development must be carried out by the IOM in a manner that ensures that the nutrient reference values issued can be used by the government sponsors for their wide array of public health policy needs. There is considerable value in clarifying the roles of all involved.

Issues/Gaps 2-2:

Interface between Sponsors and Study Committees during Initiation of DRI Activities

Communication between sponsors and study committees deserve attention because appropriate dialogue among these parties is essential to ensuring a useful and relevant outcome. The interactions also need to take place in a manner that maintains the independence and scientific integrity of study committee outcomes. A better understanding of the problem formulation step as part of the initiating activities for a DRI study would be valuable.

Discussions during Workshop2007 revealed that there was some confusion on the part of both sponsors (nutrient risk managers) and study committees (nutrient risk assessors) about how to appropriately engage each other during the entire process of DRI development, but especially at the beginning of the study. The need to more specifically engage in problem formulation is evident, an activity that is discussed in Section 5.2.2

As highlighted by a Workshop2007presenter,[24] unless those reviewing the science understand why they have been requested to carry out their activities, the

[24] Woteki, Session 4.

+outcomes will not be useful. Notably, the sponsors must specify the nature of the problem that the assessment is intended to address. The presenter noted that government representatives have expressed concern in the past about the unresponsiveness of the DRI outcomes to their needs but are increasingly recognizing that this may be mitigated by specifically engaging in setting the stage for the risk assessment.

► 2.4 International Collaboration

While the focus for DRI development has been the U.S. and Canadian populations, some international considerations may be relevant. Specifically, during Workshop2007, the concept of a framework that incorporated international collaboration and harmonization of reference values was raised.

More international expertise could be included in the DRI process so that countries could share information and knowledge and learn from each other, as suggested by several Workshop2007 participants.[25] It was considered that countries not able to support such a reference value process on their own, but willing to take part in working with others, could benefit. The value in working internationally with organizations such as the European Food Safety Authority was recognized. Some have pointed out the global harmonization possibilities offered by the risk analysis scheme.[26]

A Workshop2007 discussant[27] suggested that it would be desirable to harmonize the approach for deriving the EAR and UL. He indicated that the numbers needed globally are the equivalent of the EAR and UL (rather than values such as the RDA). The science needed to derive these could serve equally well in international efforts as it does for the United States and Canada. If the approach for deriving the EAR and UL were harmonized, different countries could, within the context of their own public health protection considerations, derive their own relevant reference values, be they the equivalent of the RDA or established on a different basis.

On a related note, a Workshop2007 participant[28] indicated that it would be useful if study committee reports could, when possible, discuss the levels of intake relevant to the range of indicators considered for a nutrient in addition to the one indicator selected for the reference value. As an example, he suggested that there were countries for which prevention of scurvy was the goal; if study committees could reveal what they discovered on such an indicator in their broader consideration of available indicators, such discussions would be a helpful addition to the report text and would have international impact.

[25] Participant, Session 1, Panel Discussion / Dwyer, Session 3 / Harris, Session 4.
[26] Aggett (2007).
[27] Garza, Session 1, Panel Discussion.
[28] Participant, Session 2, Selecting Endpoints, General Discussion.

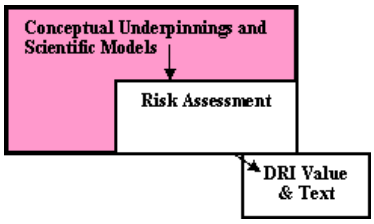
Conceptual Underpinnings and Scientific Models

3. PURPOSE OF DIETARY REFERENCE INTAKES

3.1 Values for What General Use?
- 3.1.1 Assessing and Planning Diets
  - *Issues/Gaps 3-1: Nutrient Reference Values for What?*
- 3.1.2 Basis for Food-Based Dietary Guidance

3.2 Values for What Population?
- 3.2.1 Apparently Healthy Persons
  - *Issues/Gaps 3-2: Definition of "Apparently Healthy"*
- 3.2.2 Large Groups with Applications for Individuals and Small Groups

This section focuses on several of the conceptual underpinnings for DRI development. It addresses the broad overarching purpose of DRIs as quantitative nutrient reference values. Two questions are relevant: (a) DRIs are values for what general use? and (b) DRIs are values for what population? Additionally, there is interest in whether and in what ways DRI development can be relevant to or work in collaboration with international activities focused on nutrient reference values.



The purpose of DRIs in the sense of how they are operationalized also comes into play more specifically throughout this paper. That is, the general purpose of DRIs belies a myriad of more specific questions and decision points. These are considered in sequence as the framework components are discussed in later sections.

► 3.1 Value for What General Use?

3.1.1 Assessing and Planning Diets

The role and use of quantitative nutrient reference values have expanded over the years, but their general purpose has remained essentially the same. The DRIs, like the previous RDAs and RNIs, are intended to provide standards for good nutrition and as a yardstick by which to measure progress toward that goal.[29] The 1994 DRI Plan focused on revamping the existing approach for nutrient reference values and underscored that the intent of the reference values has always been to prevent deficiency diseases and promote health through provision of an adequate diet. During Workshop2007, one presenter[30] suggested that the goal of the DRIs was to foster the application of nutrition science.

[29] IOM (2006).
[30] Beaton, Session 1.

Another[31] referred to the values as the science backbone of the government's nutrition policy.

The DRIs are essentially tools for assessing and planning diets. As illustrated in the 1994 DRI Plan and as understood during Workshop2007, the application of nutrient reference values for these general purposes are wide and diverse. They range from applications by federal government agencies in making national nutrition policy or developing federal nutrition and food assistance programs to work at the local level in assessing diets of groups and individuals. Public health protection/promotion is the common interest.

Some prefer to consider the question of the purpose of DRIs against the backdrop of what the DRIs are to accomplish regarding the health status of the population, assuming the specified levels of intake are consumed. Here, the question becomes: "Nutrient reference values for what?"

Issues/Gaps 3-1:

Nutrient Reference Values for What?

Discussions about the purpose of DRIs frequently elicit the question: "Nutrient reference values for what?" In other words, what are the desirable indicators or the most appropriate biological/physiological/clinical measures upon which the reference values are to be based given current public health concerns? The topic has become more complicated as scientific advances offer newer information about the functions and effects of nutrients. Moreover, the ability to address such questions is undoubtedly part of a larger evolving process.

There is often an array of possible indicators that can be considered and that have been used for nutrient reference value derivation (see Appendix 1). These include (a) clinical indicators, such as physical signs of deficiency, altered body composition, impairment of gastrointestinal or immune function or increased morbidity; (b) nutrient balance studies; (c) biochemical measures, such as levels in blood or levels excreted; (d) functional measures, such as bone health, hormone levels or enzyme concentrations; (e) risk of developmental abnormalities; and (f) risk of chronic disease.

The issue of what exactly the DRI values are to be based on is related to deciding which indicator would be the one to most appropriately ensure "good nutrition" given the available database. This decision has not been systematically considered or operationalized to the point where it can be specified as a single overall purpose. Rather, it is currently addressed largely on a case-by-case basis for each nutrient. The specific topic of indicators is discussed in Sections 4.2 and 5.2.4.1. However, consideration of the larger topic of "nutrient reference values for what public health end" would likely assist efforts to consider the nature and selection of indicators for nutrient reference values.

3.1.2 Basis for Food-Based Dietary Guidance

DRIs address nutrients in foods, not specific foods. Because people structure diets primarily by selecting foods as opposed to selecting a set of nutrients, an important role of government and related advisory groups has been the task of translating quantitative nutrient reference values into food-based recommendations for the generally healthy U.S.

[31] King, Session 1.

and Canadian populations, specifically *Canada's Food Guide*[32] and the *U.S. Dietary Guidelines for Americans*[33] and related eating plans including *MyPyramid.*[34] As suggested previously, the DRIs in effect serve as the science backbone for federal agencies to use in developing such nutrition policy. It could also be said that the DRIs are for use by government policy makers, nutrition scientists, dietetic practitioners and the public health community. The values, along with other information, are translated into food-based dietary guidance targeted to consumers and the lay public.

The following excerpt is from the 1994 DRI Plan and focuses on the distinction between the nutrient reference values and food-based guidance:

> Despite modifications in the definition of RDAs over time, the underlying intent of the RDAs has always been to prevent deficiency disease and promote health through provision of an adequate diet. In fact, the first three editions of the RDAs included diet plans that met the allowances, similar in concept to [U.S. Department of Agriculture] food guides.… Beginning in the early 1960s, various sets of dietary guidelines intended to help the population reduce its risk of certain chronic, degenerative diseases were developed and disseminated widely…. These guidelines are different from the RDAs, which provide quantitative information, used primarily by professionals, on specific amounts of nutrients needed to prevent deficiency diseases and maintain adequate health. Both the RDAs and dietary guidelines are the appropriate basis for diet planning…. This has led some nutrition scientists to argue that these two types of dietary advice should be brought together. However, others argue that they should remain separate due to the different purposes and audiences for which dietary guidelines and RDAs are intended and the scientific data on which they are based. With this concept paper, the FNB seeks to address, with the help of the scientific community, whether it is possible and desirable to bring these two types of advice together. [35]

During Workshop2007, some participants[36] commented that the goals of the DRIs are different from those for food-based dietary guidance and cautioned that DRI values should not "cross" into dietary guidance. Interest was expressed in distinguishing between a reference value and dietary guidance. A discussant[37] suggested that practitioners who develop menus or plan diets should rely on government food-based recommendations rather than using the DRIs directly, because the recommendations have already incorporated the DRIs.

One Workshop2007 participant[38] expressed concern about the nature of the AMDRs relative to the line between DRIs and food-based dietary guidance. He suggested that providing "semiquantitative" values for nonessential nutrients relative to chronic disease considerations may be creative but is confusing and perhaps should be carried out within the domain of dietary guidance. Another Workshop2007 presenter[39] opined that the challenges presented by chronic disease indicators resulted in a mixed approach to

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[32] Health Canada (2007).
[33] DHHS/USDA (2005).
[34] USDA. 2005. *MyPyramid: Steps to a Healthier You*. [Online]. Available: http://www.mypyramid.gov [accessed March 28, 2008].
[35] IOM (1994), pp12-13.
[36] King, Session 1 / Rosenberg, Session 1, Panel Discussion.
[37] Guenther, Session 3.
[38] Rosenberg, Session 1, Panel Discussion.
[39] King, Session 1.

establishing DRIs, which in turn undermined the ability of the DRI process to provide clear and adequate scientific information for those charged with developing food-based dietary guidance.

While several Workshop2007 participants[40] supported the idea that chronic disease indicators need to be evaluated in a different manner using different expertise from that used to consider the "more biochemical and physiological" indicators, it was suggested[41] that inclusion of chronic disease indicators directly into the DRI process was not problematic relative to dietary guidance activities. Rather, the approach to dealing with them was in a state of evolution, and more time would be needed to improve their incorporation into the DRI framework. One presenter[42] suggested that all chronic disease indicators were not the same and that both newer techniques and case-by-case consideration were needed.

One consideration is that there may be approaches to specifying a meaningful distinction between the DRI goals and the dietary guidance goals that is not dependent upon the type of indicator as the basis for the distinction. For instance, the DRIs may be viewed as reflecting quantitative reference values for a nutrient substance or limited nutrient combinations; they do not focus on guidance about what foods people should consume or on food patterns, as would dietary guidance. The case of saturated fat provides an example. Using a risk/risk analysis approach, the DRI study committees may be able to derive, for example, a UL for saturated fat by evaluating a linear no-risk curve for adverse effects of saturated fat and heart disease against the levels of saturated fat-containing foods (meats, milk, etc.) needed to meet requirements for protein, iron, zinc, etc. Such an activity is consistent with the depth and breadth of expertise common in DRI study committees. The dietary guidance advisory committees would then draw on this information regarding an upper level for saturated fat intake to specify the appropriate food patterns and provide the food-based dietary guidance.

Overall, based on Workshop2007 discussions, there appears to be agreement that the DRIs serve an important role in laying the scientific groundwork for others to develop food-based dietary guidance for use by consumers. One Workshop2007 presenter[43] noted that her experience in U.S. government would suggest that when the food-based dietary guidance committees had access to basic science reviews prepared by the IOM or in some cases the National Institutes of Health, the model for the development of guidance worked well. However, if this scientific input was lacking, the government advisory committees for such guidance experienced many more challenges. Nonetheless, there are some concerns about the AMDR components of DRIs relative to dietary guidance as well as the interface between the DRI chronic disease considerations and dietary guidance. These are addressed in Sections 4.1.4 and 4.2, which respectively deal specifically with AMDRs and the role of chronic disease indicators.

[40] King, Session 1 / Stoecker, Session 1
[41] Participants, Session 1, Discussion, Pros & Cons—Case Studies.
[42] Mayne, Session 2.
[43] Meyers, Session 4.

► 3.2 Values for What Population?

The population targeted by the DRIs is the set of apparently healthy persons in the United States and Canada. With this as their main focus, the reference values have evolved for use with large population groups. Interest in applying DRIs to individuals and smaller groups is expanding.

3.2.1 Apparently Healthy Persons

Since their inception in the 1940s by NRC in the United States and the Canadian Council on Nutrition in Canada, nutrient reference values have focused on the healthy population. They are not reference values for persons with diseases or those with nutritional metabolic abnormalities.[44] The void relative to nutrient requirements for diseased persons was recognized during Workshop2007, but it was underscored that the general purpose of the DRIs—to assist with public health activities to ensure good nutrition for the general population—is inconsistent with the clinical considerations that are needed for determining the nutritional requirements of diseased persons. Nonetheless, one discussant[45] suggested that DRI values for many nutrients, if not all, may be appropriate for persons with disease conditions and that this could be explored further in the future, as resources allow.

The concept of an apparently healthy population has a long-standing association with the development of nutrient reference values. However, some suggest that its definition warrants attention.

Issues/Gaps 3-2:

Definition of "Apparently Healthy"

The question of what constitutes a healthy population has become more complicated during the past 50 years as a result of better understandings of health and chronic disease. Just as importantly, the lifestyles of the population in the United States and Canada have changed to the point where chronic diseases as well as obesity are increasingly prevalent in the population. Workshop2007 discussions[46] highlighted an interest in more clearly defining an apparently healthy population.

Those fully experiencing a chronic disease condition are obviously not included within the concept of an apparently healthy population. However, many, if not practically all, members of the "healthy" population in the United States and Canada have the propensity to develop such diseases or conditions. Questions have been raised about including persons with identifiable risk factors as members of an apparently healthy population. Are persons with elevated serum cholesterol, with high blood pressure or classified as obese members of the apparently healthy population?

The numbers of such persons in Canada and the United States are considerable. The numbers alone may offer reason to suggest that such persons should remain as

[44] IOM (2006).
[45] Dwyer, Session 3.
[46] Participant, Session 1, Discussion, Pros & Cons—Case Studies.

members of an apparently healthy population, at least until such time as research would provide a basis for devising different nutrient reference values for those with and without identifiable risk factors. Several participants during Workshop2007 queried about the continued inclusion of these persons within the concept of an apparently healthy population, but a specific approach did not emerge. One participant[47] suggested the need to establish a "representative state of health" for the purposes of DRI development.

3.2.2 Large Groups with Applications for Individuals and Small Groups

The task of assessing and planning diets for groups of persons was one of the driving forces behind the request in the 1940s for the development of nutrient reference values, as well as their numerous revisions over time. However, these were the only values available to health professionals, so they were also used to plan and assess the diets of individuals. However, they were not ideally suited for these purposes.

To help these practitioners make better use of the reference values when the focus was an individual, the 1994–2004 DRI development process included guidance[48] for use of the nutrient values with individuals as well as approaches appropriate for groups. Now, additional questions have been raised about the need for further guidance when the group is considered "small" as opposed to "large."[49] These are the topic of Section 6 of this paper.

[47] Participant, Session 1, Discussion, Pros & Cons—Case Studies.
[48] IOM (2000, 2003).
[49] Tarasuk, Session 3.

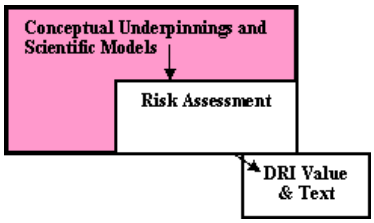
Conceptual Underpinnings and Scientific Models

4. BASIC "SETUP" FOR DIETARY REFERENCE INTAKES

4.1 Values to Be Expressed
- 4.1.1 Estimated Average Requirement (EAR)
- 4.1.2 Recommended Dietary Allowance (RDA)
  - *Issues/Gaps 4-1: Changing Perspectives on RDA*
- 4.1.3 Adequate Intake (AI)
  - *Issues/Gaps 4-2: The Future of the AI*
- 4.1.4 Acceptable Macronutrient Distribution Range (AMDR)
  - *Issues/Gaps 4-3: Further Development of the AMDR*
- 4.1.5 Estimated Energy Requirement (EER)
- 4.1.6 "Precision" of Values Expressed

4.2 Nature of Indicators Used to Develop DRI Values
- *Issues/Gaps 4-4: Addressing Chronic Disease Indicators*

4.3 Substances Appropriate for DRI Development



The basic "setup"[50] of the DRIs continues the consideration of the conceptual underpinnings and scientific models for their development. The values to be expressed are based on the needs to apply the values for assessing and planning diets for groups and individuals; in turn, the values rest on a foundation grounded in statistical principles. The general nature of the indicators used to develop the values extends the discussion of nutrient reference values "for what." Further, there are general considerations that must be addressed in order to determine "new" or emerging nutrient substances appropriate for DRI development.

► 4.1 Values to Be Expressed

Existing DRI Values

- Estimated Average Requirement, **EAR**
- Recommended Dietary Allowance, **RDA**
- Tolerable Upper Level of Intake, **UL**
- Adequate Intake, **AI**
- Acceptable Macronutrient Distribution Range, **AMDR**
- Estimated Energy Requirement, **EER**

Currently, the mainstays of DRI development are the EAR and UL. There is also continued interest in specifying the RDA, which is derived from the EAR. However, the RDA has received increasing scrutiny relative to the rationale and methodologies for its derivation from the EAR.

The AI is controversial. Its advent was not anticipated by the 1994 DRI Plan, and it was incorporated into the 1994–2004 DRI process through the experience of study committees. It has been the topic of much

[50] Setup is defined in Soukhanov (1984) as "The manner in which something is arranged or planned."

discussion, and the value would appear to have numerous detractors. However, interest has also surfaced relative to refining or adapting the value as needed.

The AMDR, which also came into being through the experience of the DRI study committees, may require further examination. It is regarded by some as an important emerging concept that is a logical outgrowth of the need to explore alternative approaches for deriving reference values for some types of nutrient substances and for addressing interrelatedness of energy-yielding nutrients. Others question the AMDR's appropriateness as a reference value.

The existing nutrient reference values evolved in response to recognition of the diverse uses of such values, expanding from a single number (the RDA or RNI) to the set of DRI values outlined above. Some Workshop2007 participants,[51] considering these developments, cautioned against concluding that it would be possible to continue to issue values or single numbers directly relevant to all applications. Instead, it may be best now to focus on the "core" values, coupled with relevant information such as the curves for requirement distributions. This would allow different users to bring different considerations to bear in deriving, from the available distributions, those reference values appropriate for their specific use. This would include reference values to ensure population coverage at an acceptable level of risk. The "core" values and their related distributions for this purpose were specified[52] as the EAR and the UL.

4.1.1 Estimated Average Requirement (EAR)

The EAR is the average daily nutrient intake level that is estimated to meet the nutrient needs of half of the healthy individuals in a life stage or gender group. Although the term "average" is used, the EAR is actually an estimated *median* requirement. Therefore, by definition, the EAR exceeds the needs of half of the group and falls short of the needs of the other half.

A Workshop2007 presenter[53] highlighted as an accomplishment of the 1994–2004 DRI development process the formal recognition of the importance of the EAR and the growing recognition that we cannot escape dealing with distributions. The 1994–2004 DRI process placed emphasis on the distribution of requirements for a population, rather than focusing on a single value constructed to "cover" the great majority of the population, as had been the case in earlier efforts. This, with the development of newer methodologies for assessing and planning adequate intakes for groups, made the EAR a central reference value, along with the UL. As one Workshop2007 participant[54] indicated, the 10 years of DRI development moved the process from a black-and-white cutoff in the form of an RDA to consideration of a probability model. Doing so made it clear that there is a distribution of requirements in the population.

[51] Beaton, Session 1 / Garza, Session 1 / Participant, Session 4, Overview, General Discussion.
[52] Garza, Session 1.
[53] Beaton, Session 1.
[54] Participant, Session 1, Discussion, Pros & Cons—Case Studies.

The EAR itself presents little controversy as an expressed reference value. Beyond the question of how to handle EAR estimation in the face of limited data, most of the issues that surround EAR development are related to the uncertainty surrounding the value and ensuring appropriate discussions about the variation in requirements. A challenge lies in obtaining adequate data to allow a reasonable approximation of the variability in requirements and hence the distribution of intakes for the requirement.

4.1.2 Recommended Dietary Allowance (RDA)

The RDA is calculated from the EAR. It is dependent upon estimating the variance around the EAR and reflects a point estimate defined—historically and currently—as two standard deviations above the EAR. While some refer to this reference value as "the requirement plus a safety factor," this is potentially misleading in that it underplays the importance of a distribution and variability around that distribution. The RDA is intended to reflect the EAR plus two standard deviations.

This RDA calculation starts with the assumption that the distribution of a nutrient requirement reflects a normal curve. However, this is not the case for a number of nutrients. There is also the need to describe the variance around the EAR. Such data are usually limited; when the variance is not known, the coefficient of variation is assumed, commonly as 10 percent. A Workshop2007 presenter[55] expressed concern that RDAs cannot be considered to be scientifically derived because too often the variance around the EAR is unknown and the assumptions made about the variance may be inappropriate. Others[56] have highlighted the considerable impact that results from the selection of the CV for both adequate intake and excess intake estimates.

The calculation of the RDA results in a value that is above the intake required for about 97-98 percent of the population. The RDA thus exceeds the requirements of nearly all members of the life stage and gender group. Current guidance[57] stipulates that the RDA is useful for some applications with individuals; it is not appropriate when working with groups of persons.

Issues/Gaps 4-1:

Changing Perspectives on RDA

Given its long history, the RDA along with the Canadian RNI, is the familiar face of nutrient reference values and is well recognized by practitioners. However, the growing recognition of the underpinnings based on distributions, risk and probability has resulted in interest in further examining the nature and role of the RDA.

The level of tolerable risk for a population may vary in different circumstances, and the broad range of practitioners and users of reference values may have different or

[55] Russell, Session 1.
[56] Renwick (2004).
[57] IOM (2000, 2003).

special considerations relevant to their use. During Workshop2007, it was discussed[58] whether it would be preferable and more appropriate to select a value along the distribution range that better suits a specific application on a case-by-case basis, rather than to rely on a preset RDA value for all uses.

In this sense, the derivation of the RDA—that is, the decision that "safety" for the population reflects two standard deviations above the mean—may be seen by some as essentially a policy decision that may rest outside the DRI framework and require special considerations. Others believe that it is currently unrealistic to expect most users to be able to apply distributions for managing risk. Moreover, as pointed out by one Workshop2007 presenter,[59] there could be value in separating the applications for dietetic professionals from those for policy makers within government, given that the needs are so different. Even those[60] who support the utility of the RDA raise questions about whether the values should be derived on a basis other than two standard deviations and whether the values should be labeled differently.

It is likely that the RDA will continue to be provided in the absence of any basis upon which to make agreed-upon changes to the value (not to mention its considerable familiarity). Nevertheless, Workshop2007 opened the dialogue on this subject. The role and nature of so-called "qualitative" risk reference values[61] such as the RDA may be examined in the future, assuming "quantitative" risk assessment for DRI development becomes more fully developed (see Section 5.1). In the meantime, the lack of information concerning the variability around EARs makes such data, or methodologies to approximate such data, a priority.

4.1.3 Adequate Intake (AI)

The AI is a controversial value. As mentioned earlier, the possibility of the AI was not discussed within the 1994 DRI Plan. The AIs emerged as a result of the deliberations of the early study committees during the implementation of the DRI process. When the available data were judged lacking for the purposes of estimating an EAR, an AI was set. The value was seen as filling the gap that would have existed had no value been issued. Nonetheless, it has become the subject of criticism.

The AI is defined as a value based on observed or experimentally determined estimates of nutrient intake by a group of people who are apparently healthy and assumed to be maintaining an adequate nutritional state. Examples of adequate nutritional states include normal growth, maintenance of normal levels of nutrients in plasma and other aspects of nutritional well-being or general health. The AI is obviously derived differently from the EAR/RDA. It is not reflective of true or known requirements. Further, no distribution of requirement can be offered, and, given the general nature of the U.S. and Canadian diets, it is likely greater than the needs of most people.

There are a number of AIs among the DRI values, and the approach to setting an AI has varied across nutrients. They were developed for a range of nutrients, including those with a high level of public health interest, such as calcium, as well as those considered to

[58] Participants, Session 1, Panel Discussion.
[59] Tarasuk, Session 3.
[60] Participant, Session 3, Panel Discussion.
[61] Qualitative risk assessment focuses on specifying a particular number (or reference value) rather than on describing the distributions and the shape of the distribution curves of interest, which is characteristic of quantitative risk assessment (see Section 5.1).

be of lesser public health interest, such as manganese. Their existence has been the subject of debate and confusion.

Issues/Gaps 4-2:

The Future of the AI

There is broad interest in addressing the AIs as a component of the DRI values, but no clear path has emerged in terms of clarifying, adapting or eliminating AIs. Nor is there agreement about directions to be taken in the future for AI development.

Part of the controversy that surrounds AIs stems from their failure to "fit" easily within the DRI framework, notably for assessing and planning diets. While the AI can be used as a guide for an individual's intake, it is not relevant to groups and has very limited uses in assessments of any type. As a result, a number of stakeholders have experienced challenges in using AIs. This has been especially problematic for total diet planning, in that a mixture of AIs and EARs must be used. An approach for logically combining these values within the context of a total diet seems absent. Guidance for applying AIs was a topic during Workshop2007 and is discussed in Section 6.

Workshop2007 also identified concerns about AIs that stem from what some might describe as a lack of transparency, rigor or proper focus. One discussant[62] expressed concern that while the AIs purported to be developed using the well-established approach of deriving a recommended intake using a population intake level, they are in fact "based on something else." Another participant[63] opined that, for some nutrients, an EAR could have been derived if a physiological function of the nutrient had been used as the criterion rather than a chronic disease indicator. During a panel discussion,[64] one person asked if AI development should continue and, if not, whether an EAR could be approximated in some fashion as an alternative. Another suggested that the AI should be eliminated. A third asked whether any "advances" had been experienced in either the application or communication of the DRIs by incorporating the AI and whether the AI in fact belongs within the DRI framework. One discussant[65] suggested that the AI should be reincarnated as an EAR with uncertainties specified.

With the exception of the suggestion that the AI may function as a reference value specifically for chronic disease indicators,[66] the value seemed not to be viewed favorably during Workshop2007. Some,[67] noting the need to provide values of some type to avoid gaps in guidance for the federal agencies making policy decisions, suggested that study committees have no other choice in the face of inadequate data. Others[68] countered that the inappropriate perception that DRI values are precise and based on solid data needs to be mitigated. Still others[69] advocated ways to more creatively use the existing data to approximate or model information useful to developing dose–response relationships or other information that would allow the estimation of EARs.

Nonetheless, AIs now exist within the set of values that constitute the current DRIs. Until such time as AIs can be specifically reconsidered, it may be best to operate under the principles that (a) AIs should be used only when absolutely necessary and (b) when AIs are used, a clear and transparent rationale and explanation for their development should be provided so that users can understand why they were necessary

[62] Habicht, Session 4.
[63] Participant, Session 1, Panel Discussion.
[64] Participant, Session 1, Panel Discussion.
[65] Guenther, Session 3.
[66] Trumbo, Session 1 / Participant, Session 1, Discussion, Pros & Cons—Case Studies.
[67] Yetley Session 1 / Miller, Session 1.
[68] King, Session 1 / Participant, Session 1, Panel Discussion / Miller, Session 4.
[69] Mayne, Session 2.

as well as the basis upon which they were derived.

It would be worthwhile to pursue specific methodologies that allow study committees to better work with limited data. There may also be value in ensuring greater discussions in the DRI text documents concerning the relative uncertainty surrounding the specific DRI values. This could encourage study committees to develop EARs rather than AIs by more specifically earmarking an effort to reveal uncertainty. Finally, the use of AI-type values for some specified types of indicators could be explored, as appropriate.

4.1.4 Acceptable Macronutrient Distribution Range (AMDR)

An AMDR is a range of intake of an energy source that is associated with a reduced risk of chronic disease. The AMDR was added to the DRI effort in response to evidence that imbalances in interrelated energy-yielding nutrients relate to chronic disease and should be addressed as part of the DRI process. The value also ensures an intake of adequate amounts of essential nutrients, given that macronutrients accompany other nutrients in foods. The AMDR was not foreshadowed in the 1994 DRI Plan.

The AMDR is expressed as a percentage of total energy intake. A key feature of each AMDR is that it has a lower and upper boundary. For example, the AMDR for carbohydrates ranges from 45 to 65 percent of total energy intake. Intakes that fall above or below this range increase the potential for an elevated risk of chronic diseases. Intakes outside the range also raise the risk of inadequate consumption of essential nutrients provided by these food components.

AMDRs address some, but not all, macronutrients. As background, it is helpful to note that vitamins, minerals, protein and energy (calories) have been the historical focus of nutrient reference values. The 1989 NRC reference values[70] that preceded the advent of the DRIs included protein. Carbohydrates, fiber and lipids were discussed in the text, and the intake levels considered appropriate by other organizations or groups were highlighted. However, reference values for these food components were not provided. More recently, there has been emerging evidence that both the amounts and types of macronutrients in the diet impact health. The emerging evidence led the DRI process to include a specific review of carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids, as well as energy in order to expand the DRIs' ability to provide reference values for public health purposes. The overall reference values or related statements concerning intake of energy-yielding nutrient substances as developed during the 10-year DRI process are shown in Table 4-1 below.

In brief, four substances known to be of public health importance—dietary cholesterol, *trans* fatty acids, saturated fatty acids and added sugars—were considered, but specific values could not be developed. Rather, information concerning the desirability of consuming low levels was offered. Fat also does not have EAR/RDA, AI or UL values. EARs/RDAs were established for protein and dietary carbohydrates, whereas AIs were issued for dietary fiber, linoleic acid and α-linoleic acid. No ULs were established, but the statements offered concerning *trans* fatty acids, saturated fatty acids, cholesterol and added sugars focused on excessive intakes.

[70] NRC (1989).

Table 4-1: IOM Nutrient Reference Values and Statements Regarding Macronutrients

Macronutrient	EAR	RDA	UL	AI	AMDR	Related statements
Protein	√	√			√	
Carbohydrates	√	√			√	
Fiber				√		
Fat					√	
Linoleic acid				√	√	
α-Linoleic acid				√	√	
Cholesterol						√
Trans fatty acids						√
Saturated fatty acids						√
Added sugars						√

In this context, the AMDRs were developed to address the special interrelatedness of certain macronutrient substances in the total diet relevant to chronic disease risk. The AMDRs for the nutrient substances in Table 4-1 reflect a reference value expressed as a range rather than as a median. The AMDRs were a topic of discussion during Workshop2007.

Issues/Gaps 4-3:

Further Development of the AMDR

Specific attention to AMDRs is needed. These values raise several issues. Questions range from the need to expand the developmental models for DRIs to address such substances to the appropriate application of reference values expressed as ranges rather than point estimates.

The approach needed to develop reference values such as AMDRs is different from that used for nutrients such as vitamins and minerals. Notably, they are interrelated and do not fit the "threshold model" (see Section 5.2.4.2). During Workshop2007, discussions[71] suggested that macronutrients overall did indeed require a different model, and one participant[72] queried whether values for macronutrients could have been obtained through the application of modeling or other special techniques. The suggestion was made[73] that AMDRs could be useful in setting maximum intake levels for nonessential nutrients without a threshold response or NOAEL. Thus, the topic of AMDRs brings up questions about developing expanded approaches and new methodologies to encompass nutrient substances that have public health impact but are different from the more traditional DRI substances such as vitamins and minerals. In turn, specific attention to ensuring expertise for reference value development related to energy-yielding nutrient substances would likewise need consideration.

[71] Participants, Session 1, Discussion, Pros & Cons—Case Studies / Garza, Session 1, Panel Discussion.
[72] Participant, Session 1, Discussion, Pros & Cons—Case Studies.
[73] Trumbo, Session 1.

In addition, the role of AMDRs should be a focus of specific discussion. One Workshop2007 discussant[74] suggested that AMDRs reflect a confusing concept and that they are more akin to dietary guidance than to DRI values. Another presenter[75] expressed a view that their link to chronic disease indicators has overly complicated DRI development and has particularly impacted dietary guidance in an adverse way. Other available reference values are point estimates, but by necessity the AMDR values are ranges. Any special challenges a range-based reference value may offer should be explored.

4.1.5 Estimated Energy Requirement (EER)

The EER is defined as the average dietary energy intake to maintain energy balance in a healthy adult of defined age, gender, weight and height and with a level of physical activity that is consistent with good health. [76] That is, they sustain a stable body weight in the range desired for good health. There is no RDA for energy, because energy intakes above the EER would be expected to result in weight gain.

The EER as a reference value was not discussed by Workshop2007 participants. Questions have arisen periodically in the past about the regression equations (and coefficients) for total energy expenditure for children, including those calculated from a doubly labeled water database on overweight and obese children.

4.1.6 "Precision" of Values Expressed

Workshop2007 discussions[77] suggested that users of DRIs attribute a higher level of "precision" to DRI values than can be justified, but, just as importantly, that there are questions about how strongly study committees should in fact strive for "precision" in estimating these values. The questions about "precision" appeared to be primarily focused on certainty (rather than the scientific meaning related with numerical exactness and detail), and were relevant to two Workshop2007 themes. One is the ability of study committees to specifically consider the level of uncertainty surrounding the DRI value and, in turn, to communicate this uncertainty to users. Users planning diets to meet DRI values or assessing diets might find it helpful to have such information. Some have queried whether the EAR should be presented as a range rather than as a median value in order to signal its lack of certainty. The second consideration is the interest in discouraging a possibly misplaced or unnecessary quest for certainty in reference value development, thereby presumably encouraging study committees to strive for an EAR rather than an AI. Some[78] have suggested that EARs could be more readily developed if caveats about the lack of certainty surrounding them could be specified for users.

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[74] Rosenberg, Session 1.
[75] King, Session 1.
[76] IOM (2006).
[77] King, Session 1 / Participants, Session 1, Panel Discussion / Dwyer, Session 3 / Miller, Session 4, Panel Discussion.
[78] Guenther, Session 3.

One participant[79] suggested that the question of certainty should be reexamined in terms of how much is actually needed (as opposed to sought) by scientists for the specific DRI values relative to their ultimate purpose. Another[80] pointed out that while accuracy is required, there is a question of how much certainty (or "precision") is actually needed for appropriate applications. As summarized by one participant,[81] the issue may center on the fact that DRI developers are too often driven by a quest for the "precision" that their training requires, but that the use does not demand.

► 4.2 Nature of Indicators Used to Develop DRI Values

The basic setup of the DRIs addresses the general nature of the indicators that can be considered. A second related consideration is the approach to be used for selecting the individual indicators, along with strategies to ensure transparency and scientific rigor in doing so. The latter is outlined in Section 5.2.4.1.

The general topic of indicators—or "endpoints," the primary term used during Workshop2007—for DRI development would be approached by some via consideration of indicators as a single group or continuum[82] of possible measures. For others, the discussion would require parsing indicators into at least two categories: the more familiar (and for lack of a better term) non-chronic disease indicators; and the newly incorporated chronic disease indicators.

The indicator—or measurable outcome reflective of the consequences of adequacy of intake or consequences of excess intake—is an important choice during DRI development because it serves as the basis for making a quantitative estimate of the requirement for the nutrient or, for upper levels of intake, the intake level that can be considered adverse. When there is more than one indicator that may be used to reflect the body's needs or adverse response for a particular nutrient, the "best" indicator is determined. The choice of one indicator over another can, of course, change the ultimate DRI value.

As one presenter[83] noted, indicators are the skeletal structure on which the EAR and UL are draped. In essence, they are an expression of the targets or goals of the DRI development process. They should be related to quantifiable or measurable attributes that in turn relate to the overall public health goal of the effort. The same presenter indicated that the selection of indicators for nutrient reference values has evolved in response to changes in nutrition science. For example, until 1974, the reference value for thiamin was based on the level of dietary thiamin that would prevent clinical signs of deficiency and produce measurable levels of thiamin metabolites in urine. In 1974, maintaining

[79] Beaton, Session 1.
[80] Miller, Session 4, Panel Discussion.
[81] Participant, Session 1, Panel Discussion.
[82] Yates, Session 1 / Participant, Session 1, Discussion, Pros & Cons—Case Studies.
[83] Rosenberg, Session 2.

transketolase activity was introduced as the criterion for establishing the reference value. Such advances sometimes revealed associations between an indicator and diet and at other times identified possible indicators through better understanding of metabolic and physiological states. Moreover, approaches for indicator selection have been variable across the DRI study committees. The presenter suggested that this is to be expected, given the differences in the biology and functions of nutrients.

Appendix 1 lists the indicators selected as well as those considered by the various DRI study committees. Overall, more than 400 indicators were considered. For the EAR, indicators range from those that reflect a clinical outcome (e.g., dental caries) to measures of intake. Indicators for AIs differ from those for EARs by including population intakes. The ULs reflect indicators that range from biochemical to clinical effects and differ in their severity and time course.

A "sidebar" topic that was discussed during Workshop2007 focused on whether the DRI process should be expanded to issue multiple reference values for a nutrient based on multiple indicators for a single life stage and gender group. The focus of the question was not the study committees' existing practice of considering an array of possible indicators before they select one to serve as the basis for a reference value, nor was it the question of whether different indicators should be selected for different life stage and gender groups, as they currently are. Rather, the issue was whether study committees should develop, so that users could choose from among, an array of reference values for the *same* group based on different indicators of interest. This approach was not supported and was considered likely to lead to misunderstandings and undermine the integrity of the process.[84] It would also be in conflict with the recent recommendations from an international effort to consider the possible harmonization of nutrient reference values.[85] Enhanced characterization of uncertainties surrounding the reference values may reduce the concerns that led to the interest in multiple reference values based on multiple indicators for a single life stage and gender group.

The 1994 DRI Plan, in response to advances in the science of nutrition, expanded the basis for nutrient reference values to specifically include measures for reducing the risk of chronic disease, when data were available. The potential impact of this decision was recognized at the time, and cautions were offered concerning the need to broaden the data evaluation criteria to include, among other considerations, the strength of the data supporting a nutrient's role in reduction of disease risk.

Issues/Gaps 4-4:

Addressing Chronic Disease Indicators

There is considerable interest—as well as more than 10 years of experience—surrounding the inclusion of chronic disease indicators within DRI development. A variety of perspectives were put forward. There is a need for focused discussions about how to

[84] Rosenberg, Session 2 / Woteki, Session 4.
[85] King (2007).

include chronic disease indicators in the DRI process, including specific approaches for addressing their confounders, identification of appropriate biomarkers, and quantifying their effects.

During the 1994–2004 DRI development process, chronic disease indicators were used to establish AIs for five nutrients (calcium, vitamin D, fluoride, fiber and potassium) and to establish a UL for one nutrient (sodium). As a general matter, the widely recognized set of challenges associated with the consideration of chronic disease risk reduction as an indicator led some Workshop2007 participants to suggest that their inclusion was inappropriate or that their consideration should be separated from that for non-chronic disease indicators. Some of the concerns relate to the nonthreshold effects of some indicators and the difficulty of using them in the current DRI model. On the other hand, others indicated that chronic disease is a major public health concern and that reference values based on such indicators are needed. That is, the goal of the DRIs is to provide a scientific backbone for government nutrition policy, and chronic disease indicators relate to this interest. They opined that the recent experience highlights the need to continue to explore and finesse the approaches for evaluating data related to chronic disease risk reduction, to recognize all indicators as existing on a continuum and to provide enhanced guidance for those facing the challenges associated with the consideration of chronic disease indicators.

A Workshop2007 presenter[86] suggested that chronic disease indicators are not a great leap for DRI consideration given that, throughout the history of nutrient reference values, chronic disease has been an implicit part of trying to set values that were "above those necessary to prevent deficiencies." Another[87] explained that concepts of chronic disease have been part of the process as far back as 1958 and have evolved as the knowledge base expands. Alternatively, a different presenter[88] noted that the challenges associated with chronic disease indicators are unique and could be addressed by setting an AI rather than an EAR. One Workshop2007 participant[89] opined that the use of a physiological indicator is preferable as it presumably offers a less complicated review process for study committees. Another[90] pointed out that at times an EAR, rather than an AI, could have been established if study committees had selected a non-chronic disease indicator when the chronic disease indicator proved too problematic.

A Workshop2007 presenter[91] offered the perspective that the specific inclusion of chronic disease indicators in the 1994 expansion created an unanticipated number of challenges that compromised, or at least greatly complicated, the utility of the DRIs, especially as they relate to providing a foundation for food-based dietary guidance. She highlighted the lack of clarity in the data, the burdens associated with the need for increased and diverse expertise within study committees and her concern that the inclusion of chronic disease indicators led to the development of mixed criteria for DRI values, with resulting disparate standards among the nutrients. She also indicated that the DRI standards/guidelines developed for cholesterol, *trans* fat, saturated fat and added sugars were not readily useful and suggested that the inclusion of chronic disease indicators led to the AMDRs, which are characterized by flaws stemming from the inadequacy of research data. The conclusion reached by this presenter was that the "standards" for preventing nutrient deficiency need to be separated from those for preventing chronic disease, because they have different goals. Thus, the two classes of indicators (chronic disease and non-chronic disease) should be reviewed by two different scientific committees with different expertise. She posed the question as to whether the reviews pertaining to chronic disease indicators are appropriate for a body such as the IOM or whether they belong within the domain of a government advisory committee

[86] Rosenberg, Session 2.
[87] Woteki, Session 4
[88] Trumbo, Session 1.
[89] Participant, Session 1, Discussion, Pros & Cons—Case Studies.
[90] Participant, Session 1, Panel Discussion.
[91] King, Session 1.

associated with dietary guidance. What was not clear from the presentation was whether the comments were focused only on energy-yielding nutrients or extended to all nutrients.

Several Workshop2007 participants expressed interest in considering chronic disease indicators separately from non-chronic disease indicators, without identifying a specific approach or relevant category of substances. No clarity was offered in terms of how nutrient reference values would be developed if different types of indicators were considered independently. In terms of separating chronic disease considerations from those for non-chronic disease, some Workshop2007 participants[92] offered the counter-perspective that indicators relative to nutritional adequacy are a continuum, and that chronic disease can be placed on that continuum. In effect, no meaningful scientific distinction exists between non-chronic disease indicators and chronic disease indicators. Rather, perceived differences are due to lack of available data or lack of new methodologies that can address the complexity and confounding associated with the indicators. It was pointed out that the more traditional adequacy indicators can also be confounded or complicated by, for example, nutrient–nutrient or nutrient–other substance interactions.[93] A presenter[94] suggested that it is unwise to "throw out" all chronic disease indicators because some are multifactorial and confounded; and that chronic disease risk reduction considerations should not be lumped together in considering their utility in the DRI process because, as indicators, they likely need individual review.

Questions about addressing chronic disease may be more fully fleshed out if additional points are offered. One consideration is that DRIs, if they are in essence public health reference values, may need to reflect the current state of the science regardless of the type of indicator. In turn, the experience of the 10 years following the introduction of DRIs may be pointing to the desirability of developing a more flexible approach or model that can more readily incorporate both chronic disease and non-chronic disease indicators in the development of reference values. The two types of indicators most commonly vary by the types of data that are useful to their consideration—for example, experimental versus observational data. Working with these differences may be in part a matter of understanding the strengths and weaknesses of each type of data and in turn finding ways to formulate results so that they are expressed on a common basis.

► 4.3 Substances Appropriate for DRI Development

Historically, the substances for which nutrient reference values have been developed were the essential or so-called classical nutrients, specifically vitamins, minerals, protein and energy (calories). As time has passed, substances found naturally in foods, ranging from fiber to carotenoids, have been incorporated into the DRI process. A few advocate a return to specifying values only for those substances demonstrated to be biologically essential in the classical sense, but others view the need for reference values to encompass other food components that impact health. While the maintenance of a focus solely on classical nutrients is attractive for its simplicity, it may overlook the emerging data demonstrating that many food components are important to ensuring health. An argument may be made for developing the capacity to consider these substances and provide reference values for them when appropriate.

[92] Yates, Session 1 / Participant, Session 1, Discussion, Pros & Cons—Case Studies.
[93] Participant, Session 1, Discussion, Pros & Cons—Case Studies.
[94] Mayne, Session 2.

During Workshop2007, the discussions related to substances of interest for DRI development included the evidence needed to ensure that the substances in question meaningfully impact health. That is, the nature of the data needed to establish health impacts and to evaluate both the risks and benefits of nutrient substances should be considered carefully. A Workshop2007 presenter[95] indicated the importance of ensuring that the effects attributed to nutrient substances relative to health/disease outcomes are real and likely to be stable over time. His conclusions offer the following perspectives:

- Efficacy data based on sound scientific evidence must be present before public health recommendations regarding nutrients are made.
- Many existing data are not sufficient, not sound and even contradictory; these need to be sorted through using systematic approaches.
- Confidence in nutrient–disease relationships can change, often in unexpected directions.
- Large randomized trials have the greatest impact in changing the level of confidence in a nutrient–disease relationship. Although these trials have an enormous cost, they are necessary.
- We need greater investment in research in the nutrition area.

As research in the field of nutrition continues to explore the impacts of various food components on health, appropriate methodologies for ensuring that these impacts are real, consistently demonstrable and stable are critical. In turn, criteria for determining the appropriateness of a substance relative to DRI development should emerge. Likewise, research related to the safe levels of intake of these substances also needs to be performed.

[95] Greenwald, Session 4.

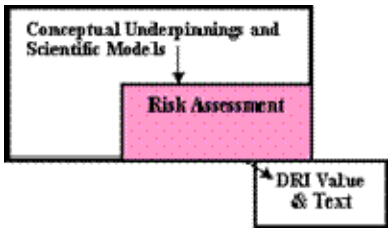
Conceptual Underpinnings and Scientific Models

5. DIETARY REFERENCE INTAKE DERIVATION: USE OF RISK ASSESSMENT

5.1 Risk Assessment Link to DRI Development
5.2 Operationalizing Nutrient Risk Assessment
- 5.2.1 Incorporating Special Characteristics of Nutrients
- 5.2.2 Problem Formulation: A Preliminary Step
- 5.2.3 Step 1: Hazard Identification or Indicator Identification
  - 5.2.3.1 Systematic Evidence-Based Reviews (SEBRs)
  - *Issues/Gaps 5-1: Tailoring SEBR to Support the Development of Nutrient Reference Values*
- 5.2.4 Step 2: Hazard Characterization or Indicator Characterization
  - 5.2.4.1 Consideration and Selection of Indicators
  - *Issues/Gaps 5-2: Identifying and Validating Biomarkers of Effect for Nutrients*
  - *Issues/Gaps 5-3: Selection of Indicator*
  - 5.2.4.2 Development of Dose–Response Relationships
  - *Issues/Gaps 5-4: Approximating Dose–Response Relationships*
  - *Issues/Gaps 5-5: Development of Methodologies for Nonthreshold Substances*
  - 5.2.4.3 Consideration of Uncertainty
  - *Issues/Gaps 5-6: Addressing Data Uncertainty*
  - 5.2.4.4 Extrapolation/Scaling
  - *Issues/Gaps 5-7: Procedures for Extrapolation or Scaling*
- 5.2.5 Step 3: Exposure Assessment or Intake Assessment
  - *Issues/Gaps 5-8: Considerations for Use of Dietary Intake Data*
- 5.2.6 Step 4: Risk Characterization
  - *Issues/Gaps 5-9: Components of Nutrient Risk Characterization*

A lesson learned from the 10-year experience in developing DRIs is that a defined, organized and accountable decision process as well as clear guidance concerning expectations and approaches for the needed tasks would enhance DRI development. It would also help to clarify the DRI process. The organizing scheme laid out by the risk assessment approach is relevant in this regard. It is essentially a stepwise decision-making process developed and used in an array of scientific fields. Although risk assessment—as a component of risk analysis (Section 2.3)—has its roots in the study of substances such as pesticides and other chemical contaminants, it is a general organizing scheme that has been adapted for a wide range of fields. In the food area, for example, it has been used for the management of microbial hazards.

► 5.1 Risk Assessment Link to DRI Development



Beginning in the 1990s, the process of risk assessment formally entered into DRI development as the basis for the model for establishing upper levels of intake of

nutrients. The approach was the subject of in-depth consideration by the Subcommittee on Upper Reference Levels of Intake of Nutrients (1996–2003); by the time the first volume of DRIs was issued in 1997, the Subcommittee had specified the key components of the approach.[96] It was based in part on earlier work carried out by the NRC.[97] Others have also adapted and used a risk assessment scheme to consider upper levels of intake of nutrients.[98]

In hindsight, at the time the DRIs were initiated it seems likely that the risk assessment organizing scheme was equally applicable to the activities focused on requirements for ensuring nutritional benefit (i.e., the EAR). In all likelihood, however, risk assessment in the mid-1990s for the purpose of DRI development was not well understood or readily seen as appropriately adaptable. In a way, risk assessment appears to have suffered from a "public relations problem," in that it has been misunderstood by some to be a fixed targeted methodology focused strictly on toxicological issues rather than a flexible, objective scientific scheme for making transparent and accountable decisions, whatever the indicator of interest.

Moreover, the word "risk" causes some in the nutrition field difficulty, in that it does not seem appropriate to link the benefits of nutrient intake to the concept of "risk," despite the ultimate purpose of reducing the risk for intakes too low to provide the health benefits. Other risk assessment terminology may also seem inappropriate, such as the decision steps labeled as hazard identification and hazard characterization. Nonetheless, the approach that evolved for estimating EARs rests on a sequence of decisions that are similar to those specified within risk assessment.

During Workshop2007, there was support for using a risk assessment scheme for overall DRI development.[99] There are advantages to applying the same organizing scheme for both ULs and EARs.[100] For instance, if study committees were to incorporate the same general decision-making process to derive both adequate and excessive intakes, it would allow side-by-side comparisons of the process as it progresses. This could be of value in identifying unintended consequences or inconsistencies among the various DRI development activities. One example is the procedures used for extrapolation relative to EAR and UL values.[101] Study committees would likely notice potential incompatibilities if the evaluations for both adequate and excess intakes were compared in a side-by-side risk assessment framework. Additionally, as the methodological challenges in the studies used to evaluate risks are likely to be associated with both inadequate and excessive intakes, a consistent framework for analyzing both is logical. Finally, risk assessment application to DRIs overall could allow concurrent examination of the prevalence of

[96] IOM (1998).
[97] NRC (1983).
[98] FSA (2003); FAO/WHO (2006); SCF (2006).
[99] Brannon, Session 1 / Stoecker, Session 1 / Yetley Session 1 / Miller, Session 1 / Woteki, Session 4.
[100] Participant, Session 1, Discussion, Pros & Cons—Case Studies.
[101] For the 1994–2004 DRI process, the default for extrapolations for ULs was reference body weight, whereas the default for extrapolations for EARs/AIs was metabolic body weight. There was no acknowledgment of, or rationale given for, the use of different defaults for these two types of reference values.

intakes above the UL and below the EAR/RDA within and across life stage groups for a particular nutrient. This is potentially important to users who are frequently faced with balancing the conflicting needs of consumers with low intakes of a nutrient against the potential for excessive intakes among other consumers.

Another advantage of the risk assessment scheme for DRI development is that risk assessment as a discipline has been focusing on new and enhanced approaches. The DRI process can benefit from these advances. For example, risk assessment as a discipline has been:

- *exploring the use of probabilistic models in order to move from "qualitative" to "quantitative" risk assessments.* Qualitative risk assessment focuses on specifying a particular number (or reference value) rather than describing the distributions and the shape of the distribution curves of interest. Several participants[102] during Workshop2007 pointed to this shift as an important one for future DRI development. In fact, such a shift has already begun, given the 1994 decision to provide EAR values coupled with distribution curves rather than just an RDA value; and
- *working to establish better defined criteria for dealing with different types and sources of uncertainty*. For example, one focal point is the use of statistical models to simulate dose–response relationships through the combined use of multiple studies that individually lack sufficient data to produce a dose–response curve. Procedures for adjusting coefficients of variability to account for altered dose–response relationships are also being explored. This has direct application to polymorphisms that alter nutrient requirements or toxicities among population groups.

The basic outline for the risk assessment scheme (sometimes also called a "model" or "approach") specifies four general steps, as shown in Figure 5-1. General activities associated with each step are also shown.

The terminology accompanying these steps may seem unfamiliar to many nutritionists, but the concepts are germane. One of the future tasks in further adapting risk assessment for use with nutrients may be to modify the terms so that they are more compatible with the nutritional perspective.

[102] Participant, Session 1, Discussion, Pros & Cons—Case Studies / Beaton, Session 1 / Yetley, Session 1 / Participant, Session 1, Panel Discussion.

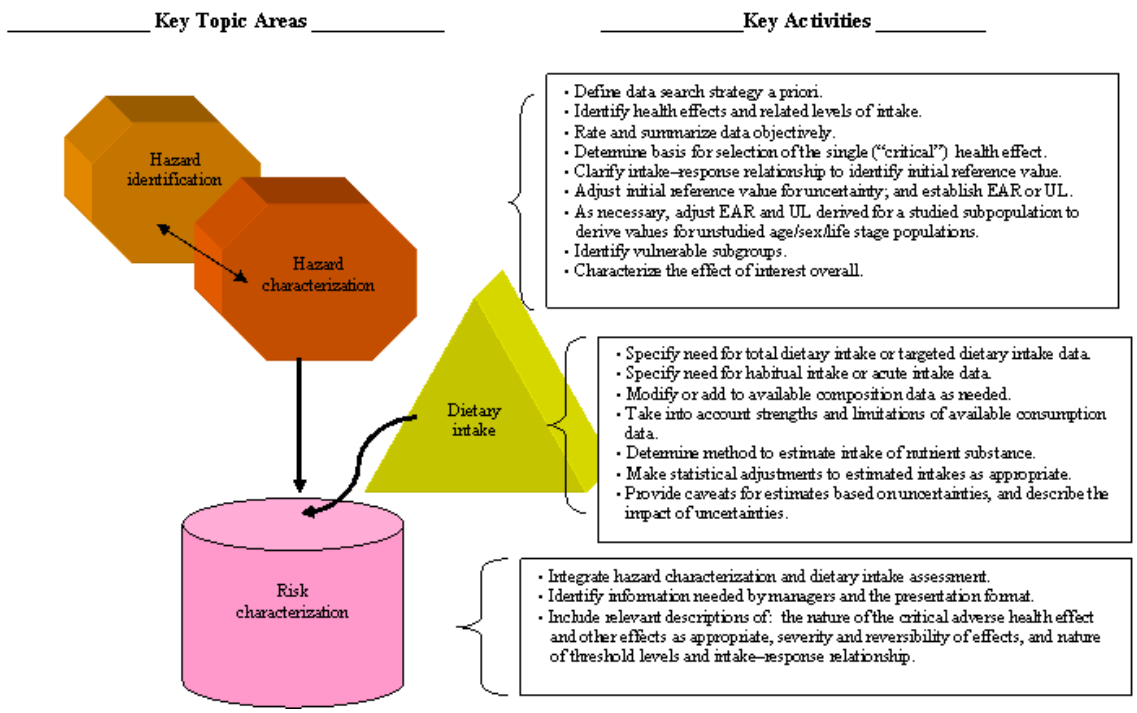


Figure 5-1: The Four Steps of General Risk Assessment[103]

► 5.2 Operationalizing Nutrient Risk Assessment

The risk assessment scheme involves four systematic steps (see Figure 5-1), each with a set of decisions. In effect, the decisions to be made for excessive levels of intake are generally similar to those to be made for adequate levels of intake. An understanding of the characteristics of nutrient substances that are unique to nutrients as well as considerations of a problem formulation step are both important to setting the stage for the four steps of nutrient risk assessment.

5.2.1 Incorporating Special Characteristics of Nutrients

The risk assessment scheme is useful for a wide range of substances, provided that the decision steps are fully informed about any special considerations unique to the general category of substances under consideration. Nutrient substances are characterized by several special considerations.

An important special characteristic is the dual risk presented by nutrient intakes. Low intakes increase the risk of deficiency (or the risk of consuming too little to experience the health benefit), whereas excessive intakes increase the risk of adverse effects or

[103] Modified from FAO/WHO (2006).

toxicity. In other words, there are increased risks associated with both excessive intakes and inadequate intakes. This is in contrast to many other substances subject to risk assessment that reflect only a risk from increasing exposure. The relationship is shown graphically in Figure 5-2.

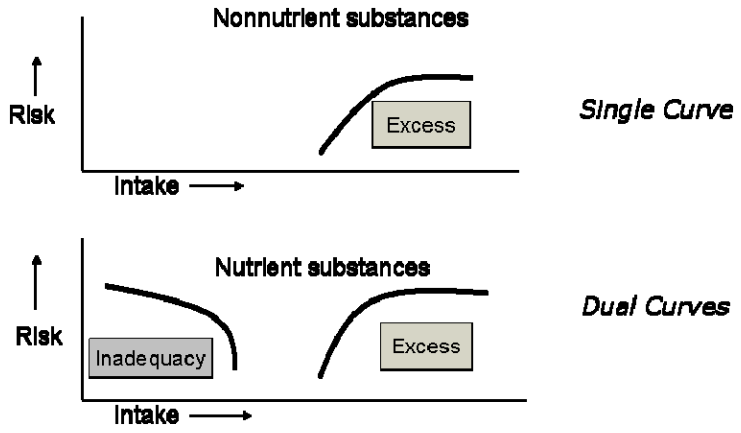


Figure 5-2: Intake versus Risk for Nonnutrient and Nutrient Substances

Figure 5-3 below illustrates the dual nature of risk for nutrient intake, resulting in dose–response curves[104] for both deficiency states (left curve) and high levels of intake (right curve). The figure also indicates the classical positioning of DRI values in relation to these risk curves. The two separate dose–response curves are almost certainly associated with different mechanisms and pathways; they are not a single U-shaped curve. Moreover, although these curves are often shown as symmetrical, they may have quite different shapes and degrees of steepness, depending upon the nutrient substance and the population.

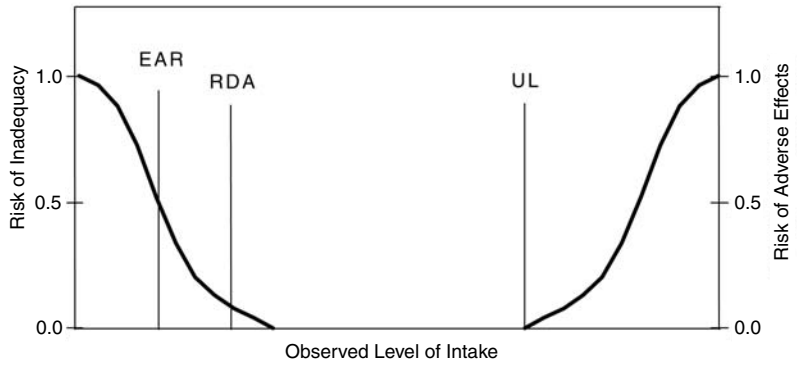


Figure 5-3: Intake versus Risk in the DRI Context

[104] Intake–response and dose–response are used interchangeably by some.

The assessment of the effects of the various levels of intake of the nutrient—or, more specifically, the assessment of risk associated with certain levels of intake—is best described as a *risk/risk* assessment. The risk/risk nature of nutrients forces some adaptations within the general risk assessment scheme; these include the need for careful consideration of adjustment factors related to uncertainty, so that the various reference values do not overlap (see Section 5.2.4.3). Some prefer the terminology *benefit/risk* assessment; in these circumstances, a broader discussion is needed to clarify that the benefit/risk comparison is in relation to the same person, meaning the same life stage and gender group. In any case, so-called benefit/risk analyses that attempt to compare the risk of the substance or intervention for one group with the benefit for another group are a different set of tasks and would require different approaches and assumptions.

Other special characteristics of nutrients that need to be incorporated into the nutrient risk assessment scheme include the following:

- homeostatic mechanisms;
- analysis specific to life stage and gender;
- existence of "background level" of exposure to nutrients;
- bioavailability/bioequivalency/biopotency;
- terminology; and
- nature of available data.

These are described briefly in Appendix 3.

5.2.2 Problem Formulation: A Preliminary Step

Problem formulation is emerging as a tool for ensuring that risk assessment outcomes are useful. It can best be illustrated as an early activity that precedes the four steps of risk assessment (Figure 5-4 below).

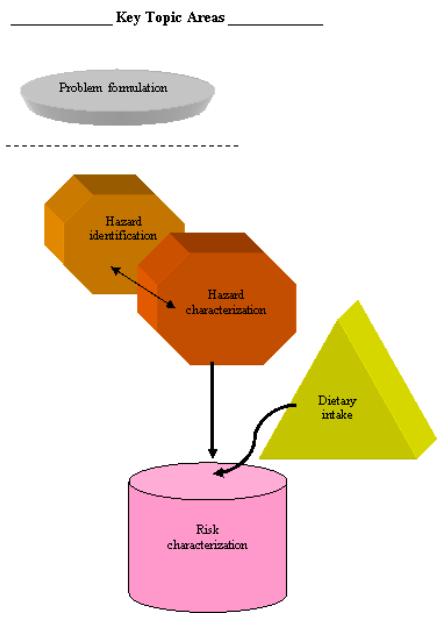


Figure 5-4: Steps of Risk Assessment Preceded by Problem Formulation[105]

Formal problem formulation fosters interactions between risk managers (usually sponsors) and risk assessors (study committees) to ensure common understanding of the problem and to refine the questions to be addressed and relevant issues, as needed. In the DRI context, some problem formulation occurs in setting up contractual agreements and some in discussion between the sponsors and study committees. Discussion between the sponsors and study committees should take place before the assessment tasks begin to ensure that the study committee members understand the information needs of the sponsors and users and that the risk assessors have the opportunity to suggest revision and clarification of the problem formulation questions, if needed. During Workshop2007, problem formulation was acknowledged[106] as a component of DRI development important to enhancing the process.

As noted in Section 2.3, the key aspects of interaction between sponsors and study committees at the initiation of the study would benefit from closer examination. In the future, problem formulation activities may be more formally recognized, consistent with the established risk analysis scheme. Nonetheless, stage setting in the form of problem formulation for DRI development—or for any risk assessment—must be carried out carefully so that sponsors provide the needed information while at the same time avoiding inputs that could be interpreted as compromising the independent scientific deliberations of risk assessment. The problem formulation step is not meant to make scientific decisions for study committees, preevaluate the worthiness of available evidence or restrict the set of scientific considerations that may be relevant to the problem. The key points are that problem formulation is recognized as an important component of the DRI process, enhancing the utility of the process, and that the

[105] FAO/WHO (2006).
[106] Participant, Russell Session 1, Open Discussion / Yetley, Session 1 / Woteki, Session 4.

boundaries separating the needs and interests of sponsors from the scientific decisions are maintained and respected.

As an aside, sponsors and risk managers have a legitimate interest in ensuring that appropriate and cutting-edge scientific methodologies are developed and available for use in the DRI process. This interest, however, is not a component of problem formulation. Rather, it is addressed through the support of conferences, workshops, consensus studies and scientific meetings that explore and refine such methodologies and, in turn, make them available for consideration and use by DRI study committees and the world at large.

From the broad perspective of nutrient reference value development, activities very similar to problem formulation have in fact been carried out in a fashion over the years—even if not recognized or specified as such. This early informal problem formulation resulted in the evolution of several widely agreed upon "expectations" for nutrient reference values. These reflect the sponsors' overall interests and include the need for values (a) to serve the purpose of assessing and planning diets, (b) applicable to the apparently healthy U.S. and Canadian populations and (c) based on life stage and gender groupings. More recently, other expectations have evolved through the same kind of informal problem formulation, and coupled with advances in scientific understandings and deliberations of scientific experts. These include (a) values expressed as EAR, RDA and UL, (b) expansion of DRI reviews to nonessential nutrient substances and (c) consideration of a wide array of indicators, including chronic disease indicators. Many of these topics were part of the discussions of Workshop2007, as described previously.

At its current juncture, problem formulation for DRI development can be expected to take a number of forms, depending upon the issues at hand. At its most basic, it is likely to initially focus on interactions and dialogue intended to shape the study to appropriately focus on the issues surrounding the "problem" from the perspective of the sponsor. At the same time, it is an iterative process that includes questions to clarify the issues and there may be suggestions for modifications, refinements and additional approaches. It may encompass information and discussions about topics including, for example, the specific forms of the nutrient that are of concern, the sources of information that may be relevant (e.g., a recent government-sponsored SEBR), the general characteristics of desirable study committee expertise and—within the confines of FACA—approaches for solicitation of input for study committees and the possibilities for public meetings and web-based consultations.

5.2.3 Step 1: Hazard Identification or Indicator Identification

The first step in a risk assessment scheme is *hazard identification* or, for nutrients, *indicator identification*. It is essentially a literature review and identifies reports related to outcomes associated with too little or too much intake.

The general criteria and basic data needs relevant to the search for information about indicators, or "effects" of nutrient substances, are generally the same regardless of

whether the interest is in determining a requirement or determining an excessive level of intake. For nutritients, this process would be predicated on initially identifying all relevant "effects," rather than limiting the search to a specific type of effect.

5.2.3.1 Systematic Evidence-Based Reviews (SEBRs)

Over the past decade, the nutrition community has increasingly used SEBRs to examine nutrient and disease relationships, and questions about their role and nature in the DRI development process have been raised. A comment sometimes heard is that nutrient reference values have always been based on evidence, and the suggestion that there is now a need for an "evidence-based" process engenders confusion and misunderstandings.

References to SEBRs for DRI development do not stem from the suggestion that consideration of evidence has not occurred in the past, but rather reflect an interest in addressing the literature that initiates and underpins the derivation of the DRIs in a transparent, comprehensive, consistent and objective manner. It offers an accepted, objective process for categorizing evidence. Conceptually, the emphasis and new considerations focus on the word "systematic" rather than the word "evidence."

While all DRI studies have included literature reviews on the part of committee members, an emerging interest is focused on incorporating the specific discipline of SEBR for the purposes of examining the available data relevant to nutrient requirements and the effects of excess intake. This focus is less one of superimposing the detailed tasks of SEBR on busy study committee members—although awareness of the SEBR principles could undoubtedly be useful to committee members—and more one of considering the options of making use of SEBR professionals outside the study committee, as appropriate. Because the DRI process relies on volunteer scientists, Workshop2007 discussions led some[107] to suggest that there is little logic in using their limited time to carry out basic screening literature reviews and summaries that may appropriately and perhaps more readily be accomplished by outside experts trained in systematic data review. Such reviews could serve as a starting point for many, but not all, of the study committee tasks, and they inform rather than replace the expert judgments to be made by DRI study committees. Further, SEBRs as conducted by groups outside the study committee may offer the opportunity to enhance transparency relative to the DRI process.

SEBR is essentially an approach to identifying, tabulating and grading the quality of available data. It emerged as a tool to enhance the practice of evidence-based medicine—the judicious use of the best current evidence in making decisions about the care of the individual patient. The basic components of SEBR[108] are as follows:

- Develop a literature search strategy based on the questions and criteria provided to the SEBR group (or "practice center") by those sponsoring the SEBR.
- Identify the review inclusion/exclusion criteria.

[107] Lichtenstein, Session 1.
[108] Ibid.

- Retrieve and screen relevant literature.
- Grade studies.
- Extract/summarize data.
- Complete a report for those requesting the SEBR.

The latter four activities are carried out by persons specifically trained in systematic, objective data review. The compiled information, typically in table format, and the accompanying summary evaluations, as completed by the SEBR group, are delivered to those requesting the SEBR. The information serves as one of the starting points for the assessment to be carried out. This work involves relevant scientists considering and interpreting the SEBR outcomes in order to make the needed conclusions and judgments, whether the needs focus on treating a patient or determining a nutrient requirement. More detailed examples of SEBRs and related table formatting can be found in other sources.[109]

The types of specification provided by those requesting a SEBR relevant to a specific nutrient review may include[110]:

- *Study populations*. For example: "Include all ages, male and female, racial/ethnic groups, persons in the general population for whom disease conditions or medication use will not alter normal relationships among intakes, intermediate markers, and outcomes…. Exclude persons for whom disease conditions will alter relationships…."
- *Comparators*. For example: "Intervention versus normal diet; No supplemental nutrient versus supplemental nutrient…."
- *Information included in summary tables*. For example: "Baseline intakes and status of study populations; Methods used for dietary assessments; Indicators of exposure or body stores, indicators of outcome; Population characteristics (age, gender, race, disease); Form and amount of nutrient, and delivery conditions; Study duration; Differentiation between primary and secondary outcomes for intervention studies."
- *Types of studies to be included.* For example: "For all except excessive intake effect evaluations, reviews will be limited to human intervention studies and prospective, cohort observational studies. For excessive intake effect, reviews will include all human studies plus relevant animal studies and review articles."

Such systematic reviews enhance transparency by providing a clear description of the methods used to ensure completeness in identifying the available data, the rationale for the selection or exclusion of studies as well as the method of evaluation. Further, SEBR can readily include meta-analyses to combine similar studies and increase the statistical power for addressing specific questions of interest.

[109] For example: FAO/WHO (2006); IOM (2008); http://www.ahrq.gov.
[110] Modified from FAO/WHO (2006), Annex 1.

As consideration is given to integrating "outside" SEBRs into the risk assessment process for DRIs, several points from Workshop2007 about SEBR are worth noting[111]:

- SEBRs can:
  - serve as a tool for use by study committees;
  - free study committees to focus on the larger picture (assuming the initial SEBR questions and search criteria are appropriate for the issues at hand); many factors go into making decisions and evaluating the data beyond a systematic analysis of the literature;
  - offer increased transparency; and
  - allow for more efficient updating as new data emerge.
- SEBRs can*not*:
  - "automate" the review process and relegate all decisions to nonexperts in the field or to computer modeling programs;
  - shift the decision-making process from the study committee to the SEBR group; or
  - diminish the need for expert opinion and scientific judgment.

While many of the components of the SEBR process as practiced in evidence-based medicine are applicable to nutrition, there are important differences between considerations related to medical evaluations, interventions and patient care and those for nutrient requirements or the effects of excessive intake. The questions for use within evidence-based medicine are usually more targeted, whereas those for DRI development could be characterized as more broad-reaching.

At least two groups have specifically considered the development of SEBR within the context of either upper levels of intake or both nutrient requirements and excess intake. First, the FAO/WHO Report contains discussion about the need to adapt the questions and criteria for SEBRs to make them specifically relevant to nutrients. This report acknowledges the merits of SEBR for nutrient considerations as (a) the a priori definition of the search strategy criteria and (b) the summarization of study results into table formats. In addition, the inclusion of ratings of the methodological quality of reviewed studies was considered very useful.

However, there are three reasons for the FAO/WHO Report's conclusion that, if SEBR is to be relevant to nutrient risk assessment, the usual clinical medicine approach outlined for such reviews must be adapted: (a) the open-ended nature of the starting questions, (b) the dependence on the integration of many types of information to obtain an adequate understanding of intake–response relationships and to develop uncertainty factors and (c) the potential need for refinements of the data search and evaluation process as the decision-making process evolves.

Second, and more recently, the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services initiated efforts to address SEBR and DRI development specifically. This government agency has developed a number of nutrient-

[111] Modified from Lichtenstein, Session 1.

related SEBRs through the use of Evidence-Based Practice Centers. To support these efforts and better clarify the appropriate process, Evidence-Based Practice Center Technical Papers on four topic areas are expected to be released in early 2008. Information about these papers can be accessed at http://www.ahrq.gov/clinic/tp/nutritntp.htm. The topics to be covered are:

- *Identifying the Challenges, Advantages, and Limitations of Conducting Nutrition-Based Evidence-Based Reviews and Integrating Them into Nutrition Applications*;
- *Evaluating Approaches for Integrating Evidence-Based Reviews into Processes for Deriving Nutrition Reference Intakes*;
- *A Critical Assessment and Recommendations for Reporting of Nutrition Evidence-Based Decision-Making Processes*; and
- *Review of Nutrient Literature to Inform a Plan for Critical Analyses to Predict Outcomes of Nutrient/Diet and Health Outcomes.*

Issues/Gaps 5-1:

Tailoring SEBR to Support the Development of Nutrient Reference Values

Recognition of the potential of SEBR for the development of nutrient reference values—coupled with the realization that the approach should be adapted as appropriate for DRI considerations—points to the need to further explore and refine SEBR as it relates to DRI development. Moreover, working to reach a common understanding about its value and limitations relative to DRI development is important.

Comments made by Workshop2007 participants[112] ranged from questions about cost and time for SEBR to concerns about loss of study committee control if SEBR is performed outside the committee. There were also questions about the ability of the SEBR format to answer all questions relevant to DRIs. It was suggested by some participants that outside SEBR groups are not charged with providing the scientific judgment necessary for deriving DRIs. Rather, the SEBR offers one source of information for deriving DRIs and could not by itself be used to derive DRI values. It was also pointed out that not every decision in a DRI process is appropriate for SEBR, and therefore many decision steps are outside the SEBR efforts. Further, the SEBR process allows study committees to carry out other tasks, rather than performing objective analytical tasks that can be done by others and summarized for use by the study committees.

A formal SEBR could be carried out as part of a DRI study committee task, but, as discussed during Workshop2007, this could be an unnecessary use of resources, for two reasons. First, such reviews often make use of considerable expertise that relates only to the objective evaluation of any set of literature, and therefore the persons with such expertise may be superfluous to a large component of the committee's activities and the needed scientific judgments. Second, since by definition a SEBR is an objective tool for the study committee deliberations and does not replace the study committees in any sense, an outside SEBR process can more readily and efficiently carry out a task that would perhaps be burdensome for committee members who volunteer their time to assist with DRI development.

These outside committee reviews may also offer a solution to concerns expressed during Workshop2007[113] that the appearance of bias in judging available data

[112] Participants, Session 1, SEBR & Risk Assessment, General Discussion.
[113] Russell, Session 1.

may be a problem within the current DRI process. Given its objective nature, the SEBR analysis activities must be independent from those requesting the review. However, to ensure that the work is relevant for its purposes, SEBR usually relies on outside expert panels to suggest and outline the appropriate questions and criteria for the review. These expert panel discussions are not recommendations, nor are they binding on the SEBR process, but they are helpful in properly framing the questions and function as a problem formulation step. One source regarding procedures developed to ensure both appropriate input and the maintenance of an independent, objective scientific review is the U.S. Preventive Services Task Force.[114]

On the other hand, outside SEBR reviews represent several challenges to study committee activities. One is timing. It would be best to have SEBRs available to study committees at the beginning of their work, but it requires that the relevant questions and criteria of interest to the study committee be anticipated by others not part of the committee. Conversely, convening a study committee so that it could in some way inform the SEBR review is not efficient in terms of resources because the committee would have considerable downtime waiting for the SEBR. It may also present challenges in terms of "developing" data sources for committee use outside the defined IOM committee process. Solutions to these obstacles should be explored.

Finally, a parallel task is the need to initiate activities to more formally adapt the SEBR approach to ensure its utility for DRI development. Moreover, as discussed in the FAO/WHO Report and highlighted by a soon-to-be-released paper,[115] even when the general workable criteria for this effort are developed, it is likely that the relatively open-ended nature of the questions to be addressed will require a somewhat iterative process for developing and finessing the questions for specific tasks. Integrating an approach for this needed task would be worthwhile.

5.2.4 Step 2: Hazard Characterization or Indicator Characterization

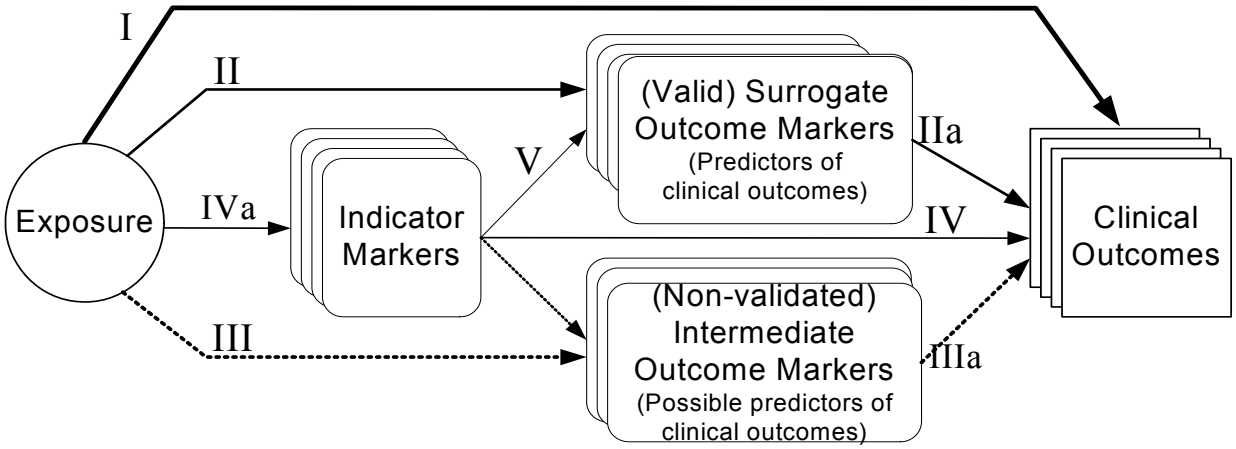
The second step of risk assessment is called *hazard characterization* or, perhaps for nutrients, *indicator characterization*. Its end product is the quantitative reference value, but this outcome is preceded by a number of critical and complicated decisions. The tasks include considering the available data about the various indicators that reflect an effect (presumably data organized by the hazard identification step) and then determining which of these is the one suited to serve as a basis for developing the reference value. Different life stage and gender groups may have DRIs based on different indicators as appropriate for their physiological and metabolic states. Limited data may not always allow a full complement of indicators for all life stage and gender groups, in which case extrapolation and scientific judgment come into play.

5.2.4.1 Consideration and Selection of Indicators

The types of indicators ultimately selected as the basis for DRIs are varied (see Appendix 1), ranging from actual clinical signs of disease and surrogate markers to measures responsive to intake and assumed to be relevant to clinical outcomes of interest. These indicators reflect a range of measures, including measures of exposure, biomarkers of exposure, biomarkers of effect and the effect itself.

[114] Harris et al. (2001); West et al. (2002).
[115] EPC (in preparation).

A generic framework for the linkage between intake and clinical outcome is shown in Figure 5-5.



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 5-5: Generic Framework for Link between Intake and Clinical Outcome[116]

The array of biomarkers used for DRIs during the 1994–2004 time period can be categorized as follows:[117]

- Biomarkers of exposure
  - Blood levels
  - Balance studies, saturation of pools, etc.
- Mechanistic/functional biomarkers
  - Enzyme saturation, other functional changes
- Biomarkers of effect
  - Efficacy: Alter course of known disease process
  - Efficacy: Modify outcome (but may not resolve disease)
  - Efficacy: Alter presence/absence of disease
  - Surrogate: Recognized predictor of disease outcome
- Clinical outcome
  - Dental caries, macular degeneration

[116] From EPC (in preparation).
[117] Susan Mayne, Yale University; IOM/FNB Planning Meeting, Evidentiary Framework for Identifying and Validating Biomarkers of Effect, February 2008 (unpublished).

While all biomarkers are of interest, biomarkers of effect may need special attention given their utility for the purposes of developing DRIs, particularly when chronic disease considerations are important. Further, biomarkers of effect have been highlighted[118] as useful, appropriate and of interest relative to nutrient substances because they:

- reduce research burden/costs;
- provide early warning for adverse effects;
- assist with monitoring of the population of interest; and
- offer the ability to provide risk prediction (individual/population).

While biomarkers of effect for nutrients were not a targeted focus of Workshop2007, their utility in filling data gaps makes them a critical component of enhancing the DRI development process.

Issues/Gaps 5-2:

Identifying and Validating Biomarkers of Effect for Nutrients

With few exceptions, the approach to identifying and validating biomarkers of effect is generally not as well developed in the nutrient area as it has been in other fields, such as pharmaceuticals. The particular concerns are at least threefold: (a) appropriate and agreed-upon terminology, (b) methods for identifying and validating biomarkers and (c) considerations about their appropriate application to nutrients. The issues as well as the principles for specifying biomarkers of effect associated with nutrients need to be more clearly identified and agreed upon so that work in this area can progress.

As generally described, a biomarker of effect is any measurable biochemical or physiological change that is predictive of health impairment or disease. While there are many biochemical and physiological measures that are known to fluctuate in response to changes in nutrient intake, many of them are not predictive of health impairment (including deficiency or toxicity) or disease. Thus, they do not reflect what can be considered a valid biomarker of effect. Some may refer to this as validation of "biomarker usefulness" to distinguish it from an assay validation associated with reproducibility across laboratories.

There is a need to more specifically determine those changes in response to nutrient intake that are predictive of health impairment or disease. Levels of nutrient intake must be linked to a health impairment or disease condition (not just to perturbation in the system) in order to provide the appropriate basis for carrying out a range of public health-related activities, including establishing recommended levels of intake to ensure adequate intake and avoid excessive intake. This need is particularly relevant to the validation of the biomarkers for chronic diseases. Chronic disease risk reduction is an emerging area associated with nutrient reference values, yet the understanding of indicators useful to chronic disease prediction faces complicated challenges. Further, biomarkers of effect for all clinical outcomes can be extremely helpful in the critical step of elucidating the full dose–response curve for the relationship between the intake of the nutrient and the occurrence of the adverse health effects associated with inadequate intake and excessive intake.

[118] IOM/FNB Planning Meeting, Evidentiary Framework for Identifying and Validating Biomarkers of Effect, February 2008 (unpublished).

What is lacking currently is an agreed-upon approach for identifying and validating such biomarkers within the nutrition and food context. Principles and data requirements developed for other substances can form the basis for initiating efforts to specify a process, but considerable care must be taken to first adapt these so that they are relevant to nutritional considerations. Such efforts when coupled with the exploration of animal models and the development of newer methodologies may help to link such data and to assist in generalizing data to humans as appropriate. As appropriate, other measures such as biomarkers of exposure and mechanistic biomarkers can also be taken into account.

While the general nature of indicators has been described in Section 4.2, the actual selection of the final indicator from the array of possible indicators is an issue for which questions have been raised.

Issues/Gaps 5-3:

Selection of Indicator

General criteria for the selection of indicators are considered to be a notable gap in the DRI development process. While study committees must often make decisions about selecting the DRI indicator on a case-by-case basis, the apparent lack of clearly articulated guiding principles can suggest to stakeholders that decisions about relevant indicators may be too arbitrary, inconsistent or obtuse.

General criteria for the selection of indicators were noted as lacking by Workshop2007 participants.[119] The absence of specific criteria is likely due to the fact that limited data have caused difficulties in prioritizing, comparing and considering indicators. Further, as one Workshop2007 presenter[120] pointed out, the differences in the biology and functions of nutrients make a uniform approach very challenging.

The indicators selected as the basis for EARs (or AIs) and ULs cover a wide range of possibilities (as shown in Appendix 1) and at times may appear to present a confusing array to DRI users. Some[121] have questioned whether the basis for selecting an indicator is simply the availability of data rather than "public health significance." Others[122] have indicated that from a pragmatic point of view, data availability often drives DRI decisions. One participant[123] stated that there is some opportunity for parallelism across indicators and that the notion of consistency in this area is important, but pointed out that parallelism and consistency should not always be expected. Key considerations may vary by nutrient and need to be addressed in different ways. Another[124] added that DRI developers should not be hobbled by consistency and that consistency should not preempt scientific rigor.

Perhaps central to the issue of the selection of indicators are (a) whether their selection can be governed by general rules, and to what extent, and (b) whether the documentation of their selection process can be enhanced so that their derivation is clearly explained. Enhanced documentation and description, particularly along with the identification of the key components of a "good" indicator, would be helpful in assuring DRI users that basing a requirement on, for example, urinary excretion for one nutrient and on teratogenicity for another nutrient is compatible with appropriate public health

[119] Participants, Session 1, Panel Discussion.
[120] Rosenberg, Session 2.
[121] Participants, Session 1, Panel Discussion.
[122] Russell, Session 1.
[123] Participant, Session 1, Panel Discussion.
[124] Participant, Session 1, Panel Discussion.

decision making. As the reference values must serve those in government agencies who develop nutrition policy, clarity and transparency in this area are important.

In contrast, expectations that all DRIs will be based on the same type of measure—with the same level of severity or public health impact—and that they will adhere to a set of specific checklist considerations may be at best premature or at worst not realistic. However, in the absence of being able to specify and in turn apply prescribed criteria for indicator selection, clarity about the overall goals and general nature of appropriate indicators along with efforts to enhance transparency in decision making could alleviate concerns.

5.2.4.2 Development of Dose–Response Relationships

The group of identified indicators for the effects of a nutrient is narrowed to the one most appropriate for use as the basis for a reference value. Obviously, different indicators are used for EARs and ULs. Different indicators may also be selected for different life stage and gender groups as appropriate, given the nutrient's effect. Next, risk "curves" or dose–response relationships can be assessed. As shown in Figure 5-3 above, there can be curves for responses both for nutrient intake related to reducing the state of inadequacy and for intake related to increasing the number of toxicities.

In the case of considerations focused on adequacy levels, the dose–response curve—that is, the distribution curve for the desired effect of the nutrient substance—is used to identify an EAR. If data are sufficient to estimate a dose–response curve for excessive intake—that is, a distribution curve for adverse health effects—the curve can be used to identify a "benchmark dose." However, DRI study committees have lacked sufficient dose–response data for a number of nutrients. In the case of the adequacy determinations, if the study committees lacked dose–response data, they derived an AI. In the case of the UL, if they lacked dose–response data, committees used available data, such as the NOAEL or LOAEL as the basis for deriving the UL. The NOAEL is the highest intake of a nutrient at which the adverse health effect of interest has not been observed. The LOAEL is the lowest intake at which the adverse health effect has been observed.

One Workshop2007 participant[125] opined that it will be expensive to explore the nature of the distributions of interest in detail, but there is a need for at least general information, such as breadth and skew. Given the limited data in the nutrition field, it is recognized that the ability to develop a dose–response relationship for the indicator of interest is one of the most common challenges in DRI development. So, methods for approximating or simulating dose–response relationships in the face of limited data are of interest.

Issues/Gaps 5-4:

Approximating Dose–Response Relationships

New methodologies—many from other fields of study—are emerging and can be useful for examining and approximating dose–response relationships when available data

[125] Participant, Session 1, Panel Discussion.

are limited.[126] These should be more closely examined and incorporated into the DRI process as appropriate.

Solutions to the problem of limited dose–response data can be grouped into two general approaches. The first is the statistical or modeling approach which refers to various models for characterizing dose–response relationships. The second is the biological approach.

According to a Workshop2007 presenter,[127] the advantage of the statistical approach is that it can take into account both observational studies and clinical trials. However, one disadvantage is that the intake data in these large population studies are often susceptible to measurement error. Statistical approaches may be especially useful, according to the presenter, in considering dose–response for chronic disease indicators. The traditional single-study approach involves examining nutrient intake or status in relation to the indicator. The typical approach is to quantile the intake or status data, then examine the relationships across these quantiles and test for linear trends using statistical testing. Nutrient intake or status can also be examined as a continuous variable. The relationship between intake or status of nutrient X and disease Y can be modeled using regression. However, both of these approaches typically assume a linear relationship. Because dose–response associations involving nutrients and disease, especially chronic disease, may be nonlinear, modified approaches are needed. One alternative to linear models is *restricted cubic spline models*, also known as *piecemeal polynomial curves*. Combining data from multiple studies and using the data to estimate dose–response relationships is also possible. However, observational studies in this case present problems.

The Workshop2007 presenter also commented on the biological approach, which uses a mode of action framework. The idea is that in order to approximate a dose–response, we need to understand the mode of action of nutrients. This has straightforward application to ULs, but it can apply equally to nutrient deficiency. Key molecular and biological systems and pathways that are modulated by nutrients need to be identified. A background paper[128] for Workshop2007 on the biological approach describes the tools and technologies in use in other fields that may be helpful in establishing dose–response in the nutrition literature. Relevant discussions underscore the utility of exploring animal models.

In brief, more formal study and incorporation of the dose–response approximation, estimation and simulation techniques available through both statistical and biological means would be a helpful addition to DRI development. While such activities do not replace the desire for more data, they can offer some alternatives for the current challenges faced.

Typically, dose–response relationships are associated with "threshold responses" or "threshold models," meaning that the substance is assumed to be ineffective (in the case of adequacy measures) or nonproblematic (in the case of excessive intakes) until a certain intake level, at which point the response is triggered. However, the experience of years of DRI development is that not all nutrient substances of interest may be characterized as having threshold responses. This issue was introduced in Section 4.1.4 concerning AMDRs.

[126] Mayne, Session 2.
[127] Ibid.
[128] http://www.iom.edu/driworkshop2007 (Workshop2007 background materials).

Issues/Gaps 5-5:

Development of Methodologies for Nonthreshold Substances

The long experience of nutrient reference value development has focused on the familiar and classic threshold effect—that is, the substance fails to provide the effect until a certain threshold of intake is passed and the response is triggered. While this is true for many nutrients, typically vitamins and minerals, it is not true for all nutrient substances of current public health interest. More attention to approaches for developing DRIs for nonthreshold substances is warranted.

Nonthreshold responses are exemplified by *trans* fatty acids and saturated fat, for which no level of intake can be considered benign; hence, no threshold of response can be identified and thereby incorporated into a threshold model for estimating dose-response relationships. Also, these interrelated energy-yielding substances often do not fit the classical threshold response typical of a vitamin or mineral and hence also require a different approach.

Failure to address such substances can lead to the conclusion that the DRI framework does not work for certain classes of substances when, perhaps, the issue may be a need for expanded or additional methodologies to effectively deal with them. Nutrients for which a threshold model or other aspects of DRI development do not suit could be identified and alternative strategies explored for deriving reference values. Without such efforts, study committees may find themselves addressing the classical problem of fitting a square peg into a round hole. Just as importantly, government nutrition policy makers may be hampered by the lack of needed and relevant information about these substances from the perspective of impact on public health.

5.2.4.3 Consideration of Uncertainty

Uncertainties surrounding the available data are to be considered as part of hazard characterization. Activities to consider uncertainty must be carried out, and the nature and seriousness of those uncertainties described in the text accompanying the quantitative values issued. An uncertainty "correction factor" can be applied (assuming its derivation is carefully documented) to adjust the values that would form the basis for a reference value. This in effect could serve to quantify uncertainty.

For the most part, the use of uncertainty factors has centered on estimates for deriving ULs, most probably because their development process has been closely based on the risk assessment model which includes steps for addressing uncertainty. The use of uncertainty factors has been relatively rare in deriving values for specifying levels of adequacy. However, it is possible, as illustrated by the derivation of one of the reference values for vitamin D. The study committee multiplied the observed intake of the vitamin by two to raise the AI above the observed dose–response relationship to account for uncertainties in background exposure to sunlight and study design inadequacies.

Whether dealing with risk associated with inadequate intakes or excessive intakes, uncertainties should be documented and then addressed in a manner that errs on the side of public health protection. A risk assessment framework identifies the need to deal with uncertainties in the available evidence, but does not specify a methodology to deal with the identified uncertainties. This allows maximum flexibility in applying this organizing

framework to different situations, but requires that each field develop its own methodologies for data uncertainty.

Issues/Gaps 5-6:

Addressing Data Uncertainty

Carrying out activities to correct or adjust for uncertainty or shortcomings in the available data is a hallmark of the risk assessment approach, and such activities are relevant to DRI development. However, their inclusion in the DRI process is in need of a systematic approach. Moreover, while they are well recognized in the case of derivation of ULs, they appear to have been less systematically considered for EARs. Strategies and methodologies to quantify uncertainty for DRIs would be useful.

Adjusting for data uncertainty must be handled carefully and in a transparent manner. It is not uncommon to hear the suggestion that uncertainty corrections are merely "fudge" factors used so that scientists "can get the nutrient reference value they want."

In rare circumstances—at least for DRI development—it may be possible that the data allow the magnitude of uncertainty to be defined. This, in turn, provides for so-called quantitative adjustments, which are data-derived factors that provide a basis for adjusting the reference values either upward or downward. These adjustments are objective and based on specific data.[129] While quantitative adjustments are theoretically possible for all uncertainties, in practice available data for nutrients usually allow relatively few quantitative adjustments to be made.

Uncertainty factors have come into play because quantitative adjustments as described above are not possible. Such uncertainty factors are commonly used to address interspecies differences, interindividual variability in humans, inadequacy of the overall database or of certain pivotal studies and the nature of the adverse health effects.

Uncertainty factors for *non*nutrient substances have relied on relatively "conservative" default factors, such as 10-fold corrections for species differences and 10-fold corrections for human variability. However, the general use of these large precautionary factors poses a potential problem for nutrient substances in that the resulting UL could be a value that is below the intake required to ensure nutritional adequacy, or vice versa. However, it is recognized that the use of such large factors, which have the advantage of providing considerable assurances about the safety associated with an estimate, are not usually applicable to nutrient risk assessment. The nutritionist must address the adjustment process keeping in mind that the adjustments cannot overcorrect. That is, the dual risk curves for nutrients described previously and the resulting need for determinations on a case-by-case basis must be taken into account.

Regarding the development of an overall set of criteria for the derivation and use of uncertainty adjustments, a Workshop2007 presenter[130] suggested that uncertainty should be characterized with respect to its nature and magnitude, and different types of uncertainty should be ranked according to their impact on the results of the procedure. She cautioned that we should try to obtain these data, but should also recognize that we will likely have to do so for each nutrient individually due to the different and multiple physiological functions of different nutrients in the human body.

[129] IPCS (1994).
[130] Przyrembel, Session 2.

5.2 4.4 Extrapolation/Scaling

Establishing reference values for both inadequate and excessive intakes often involves extrapolating—some prefer the term "scaling"[131]—the data available for a group that has been studied (e.g., adults) to a group for which there are no data (e.g., children). In addition to many other possible confounding factors, there is also the perhaps erroneous assumption that the indicator appropriate for the group with data is appropriate for the group that lacks data.

It would seem that the approaches for carrying out this important procedure need focused attention.

Issues/Gaps 5-7:

Procedures for Extrapolation or Scaling

Further exploration of and the development of guidance for extrapolation or scaling of data for DRI purposes are needed. As these efforts are carried out, extrapolation or scaling as it occurs should provide an explanation based on scientific evidence regarding the choice of the scaling method for a particular nutrient substance.

Lack of data for certain subpopulations resulted in extensive use of extrapolation models during the DRI development process. About 60 percent of the DRIs for 1- to 18-year-olds were derived by extrapolation.[132] Careful consideration of extrapolation methods is needed to ensure that extrapolation is carried out in the best manner, until that point when data are available and DRI reference values can be set without the need for extrapolation. Various strategies for extrapolation have been used, which in turn has led to apparent inconsistencies in reference values among age groups.[133]

Focused work related to methodologies for extrapolation and scaling is worth pursuing. As a starting point, the FAO/WHO Report suggested three possibilities for adjusting or scaling adult reference values to estimate values for children: adjustment based on (a) the quantified reference body weight established for the age group; (b) body surface area, which is calculated using the reference body weight taken to the power of 0.66 (i.e., $BW^{0.66}$); or (c) energy requirement, which is sometimes referred to as metabolic body weight and is calculated using the reference body weight taken to the power of 0.75 (i.e., $BW^{0.75}$).

Although an approach based more directly on knowledge of differences in the metabolism, homeostatic mechanisms and toxicokinetics between children and adults would be preferable, in the absence of such data appropriate scaling is needed, as pointed out by the FAO/WHO Report. The discussions in the report conclude that scaling according to basal metabolic rate ((c) above), which is a function of metabolically active body mass, appears to be a more logical approach than scaling according to body weight. However, such an adjustment does not take into account differences in adaptive and homeostatic mechanisms among the nutrient substances with regard to absorption

[131] Atkinson, Session 2: In North America, *extrapolation* is used in DRIs to adjust for physiological differences between groups of varying body size or age to establish a reference value for an unstudied age/gender group. In Europe, *scaling* has been used since the early 1800s with regard to expressions of body weight or compartments scaled to height (e.g., the body mass index). "Scaling" may be the more appropriate term to use for the purposes of DRI development.
[132] Atkinson, Session 2.
[133] Ibid.

and elimination, nor does it take into account differences in metabolism and in the synthesis of body tissue during growth. Additional exploration regarding of these issues would be valuable for DRI purposes.

5.2.5 Step 3: Exposure Assessment or Intake Assessment

The third step of risk assessment, *exposure assessment* (or *intake assessment*, as preferred by some in the nutrition field), uses population-based intake data to estimate the prevalence of dietary intakes above or below the derived reference values. The same exposure assessment is usually relevant to reference values for both adequacy and excessive intake. Exposure biomarkers, when available, can also be used to estimate prevalence of inadequate or excessive intakes.

Exposure assessment focuses on the usual dietary intake of the population of interest. Specification of *dietary intake* has been considered useful in the context of risk assessment, and a definition has been offered by others[134]:

> Dietary intake is the quantitative amount of the nutrient substance ingested from sources that generally include food (and beverages), fortified food, specially formulated foods (sometimes called functional foods), dietary/food supplements, water, and other non-drug products such as botanicals and plant extracts.

The process of exposure assessment uses data on the composition and amounts of the dietary items consumed to estimate the total nutrient substance intake for the population. The exposure assessor compiles the data, conducts analyses and makes the appropriate statistical adjustments. This information is then compared with the nutrient reference values. In short, by providing a quantitative estimate of the total usual intake of a nutrient substance by the population of interest, exposure assessment provides the information needed to estimate the proportion of the population that is likely to meet the required intake or to exceed the upper level of intake.

When combined with the reference values and other information gleaned from the indicator (hazard) identification and characterization steps, the dietary exposure assessment is essential to describing the risk of inadequacy or excess. This forms the basis for carrying out the next step of the process, risk characterization (step 4).

The dietary exposure assessments for DRIs have been based on 24-hour recalls for food and quantitative assessments of water as well as supplement intakes from nationally representative U.S. surveys. They have also incorporated Canadian data drawn from several provincial surveys, including 24-hour recall outcomes and assessment of supplement intake. During the DRI process, the data were used to estimate the distributions of usual intake for different age, gender and life stage populations, adjusted for day-to-day variation in individuals' intakes. To offer information on the magnitude of the risk of inadequacy or excess in the population, the DRI process compared the estimated distributions of usual intakes from food and supplements for specific age, gender and life stage groups with the derived reference values for those groups.

[134] FAO/WHO (2006), p49.

The strengths and weaknesses of dietary intake data need to be recognized during the DRI process and taken into account as appropriate.

Issues/Gaps 5-8:

Considerations for Use of Dietary Intake Data

As a risk assessment step, the uncertainties surrounding dietary intake assessments should be recognized and addressed as part of the process of DRI development. Nonsystematic biases relative to the estimation of intake distributions can be due to a variety of reasons and can introduce considerable uncertainty into the DRI process.

No matter how dietary intakes are determined, they are estimates of intake. As such, they can introduce uncertainty into the risk assessment process and, hence, into DRI development. These uncertainties may be due to the methodologies that are used to estimate intake, the quality of the food composition and consumption data, or even the methods used to combine data from different sources. Moreover, true intake (or exposure) cannot be known precisely because it is affected by the absorption, assimilation and transport of nutrients, all of which are variable and not well quantified.

Enhancing the DRI process requires specifically identifying these uncertainties and developing strategies for taking them into account in carrying out the final risk characterization step. One Workshop2007 presenter[135] offered a starting point by describing the strengths and limitations of such data for DRI use.

The use and consideration of dietary exposure assessments during DRI development may benefit from a more organized, systematic approach. The experience of DRI development suggests that dietary assessment tasks may have been addressed in different ways and to different extents. Additionally, more information and transparency would be useful. Clarification of appropriate methods for handling uncertainties in the intake estimates and the potential impact of the uncertainties on risk characterization would also be valuable. As a parallel matter, newer and better methodologies for the application of statistics and statistical adjustments for intake estimates remain a high priority for all purposes.

5.2.6 Step 4: Risk Characterization

The fourth step of risk assessment is *risk characterization*. It is an impactful activity from the perspective of all users, but particularly for federal agencies that rely on these values to develop sound and appropriate nutrition policy. That is, once the scientific risk assessment has reached its final stages, the results need to be expressed in a manner that will maximize their utility to sponsors and other users. During Workshop2007, several participants[136] pointed out that this important step may not have been developed as fully as needed in the DRI efforts, notably for EARs and AIs. Although DRI text discussions concerning ULs contained sections on risk characterization, some considered that it could have been more fully developed.[137]

[135] Subar, Session 3.
[136] Participants, Session 1, Panel Discussion / Woteki, Session 4.
[137] Participants, Session 1, Panel Discussion.

While risk characterization is a term not necessarily familiar to nutritionists, its activities, when carried out by DRI study committees, should provide a description of the nature of "risks" or public health problems associated with inadequate or excessive intake and an indication of the percentage of the population exceeding the UL or failing to meet the EAR/RDA or AI. The public health consequences of not meeting an EAR/RDA or AI and exceeding a UL should also be discussed so that risk managers are fully informed.

Consistent with the purpose of risk characterization, a DRI study committee would be expected to indicate whether or not information that, for example, 20 percent of children in a population are consuming a nutrient at a level above the UL suggests a serious public health problem. However, the solution to the problem is not the responsibility of the risk assessor or the purpose of risk assessment, and it is not a part of risk characterization. That responsibility remains with the risk manager, who will use the information from the risk characterization, combine it with other data and considerations, and ultimately devise an approach for managing the risk for the population (see related examples in Appendix 2).

The FAO/WHO Report on nutrient risk assessment—which focused on upper levels of intake, but the principles would be similar for nutrient requirements—described risk characterization as follows:

> nutrient risk characterization functions to integrate the outcomes of the earlier steps into a set of conclusions that address the nutrient risk managers' need for scientific information to make risk management decisions. The information provided to the risk manager is both quantitative and qualitative…. Like hazard identification/characterization, risk characterization often is an iterative and evolving process. Quantitative information includes upper levels of intake…. and estimates of risk at different levels of intake, while qualitative information includes specification of (sub)populations believed to be at highest risk, reasons for the risk, and descriptions of the nature and severity of the risk. Furthermore, risk characterization outlines all key assumptions and gives a clear explanation of the uncertainties involved in the assessment. For example, when the risk assessment is based on animal data, the validity of such data needs to be specified and supported. Also, uncertainties associated with the extrapolation of data from studies in animals to predict human risk should be presented. Finally, scientific information should be specified on susceptible subpopulations, including those with greater potential exposure and/or specific physiological conditions or genetic factors. To facilitate improved communication, the information for risk managers can be in the form of a comparison of the relative risks among risk management options.[138]

Given that risk characterization is the form in which the risk assessor "talks" to the risk manager, interest in clarifying the roles of the risk assessor in this communication process arose during the FAO/WHO discussions. The FAO/WHO Report notes that each of the three national studies on upper levels of intake reviewed in the report appeared to include some statements within the risk characterization step that might be considered overly prescriptive in terms of risk reduction. According to the general principles of risk assessment, the risk assessor may have been taking on the role of the risk manager. Examples given are directed advice to provide warnings that women planning to become pregnant should not consume cooked animal liver; and advice that men and postmenopausal women should avoid iron supplements and foods highly fortified with iron. Noting the impact of such behaviors and the options available would have been

[138] FAO/WHO (2006), p72.

appropriate for risk characterization, but the specification of the solution or appropriate activity to deal with the situation resides with the risk manager, who must integrate a range of information into the final decision.

Finally, it is worth noting that risk characterization can include information about the uncertainties associated with the derived reference values, as well as any other scientific information that could place the reference values in proper context for use by risk managers and stakeholders. Risk characterization is essentially a science-based discussion intended to provide valuable input and clarification for users of the reference values. In a case where there is a high prevalence of persons failing to meet the recommended intake levels, it would be relevant to note the scientific uncertainties surrounding the reference value estimation and perhaps also, for example, the absence of clinical signs of deficiencies in the population. Such discussions can serve to mitigate or underscore public health concern. Risk assessors could also use the risk characterization step to specify the public health priority of their outcomes, noting those nutrients that may need immediate attention as opposed to those that appear to be less problematic.

Issues/Gaps 5-9:

Components of Nutrient Risk Characterization

Consistent inclusion of risk characterization discussions as part of the DRI development process enhances the transparency of the process and is essential to ensuring the utility of the DRIs to stakeholders, especially government nutrition policy makers. However, the actual operationalization of nutrient risk characterization for DRIs remains unspecified and would benefit from an organized effort to create guidance for its development and to articulate its key components.

Risk characterization is regarded as sufficiently important for the assessment of nonnutrients that special reports have been devoted to outlining risk characterization as an activity.[139] During Workshop2007, the importance of ensuring an appropriately targeted, clear, documented nutrient risk characterization component as part of DRI development was highlighted,[140] and its ability to enhance transparency and make the reference values more useful to stakeholders was stressed. Some noted that it can serve as a way to communicate the level of uncertainty surrounding the values, which would be very helpful to users.

The FAO/WHO Report underscored this interest and suggested that there is value in developing a standard approach, or at least a specified process, for nutrient risk characterization to ensure that the information important to the risk manager are included. Such guidelines would allow the basic scientific components of nutrient risk characterization to be addressed consistently and, in turn, provide the risk assessors yet another opportunity to "reality check" their outcomes. It also has the advantage of assisting with the differentiation between risk assessment and risk management.

[139] NRC (1994, 1996).
[140] Participants, Session 1, Panel Discussion / Woteki, Session 4.

6. GUIDANCE FOR USERS OF DIETARY REFERENCE INTAKES

6.1 Context for General Guidance
6.2 Challenges
Issues/Gaps 6-1: Improving Guidance for All Users—Knowledge Base and Methodologies
Issues/Gaps 6-2: Enhancing Guidance for Practitioners

► 6.1 Context for General Guidance

As discussed in the 1994 DRI Plan, the FNB anticipated that considerable guidance would be needed to generally assist DRI users—ranging from federal agency officials to individual dietetic practitioners—in the transition from using the former RDAs and RNIs to using the new DRIs. The Subcommittee on Interpretation and Uses of Dietary Reference Intakes (see Figure 1-1 in Section 1 above) was convened and charged with developing guidance on the general applications of the various DRI component values. The Subcommittee reports[141] included discussions on appropriate use of each of the available DRI values in assessing nutrient intakes of groups and of individuals, as well as uses related to the planning of diets for groups and for individuals. A summary of the key components of their work can be found in Part I of *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*.[142] There are also discussions on application in each individual DRI report.

The starting point for guidance for users has been the commonly recognized general tasks of assessing and planning dietary intakes for groups and individuals. These four activities have been illustrated using a two-by-two table, as shown in Figure 6-1.

Assessing Groups	Planning for Groups
Assessing Individuals	Planning for Individuals

Figure 6-1: "Two-by-Two Table" for General Applications of Dietary Reference Intakes

[141] IOM (2000, 2003).
[142] IOM (2006).

The existing guidance derives from a statistical foundation and is based on understandings of distributions, as well as the concepts of normality and probability. As outlined within the two Subcommittee reports, the DRI value to be used will differ depending on which of the four activities in the two-by-two table is to be carried out. Briefly, in the case of guidance for assessing groups, the focus is on using the EAR (not the RDA) with a probability approach and in some cases the proxy cutpoint method developed by the Subcommittee. For guidance related to planning for groups, the goal is identified as a low prevalence of inadequate and excessive intakes. Consideration is also given to definitions of acceptable prevalence of inadequate intakes. For assessing individuals, the guidance contains both qualitative and quantitative discussions. Guidance for planning for individuals suggests that, from a practical standpoint, the use of the RDA may be preferable to the use of the EAR because of uncertainties and difficulties in calculating a confidence of adequacy. When AIs must be used because an EAR/RDA is lacking, there is a greater level of uncertainty.

► 6.2 Challenges

Workshop2007 discussions acknowledged that the guidance for the general application of the DRIs has made important contributions in assisting users, especially for assessment of groups. However, it was suggested that the existing guidance contains gaps, and at times the guidance may be inconsistent with the reality of the applications or even confusing for users.

Issues/Gaps 6-1:

Improving Guidance for All Users—Knowledge Base and Methodologies

Guidance for users warrants further attention. A number of issues were raised during Workshop2007, most focused on the need for more knowledge and enhanced methods to better inform the development of guidance. These interests include the conceptual underpinnings specified by the two-by-two table, approaches for planning diets for groups and assessing diets of individuals, and addressing applications when the statistical foundation is not applicable.

Some Workshop2007 discussions queried whether the concepts reflected in the two-by-two table framework readily match the real-world situations faced by users. One participant[143] noted that the two-by-two table was useful conceptually, but that it is too simplistic. Further, its inflexibility can preclude rational solutions to the problems faced. She pointed out that tasks for which DRIs are needed may fall into more than one category simultaneously, especially in the case of government policy activities. She suggested that a more productive approach might be to more specifically marry the public health ramifications with the available science and then overlay statistical considerations.

Experience with the two-by-two table, according to a Workshop2007 participant,[144] pointed to the need to more closely examine the interface between individuals and groups. This would include exploring more specifically the risk for an

[143] Participant, Session 3, Special Challenges, Issues Related to Framework, General Discussion.
[144] Participant, Session 3, Special Challenges, Planning and Assessing Diets, General Discussion.

individual in a population that is at low risk. As noted by a presenter,[145] the two-by-two framework draws firm lines between individuals and populations; however, she suggested that this is likely an oversimplification given experiences during its application, particularly for regulatory and public policy. She expressed concern that using the RDA as the goal in planning for an individual assumes that one will achieve a usual intake approximately equal to the RDA, but that this is not realistic for population-level applications. She further stressed that the core concepts that underpin the guidance for users are sound, but information about the nature of the interfaces between applications for individuals and those for groups now needs to be explored. From her perspective, all applications of the DRIs have the individual as their end user, and so parsing issues on the basis of applications to individuals or to groups is not helpful. She called for future consideration of the concepts rather than the numbers involved.

Users have faced many challenges in adopting the paradigm for total diet planning, according to a Workshop2007presenter[146]; to date, there are few examples of its successful implementation. It could be that a better knowledge base is needed to examine the question of whether the approach based on "shifting distributions" is appropriate for planning. A discussant[147] acknowledged that the guidance for use of the RDAs, ULs and AMDRs in planning diets of individuals has been helpful, as has guidance on use of EARs to assess the diets of populations. However, she agreed that there are challenges in carrying out the applications related to planning diets for groups and assessing diets of individuals. It was suggested that this was due to a lack of fully developed statistical methods within the guidance reports. The discussant also suggested that the confidence of adequacy approach for assessing individual diets seemed impractical, whereas the probability of adequacy approach would require knowledge of an individual's long-term nutrient intake, which is impossible to measure accurately. Additionally, a presenter[148] pointed out that the strength of the guidance relates to applications with groups, not individuals, and thereby misses the mark for many practitioners. She added that a related challenge is the questionable applicability of the guidance to small groups (as opposed to large groups).

While it is acknowledged that the statistical foundation has greatly advanced the efforts to provide relevant guidance to users, a Workshop2007 presenter[149] underscored that a number of DRI reference values—notably the AI, AMDR and UL—cannot be applied using the DRI probability theory because these values are not based on consideration of distributions. This can undermine users' applications, particularly when planning and assessing total diets. A discussant[150] agreed and suggested that the existence of AIs is problematic for the current approach to guidance. Another participant[151] commented on the problems associated with implementing an intervention that must adhere to the assumption that there will be a shift and no skew when the intent of the intervention is to skew the distribution. One presenter[152] cautioned that the enthusiasm for offering solutions for the needs of users should avoid efforts that go beyond the data.

Further, Workshop2007 identified interest on the part of practicing dietitians and others in related health professions in receiving assistance and support in understanding and applying the DRIs in their work settings.

[145] Tarasuk, Session 3.
[146] Barr, Session 3.
[147] Guenther, Session 3.
[148] Tarasuk, Session 3.
[149] Ibid.
[150] Guenther, Session 3.
[151] Participant, Session 3, Special Challenges, Planning and Assessing Diets, General Discussion.
[152] Beaton, Session 1.

Issues/Gaps 6-2:

Enhancing Guidance for Practitioners

Practitioners such as dietitians and local health professionals have needs for guidance that in some cases differ from those relevant to policy makers in government agencies. There are challenges in meeting these needs; notably, the efforts must balance the interest in simplified guidance against the interest in ensuring appropriate application of DRIs in these health care settings. Development of a practitioners' manual may be warranted.

As a starting point for the purposes of providing guidance for dietetic professionals and others who engage in nutrition counseling, a Workshop2007 presenter[153] suggested that a separation be made between such users and those who make applications for public policy purposes. Despite some commonalities, there are considerable differences relevant to the needs of these types of users, and, in turn, future guidance development must take this into account.

Overall, Workshop2007 discussions suggested that practitioners such as dietitians and local/state public health nutritionists believe they need more guidance, but of the type that is clear, succinct and easy to apply. This prompted some[154] to caution that the issues are complex and that "simple" guidance may therefore be unrealistic. The concern is that it is more important to ensure appropriate use of the DRIs than it is to provide simple solutions for ready application.

Although resources have been developed to help practitioners such as dietitians, one Workshop2007 presenter[155] pointed out that the materials are not easy to understand and require a considerable investment of time, energy and, sometimes, money. She suggested that another challenge relates to data and software. For example, before using this approach, a dietitian working in an assisted living facility would need to obtain 24-hour recalls from the residents, obtain repeat recalls on a subsample, analyze the food records to derive nutrient intakes and then use sophisticated software to obtain the usual nutrient intake distributions. This would require access to software and the time and ability to use it.

A Workshop2007 discussant[156] suggested that practitioners need training and education in the meaning and uses of DRIs beyond providing the numbers and an easy-to-use guide. Another presenter[157] suggested that important challenges exist in terms of providing better communication about the concepts associated with the uses of the DRIs to groups such as dietitians and related practitioners.

[153] Tarasuk, Session 3.
[154] Participant, Session 3, Overview, General Discussion.
[155] Barr, Session 3.
[156] Dwyer, Session 3.
[157] Murphy, Session 3.

7. SUMMARY

The DRI framework outlined in this paper is briefly summarized below (Figure 7-1) using a schematic to illustrate its foundation and key components. This structure would be similar for all nutrients and for the derivation of both the EAR and UL. Different nutrients, undoubtedly, will present different challenges and some study committee tasks will vary from that of others on a case-by-case. Emerging approaches for nutrients such as those with nonthreshold effects or that manifest other challenges compared to classic nutrient substances can readily be incorporated into the existing approach. There may be special circumstances for which a study committee may modify components of the approach and, in turn, provide a documented rationale for doing so.

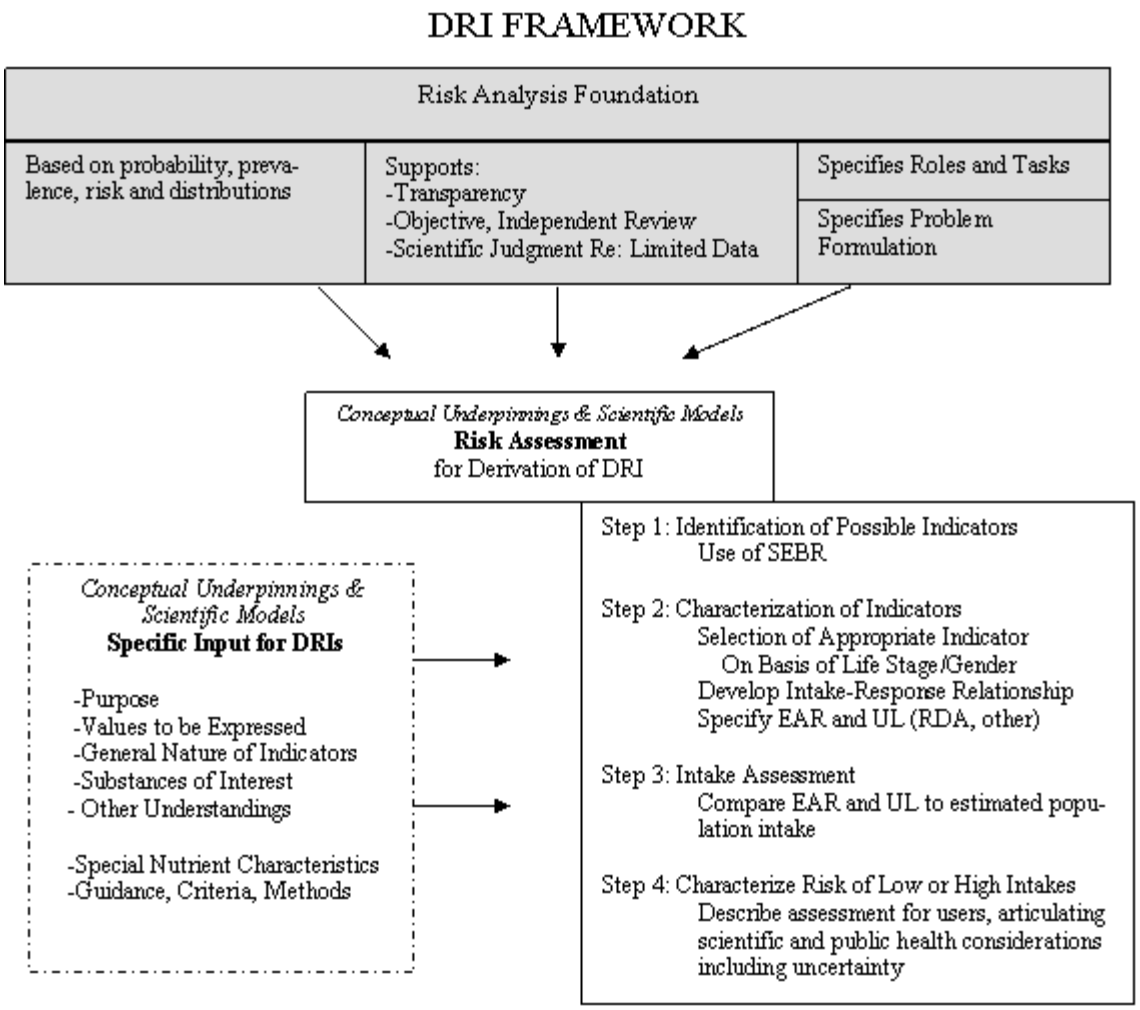


Figure 7-1: Brief Summary of DRI Framework Based on Link to Risk Analysis and Risk Assessment

This DRI framework outlined here should be considered a "living document" that can be updated when newer understandings or knowledge emerge. There are a number of activities that can be undertaken to continue to clarify the DRI development process, to enhance its activities, and to provide specific guidance or criteria for study committee decision making. Basic research is of course commonly highlighted as an important need in the DRI arena[158] and is often linked with a call for a research agenda.[159] However, relative to the DRI development process per se, there are gaps in understandings, guidance, criteria or methods that need focused attention. These are listed below. As resources become available these issues can be the subject of conferences, workshops, special studies, or new research. The outcomes of such deliberations and work can be added to the DRI framework.

Criteria for Revisiting Existing DRI Values (2-1)

Given the prospect that DRI development in the future will not include periodic, across-the-board updates for nutrients, as were carried out in the past, relevant criteria and processes should be identified to facilitate specific nutrient updating and allow these updates to take place in a timely, transparent, appropriate and accountable fashion.

Interface between Sponsors and Study Committees during Initiation of DRI Activities (2-2)

Communication between sponsors and study committees deserve attention because appropriate dialogue among these parties is essential to ensuring a useful and relevant outcome. The interactions also need to take place in a manner that maintains the independence and scientific integrity of study committee outcomes. A better understanding of the problem formulation step as part of the initiating activities for a DRI study would be valuable.

Nutrient Reference Values for What? (3-1)

Discussions about the purpose of DRIs frequently elicit the question: "Nutrient reference values for what?" In other words, what are the desirable indicators or the most appropriate biological/physiological/clinical measures upon which the reference values are to be based given current public health concerns? The topic has become more complicated as scientific advances offer newer information about the functions and effects of nutrients. Moreover, the ability to address such questions is undoubtedly part of a larger evolving process.

Definition of "Apparently Healthy" (3-2)

The question of what constitutes a healthy population has become more complicated during the past 50 years as a result of better understandings of health and chronic disease. Just as importantly, the lifestyles of the population in the United States and Canada have changed to the point where chronic diseases as well as obesity are increasingly prevalent in the population. Workshop2007 discussions highlighted an interest in more clearly defining an apparently healthy population.

[158] IOM (2007).
[159] Woteki , Session 4.

Changing Perspectives on RDA (4-1)

Given its long history, the RDA, along with the Canadian RNI, is the familiar face of nutrient reference values and is well recognized by practitioners. However, the growing recognition of the underpinnings based on distributions, risk and probability has resulted in interest in further examining the nature and role of the RDA**.**

The Future of the AI (4-2)

There is broad interest in addressing the AIs as a component of the DRI values, but no clear path has emerged in terms of clarifying, adapting or eliminating AIs. Nor is there agreement about directions to be taken in the future for AI development.

Further Development of the AMDR (4-3)

Specific attention to AMDRs is needed. These values raise several issues. Questions range from the need to expand the developmental models for DRIs to the appropriate application of reference values expressed as ranges rather than point estimates.

Addressing Chronic Disease Indicators (4-4)

There is considerable interest—as well as more than 10 years of experience—surrounding the inclusion of chronic disease indicators within DRI development. A variety of perspectives were put forward. There is a need for focused discussions about how to include chronic disease indicators in the DRI process, including specific approaches for addressing their confounders, identification of appropriate biomarkers, and quantifying their effects.

Tailoring SEBR to Support the Development of Nutrient Reference Values (5-1)

Recognition of the potential of SEBR for the development of nutrient reference values—coupled with the realization that the approach should be adapted as appropriate for DRI considerations—points to the need to further explore and refine SEBR as it relates to DRI development. Moreover, working to reach a common understanding about its value and limitations relative to DRI development is important.

Identifying and Validating Biomarkers of Effect for Nutrient (5-2)

With few exceptions, the approach to identifying and validating biomarkers of effect is generally not as well developed in the nutrient area as it has been in other fields, such as pharmaceuticals. The particular concerns are at least threefold: (a) appropriate and agreed-upon terminology, (b) methods for identifying and validating biomarkers and (c) considerations about their appropriate application to nutrients. The issues as well as the principles for specifying biomarkers of effect associated with nutrients need to be more clearly identified and agreed upon so that work in this area can progress.

Selection of Indicator (5-3)

General criteria for the selection of indicators are considered to be a notable gap in the DRI development process. While study committees must often make decisions about selecting the DRI indicator on a case-by-case basis, the apparent lack of clearly

articulated guiding principles can suggest to stakeholders that decisions about relevant indicators may be too arbitrary, inconsistent or obtuse.

Approximating Dose–Response Relationships (5-4)

New methodologies—many from other fields of study—are emerging and can be useful for examining and approximating dose–response relationships when available data are limited. These should be more closely examined and incorporated into the DRI process as appropriate.

Development of Methodologies for Nonthreshold Substances (5-5)

The long experience of nutrient reference value development has focused on the familiar and classic threshold effect—that is, the substance fails to provide the effect until a certain threshold of intake is passed and the response is triggered. While this is true for many nutrients, typically vitamins and minerals, it is not true for all nutrient substances of current public interest. More attention to approaches for developing DRIs for nonthreshold substances is warranted.

Addressing Data Uncertainty (5-6)

Carrying out activities to correct or adjust for uncertainty or shortcomings in the available data is a hallmark of the risk assessment approach, and such activities are relevant to DRI development. However, their inclusion in the DRI process is in need of a systematic approach. Moreover, while they are well recognized in the case of derivation of ULs, they appear to have been less systematically considered for EARs. Strategies and methodologies to quantify uncertainty for DRIs would be useful.

Procedures for Extrapolation or Scaling (5-7)

Further exploration of and the development of guidance for extrapolation or scaling of data for DRI purposes are needed. As these efforts are carried out, extrapolation or scaling as it occurs should provide an explanation based on scientific evidence regarding the choice of the scaling method for a particular nutrient substance.

Considerations for Use of Dietary Intake Data (5-8)

As a risk assessment step, the uncertainties surrounding dietary intake assessments should be recognized and addressed as part of the process of DRI development. Nonsystematic biases relative to the estimation of intake distributions can be due to a variety of reasons and can introduce considerable uncertainty into the DRI process.

Components of Nutrient Risk Characterization (5-9)

Consistent inclusion of risk characterization discussions as part of the DRI development process enhances the transparency of the process and is essential to ensuring the utility of the DRIs to stakeholders, especially government nutrition policy makers. However, the actual operationalization of nutrient risk characterization for DRIs remains unspecified and would benefit from an organized effort to create guidance for its development and to articulate its key components.

Improving Guidance for All Users—Knowledge Base and Methodologies (6-1)

Guidance for users warrants further attention. A number of issues were raised during Workshop2007, most focused on the need for more knowledge and enhanced methods to better inform the development of guidance. These interests include the conceptual underpinnings specified by the two-by-two table, approaches for planning diets for groups and assessing diets of individuals, and addressing applications when the statistical foundation is not applicable.

Enhancing Guidance for Practitioners (6-2)

Practitioners such as dietitians and local health professionals have needs for guidance that in some cases differ from those relevant to policy makers in government agencies. There are challenges in meeting these needs; notably, the efforts must balance the interest in simplified guidance against the interest in ensuring appropriate application of DRIs in these health care settings. Development of a practitioners' manual may be warranted.

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APPENDIX 1: INDICATORS FOR DIETARY REFERENCE INTAKES, 1994–2004[160]

(GROUPED CHRONOLOGICALLY BY STUDY COMMITTEE PUBLICATION DATE)

Nutrient	Reference value	Indicator used in setting reference value	Other indicators considered but not selected
		1997	
Calcium	*Adequacy* AI	• Calcium retention—desirable rates as determined by calcium balance studies, factorial estimates of requirements, bone mineral density (BMD) and bone mineral content (BMC)	• Calcium intake and fracture risk • Bone mass measurements (BMC and BMD) • Calcium intake and bone mass • Calcium intake and risk of chronic diseases other than osteoporosis (hypertension, colon cancer)
	Excess UL	• Nephrolithiasis • Calcium/mineral interaction (iron, zinc, magnesium, phosphorus)	
Phosphorus	*Adequacy* EAR	• Phosphorus balance (children and adolescents) • Serum inorganic phosphate (adults)	
	Excess UL	• Hyperphosphatemia leading to risk of - adjustments in calcium-regulating hormones (parathyroid hormone) - metastatic calcification of soft tissues - skeletal porosity - interference with calcium absorption	

[160] Modified from Workshop2007 background materials http://www.iom.edu/driworkshop2007

Magnesium	*Adequacy* EAR	• Magnesium balance studies	• Serum magnesium • Plasma ionized magnesium • Intracellular magnesium • Estimates of tissue accretion during growth • Magnesium tolerance test • Epidemiological studies and meta-analyses (cardiovascular disease and osteoporosis)
	Excess UL	• Hypermagnesemia - Diarrhea (applies to nonfood sources of magnesium only)	
Vitamin D	*Adequacy* AI	• Serum 25-hydroxyvitamin D (older infants, children, adolescents, adults) • Evaluation of skeletal health (infants <6 months: linear growth and bone mass; adults >50–70 years: bone loss; adults >70 years: bone loss, fractures, parathyroid hormone)	• Serum vitamin D • Serum 1,25-dihydroxyvitamin D
	Excess UL	• Hypercalcemia of hypervitaminosis D	• Renal disease (calcification of renal tissue not associated with hypercalcemia) • Cardiovascular effects (arteriosclerosis with calcium deposition)
Fluoride	*Adequacy* AI	• Prevention of dental caries	• Bone mineral content • Fluoride balance
	Excess UL	• Adverse cosmetic effect: enamel fluorosis (infants and children 0–8 years) • Adverse functional effect: skeletal fluorosis (all age groups >8 years)	

		1998	
Thiamin	*Adequacy* EAR (*UL was not set*)	• Urinary thiamin excretion (values for all age groups except infants; values for children extrapolated from adults)	• Erythrocyte transketolase activity • Erythrocyte thiamin
Riboflavin	*Adequacy* EAR (*UL was not set*)	• Concurrent analyses (erythrocyte glutathione reductase [EGR] activity coefficient, urinary excretion, erythrocyte flavin, clinical signs of deficiency) (values for all age groups except infants; values for children extrapolated from adults)	• EGR • Erythrocyte flavin • Urinary flavin • Clinical signs of deficiency • Indicators of carbohydrate metabolism (lactic and pyruvic acid concentrations) • Possible reduction of chronic disease risk (site-specific cancers [e.g., esophageal], lens opacities—risk of cataracts)
Niacin	*Adequacy* EAR	• Urinary excretion of N^1-methylnicotinamide and its 2-pyridone derivative N^1-methyl-2-pyridone-5-carboxamide (values for all age groups except infants; values for children extrapolated from adults)	• Plasma concentration of the 2-pyridone derivative • Erythrocyte nicotinamide adenine dinucleotide (NAD) concentration • Transfer of adenosine diphosphate ribose (functional measure of polyadenosine diphosphate ribosylation—assays to assess status not available) • Pellagra
	Excess UL	• Vasodilatory effects (flushing), applies only to nicotinic acid and nicotinamide as supplements, food fortificants or pharmacological agents	• Gastrointestinal effects • Hepatotoxicity (jaundice, increased levels of serum transaminases, fulminant hepatitis, etc.) • Glucose intolerance • Ocular effects (blurred vision, toxic ambylopia, macular edema and cystic maculopathy)

Vitamin B_6	*Adequacy* EAR	• Concurrent analyses (plasma pyridoxal 5′-phosphate, urinary pyridoxic acid, tryptophan metabolites, erythrocyte aspartate aminotransferase [α-EAST], erythrocyte alanine aminotransferase [α-EALT]) (values for all age groups except infants; values for children extrapolated from adults)	• Plasma pyridoxal 5′-phosphate (reflects tissue stores) (adult women) • Erythrocyte and total blood pyridoxal 5′-phosphate • Blood total vitamin concentrations • Urinary pyridoxic acid and total vitamin B_6 • α-EAST and α-EALT • Tryptophan metabolites • Plasma homocysteine • Possible reduction of chronic disease risk (myocardial infarction and coronary heart disease) • Cognitive function
	Excess UL	• Sensory neuropathy	• Other adverse effects - dermatological lesions - congenital defects and vitamin B_6 dependency of the newborn (not confirmed; no evidence of teratogenicity in experimental animals)
Folate	*Adequacy* EAR	• Combination of erythrocyte folate, serum or plasma folate and plasma homocysteine (values for all age groups except infants; values for children extrapolated from adults)	• Erythrocyte folate • Plasma homocysteine • Serum folate • Urinary folate • Indicators of hematological status • Risk of neural tube defects and chronic degenerative diseases (EAR does not accommodate neural tube defect prevention as an appropriate criterion because by definition only 50 percent protection)

	Excess UL	• Neurological effects of supplemental folate in individuals with vitamin B_{12} deficiency	• Neurotoxicity and epileptogenicity in experimental animals • General toxicity (mental changes, sleep disturbances and gastrointestinal effects) • Reproductive and developmental effects • Carcinogenicity • Hypersensitivity • Intestinal zinc absorption
Vitamin B_{12}	*Adequacy* EAR (*UL was not set*)	• Indicators of hematological response (stable hemoglobin value, normal mean corpuscular volume [MCV], normal reticulocyte response) (primary criterion) (values for children and adolescents except infants; values extrapolated from adults) • Serum and plasma vitamin B_{12}	• Methylmalonic acid • Homocysteine • Formiminoglutamic acid, propionate and methylcitrate • Holotranscobalamin II
Pantothenic acid	*Adequacy* AI (*UL was not set*)	• Pantothenic acid intakes (values for children and adolescents extrapolated from adults)	• Urinary excretion • Blood levels of pantothenic acid - whole blood - serum, plasma - erythrocytes
Biotin	*Adequacy* AI (*UL was not set*)	• Biotin intake of infants fed exclusively on human milk (extrapolated to older infants, children, adolescents and adults)	• Biotin and 3-hydroxyisovalerate excretion • Plasma biotin • Odd-chain fatty acid composition of plasma lipids
Choline	*Adequacy* AI	• Markers of liver dysfunction (amounts to prevent increases in alanine aminotransferase in men extrapolated to children, adolescents and adult females)	• Plasma concentrations • Reduction in risk of chronic disease (dementia, cardiovascular disease, cancer)

	Excess UL	• Body odor, sweating and salivation (fishy body odor, vomiting, gastrointestinal effects) • Hypotension (primary indicator)	• Hepatotoxicity (attributed to salicylate in choline salt) • Nonspecific toxicity (tinnitus, pruritus attributed to salicylate in choline salt)
		2000	
Vitamin C	*Adequacy* EAR	• Antioxidant functions in leukocytes (near maximal neutrophil concentration with minimal urinary excretion of ascorbate)	• Antioxidant functions • Oxidative deoxyribonucleic acid (DNA) and chromosome damage (cellular DNA damage, urinary markers of DNA damage, ex vivo damage, cancer biomarkers) • Immune function • Collagen metabolism • Carnitine biosynthesis • Periodontal health • Relationship of vitamin C intake to chronic disease - Cardiovascular disease - Cancer (breast, cervical, colorectal, pancreatic, lung, gastric) - Cataracts - Asthma and obstructive pulmonary disease - Common cold - Cognitive function and memory

	Excess UL	• Gastrointestinal effects (nausea, abdominal cramps, diarrhea) •	• Increased oxalate excretion and kidney stone formation • Increased uric acid excretion • Excess iron absorption • Lowered vitamin B_{12} levels • Systemic conditioning to high levels • Prooxidant effects • Other adverse effects - High-altitude resistance - Delayed-type allergic response • - Erosion of dental enamel
Vitamin E	*Adequacy* EAR	• Plasma α-tocopherol concentration (extrapolated to children, adolescents from adult values) • Hydrogen peroxide-induced hemolysis (extrapolated to children, adolescents from adult values)	• Lipid peroxidation markers • Oxidation products of DNA or proteins • Vitamin E metabolite excretion • Vitamin E biokinetics • Vitamin E deficiency symptoms • Relationship of vitamin E intake to chronic disease - Cardiovascular disease - Diabetes mellitus (oxidative stress, platelet hyperactivity, diabetic neuropathy) - Cancer - Immune function - Cataracts - Central nervous system disorders (Parkinson's disease, Alzheimer's disease, Down's syndrome, tardive dyskinesia)

	Excess UL	• Hemorrhagic toxicity in experimental animals	• Hemorrhagic toxicity in humans (stroke) • Platelet effects in humans (in vitro inhibition of platelet aggregation and adhesion) • Other adverse effects in humans • (Uncontrolled studies: fatigue, emotional disturbances, thrombophlebitis, breast soreness, creatinuria, altered serum lipid and lipoprotein levels, gastrointestinal disturbances and thyroid effects) • Adverse effects in premature infants (increased incidence of necrotizing enterocolitis, intracranial hemorrhage) • Other adverse effects in animals (lung lesions)
Selenium	*Adequacy* EAR	• Glutathione peroxidases and selenoprotein P in blood (levels to achieve plateau concentrations of plasma selenoproteins)	• Keshan disease • Selenium in hair and nails • Selenium in blood • Cancer • Urine • Labeled selenium
	Excess UL	• Chronic selenosis (hair and nail brittleness and loss; other symptoms: gastrointestinal disturbance, skin rash, garlic breath odor, fatigue, irritability, nervous system abnormalities)	• Acute toxic effects—fatal or near-fatal selenium poisoning • Biochemical indicators of selenium toxicity (total tissue concentration including plasma and blood; chronic intake of protein-bound selenium as toxic as inorganic selenium)

β-Carotene and other carotenoids	Not determined	• Plasma and tissue concentrations (3–6 mg β-carotene/day from food sources "prudent" to maintain plasma β-carotene levels in the range associated with a lower risk of various chronic disease outcomes)	• Vitamin A equivalency (requirements for carotenoids based on vitamin A activity considered with the evaluation of the requirements for vitamin A) • Markers of antioxidant activity • Gap junctional communication • Immune function • Relationship of carotenoid intake to chronic disease - All-cause mortality - Cancer (all cancers combined, lung, oral cavity, pharynx, larynx, cervical) - Cardiovascular disease - Age-related macular degeneration - Cataracts
2001			
Vitamin A	*Adequacy* EAR	• Amount of dietary vitamin A required to maintain a given body pool size in well-nourished adults (extrapolated to children, adolescents from adult values): A × B × C × D × E × F A = Percentage of body vitamin A stores lost per day when ingesting a vitamin A-free diet B = Minimum acceptable liver vitamin A reserve C = Liver weight to body weight ratio D = Reference weight for a specific age group and gender E = Ratio of total body to liver vitamin A reserves F = Efficiency of storage of ingested vitamin A	• Dark adaptation • Plasma retinol concentration • Total liver reserves by isotopic dilution • Relative dose–response and modified relative dose–response • Conjunctival impression cytology • Immune function

	Excess UL	• Teratogenicity (basis for UL in women of child-bearing age) • Liver abnormalities (reversibly elevated liver enzyme activity → widespread fibrosis and cirrhosis → sometimes death) • Adverse effects in infants and children (intracranial [bulging fontanel] and skeletal abnormalities, bone tenderness and pain, increased intracranial pressure, desquamation, brittle nails, mouth fissures, alopecia, fever, headache, lethargy, irritability, weight loss, vomiting and hepatomegaly)	• Acute toxicity (nausea, vomiting, headache, increased cerebrospinal fluid pressure, vertigo, blurred vision, muscular incoordination) • BMD (evidence ranges from BMD to hip fractures and osteoporosis) • Adverse interactions (alcohol)
Vitamin K	*Adequacy* AI (*UL was not set*)	• Vitamin K intakes of apparently healthy groups (adults, children and adolescents, except infants)	• Prothrombin time • Factor VII • Plasma and serum phylloquinone • Urinary γ-carboxyl glutamyl residues • Undercarboxylated prothrombin (proteins induced by vitamin K absence [PIVKA]) • Under-γ-carboxylated osteocalcin • Relationship of vitamin K intake to chronic disease - Osteoporosis - Atherosclerosis

Chromium	*Adequacy* AI (*UL was not set*)	• Chromium content per 1000 kcal in well-balanced and well-designed adult diets multiplied by the highest energy intakes for adults and extrapolated to children and adolescents	• Balance studies • Urinary chromium excretion • Plasma chromium concentration • Blood glucose and insulin concentrations • Chronic renal failure • Genotoxicity • Carcinogenicity • Hepatic dysfunction • Reproductive effects • Other adverse effects (rhabdomyolysis)
Copper	*Adequacy* EAR	• Combination of ceruloplasmin concentration, erythrocyte superoxide dismutase activity, platelet copper concentration and cytochrome c oxidase activity, plasma copper concentration and factorial analysis	• Ceruloplasmin concentration • Erythrocyte superoxide dismutase activity • Platelet copper concentration and cytochrome c oxidase activity • Urinary copper • Leukocyte copper concentration • Lysyl oxidase activity • Peptidyl glycine α-amidating monooxygenase activity • Diamine oxidase activity • Copper balance • Factorial analysis
	Excess UL	• Liver damage	• Gastrointestinal effects (abdominal pain, cramps, nausea, diarrhea, vomiting) • Other systemic effects

Iodine	*Adequacy* EAR	• Iodine accumulation and turnover (adults extrapolated to children and adolescents 9–18 years) • Iodine balance (children 1–8 years)	• Urinary iodine • Thyroid size • Serum thyroid stimulating hormone concentration • Serum thyroglobulin concentration • Thyroxine and triiodothyroxine concentrations
	Excess UL	• Hypothyroidism, elevated thyroid stimulating hormone	• Acute iodine poisoning (burning mouth, throat, stomach, abdominal pain, fever, nausea, vomiting, diarrhea, weak pulse, cardiac irritability, coma, cyanosis) • Goiter • Thyroid papillary cancer • Thyroid effects in newborns • Other adverse effects (iodermia, hyperthyroidism)

Iron	*Adequacy* EAR	• Indicator of adequacy—normal functional iron concentration but only minimal stores (serum ferritin 15 µg/L) calculated by factorial modeling because distribution of iron requirements is skewed	• Functional indicators (associated with degree of iron deficiency sufficient to cause measurable anemia—decreased physical work capacity, delayed psychomotor development in infants, impaired cognitive function) • Biochemical indicators - Serum ferritin concentration - Total iron binding capacity - Early iron deficiency - Serum transferrin saturation - Erythrocyte protoporphyrin concentration - Soluble serum transferrin receptor concentration - Iron deficiency anemia - Hemoglobin concentration and hematocrit - Erythrocyte indexes (mean corpuscular hemoglobin [MCH], MCV) - Surrogate laboratory indicators (ferritin model: serum ferritin concentration, erythrocyte protoporphyrin concentration and transferrin saturation / MCV model: MCV, transferrin saturation and erythrocyte protoporphyrin concentration—two or more abnormal indicators indicative of iron deficiency) • Factorial modeling used when distribution of nutrient requirements is skewed • Iron balance studies

	Excess UL	• Gastrointestinal effects (constipation, nausea, vomiting, diarrhea)	• Acute adverse effects (vomiting, diarrhea, with involvement of five organ systems—cardiovascular, central nervous system, kidney, liver and hematological) • Iron–zinc interactions • Secondary iron overload (parenteral iron, blood transfusions, hematological disorders) • Cardiovascular disease • Cancer
Manganese	*Adequacy* AI	• Intake levels used as basis for AI; adult AIs based on highest intake levels reported for four age groups due to underreporting of intakes; children's AI based on mean intakes	• Balance and depletion studies • Serum and plasma manganese concentrations • Blood manganese concentrations • Urinary manganese • Arginase activity • Manganese superoxide dismutase activity
	Excess UL	• Elevated blood manganese and neurotoxicity	• Neurotoxicity in laboratory animals • Ecological studies in humans
Molybdenum	*Adequacy* EAR	• Molybdenum balance (children and adolescents extrapolated from adult male data)	• Plasma and serum molybdenum concentrations • Urinary molybdenum
	Excess UL	• Reproductive effects in rats and mice (rats: prolonged estrus cycle, decreased gestational weight gain in pups, adverse effects on embryogenesis; mice: early deaths of offspring, dead litters, maternal deaths and failure to breed)	• Renal failure (mild) • Increased uric acid in plasma and urine in humans • Impaired copper utilization (ruminants) • Cancer • Hemoglobin and hematocrit decrease • Growth depression

Zinc	*Adequacy* EAR	• Minimal quantity of absorbed zinc required to match the total excretion of endogenous zinc plus growth where appropriate calculated using the factorial method adjusted for fractional absorption (older infants, children, adolescents, adults) • Physical growth response to zinc supplementation (used to check EAR derived by factorial method in older infants and young children 7 months – 3 years)	• Size and turnover rates of zinc pools • Plasma and serum zinc concentrations • Zinc concentration in erythrocytes • Zinc concentration in hair • Activity of zinc-dependent enzymes • Metallothionein and zinc-regulated gene markers • Indexes of immune status • Hormones • Circulating hepatic proteins
	Excess UL	• Reduced copper status • Serum copper and cholesterol concentrations in infants	• Acute effects (epigastric pain, nausea, vomiting, loss of appetite, abdominal cramps, diarrhea and headaches) • Immunological response (functional impairment) • Lipoprotein and cholesterol • Zinc–iron interactions • Other indicators
Arsenic	There have been no studies to determine the nutritional importance of arsenic for humans.		
Boron	(*EAR/AI were not set*) *Excess* UL	• Reproductive and developmental effects in animals (rats, dogs and mice: adverse effects in the testes and on male fertility)	• Acute effects (nausea, gastric discomfort, vomiting, diarrhea, skin flushing, excitation, convulsions, depression and vascular collapse) • Chronic effects in humans (dermatitis, alopecia, anorexia, indigestion) • Genotoxicity • Pharmacokinetics • Other effects (mice: increased mortality, extramedullary hematopoiesis, hyperkeratosis and hyperplasia of forestomach; rats and mice: testicular atrophy)

Nickel	(*EAR/AI were not set*) *Excess* UL	• UL applies to excess nickel intake as soluble nickel salt • Acute effects in humans (nausea, abdominal pain, diarrhea, vomiting, shortness of breath, altered hematological parameters, transient hemianopsia, contact dermatitis-like symptoms) • Subchronic and chronic effects in animals - increased mortality - clinical signs of general systemic toxicity - decreased body weight gains - changes in absolute and relative organ weights - fetotoxicity and interference in reproductive capacity of male rats	
Silicon	Not determined.		
Vanadium	(*EAR/AI were not set*) *Excess* UL	• Renal toxicity (rats: histopathological lesions and increased urea, uric acid and creatine, decreased weight gain; mice: acute tubular necrosis)	• UL applies to total vanadium from food, water and supplements • Acute toxicity (rats: desquamation enteritis, mild liver congestion with fatty changes and slight parenchymal degeneration of the renal convoluted tubules; mice: acute tubular necrosis) • Gastrointestinal effects in humans (abdominal cramps, loose stool) • Hematological effects • Cardiovascular effects (rats: increased blood pressure and heart rate) • Reproductive effects (humans: none, rats: decrease in pregnancy rate) • Other adverse effects in humans (green tongue, fatigue, lethargy, focal neurological lesions)

	2002/2005		
Dietary carbohydrates	*Adequacy* EAR (*UL was not set*)	• Glucose utilization by the brain (the amount of digestible carbohydrate in an energy-sufficient diet that would provide the brain [central nervous system] with an adequate supply of glucose fuel without the requirement for additional glucose production from ingested proteins or triacylglycerols)	
Sugars	Not determined; Statement made regarding added sugar.		
Starches	Not determined; Statement made regarding starches.		
Total fiber	*Adequacy* AI (*UL was not set*)	• Prevention of hyperlipidemia, hypertension and coronary heart disease	• Colon health (constipation, laxation, fecal weight; fiber fermentation products—energy source for colon; prevention of diverticular disease) • Prevention of colon cancer • Protection against breast cancer • Other cancers (endometrial, ovarian) • Glucose tolerance, insulin response and amelioration of diabetes • Fiber intake, satiety and weight maintenance
Dietary fiber	Not determined.		
Functional fiber	Not determined.		
Total fat	Not determined.		
Saturated fatty acids	Not determined.		
Mono-unsaturated fatty acids	Not determined.		

Linoleic acid	*Adequacy* AI (*UL was not set*)	[Median intakes in U.S. population]	• Correction of deficiency in infants and adults on total parenteral nutrition
Linolenic acid	*Adequacy* AI (*UL was not set*)	[Median intakes in U.S. population]	• Correction of deficiency in patients on total parenteral nutrition
Trans fatty acids	Not determined; Statement made regarding *trans* fatty acids.		
Cholesterol	Not determined; Statement made regarding cholesterol.		
Protein and amino acids	*Adequacy* EAR (*UL was not set*)	• Nitrogen balance	• Factorial method
		2005	
Water	*Adequacy* AI (*UL was not set*)	• Hydration status measured by serum osmolality	• Water balance • AI based on median intakes of total water from the Third National Health and Nutrition Examination Survey (NHANES III)
Potassium	*Adequacy* AI	• Salt-sensitive blood pressure (children and adolescents extrapolated from adults on basis of median energy intakes) • Blood pressure • Prevention of kidney stones	• Potassium balance • Serum potassium concentration • Hypokalemia • Prevention of cardiovascular disease • Prevention of bone demineralization • Prevention of impaired pulmonary function

Sodium	*Adequacy* AI	• Amount based on meeting the sodium needs of moderately active, apparently healthy individuals in a temperate climate as well as that of other important nutrients using foods found in a Western-type diet (children and adolescents extrapolated from adults using relative energy intakes)	• Sodium balance • Chloride balance • Serum or plasma sodium concentration • Plasma renin activity • Elevation in blood pressure • Blood lipid concentrations • Insulin resistance
	Excess UL	• Blood pressure •	• Stroke • Coronary heart disease • Renal disease • Left ventricular mass • Calcium excretion, BMD and kidney stones • Pulmonary function (asthma) • Gastric cancer
Chloride	*Adequacy* AI	• Equimolar to sodium •	•
	Excess UL	• Equimolar to sodium	•
Sulfate	Not determined; Met by requirements for sulfur amino acids.	•	•

APPENDIX 2: EXAMPLES OF INFORMATION USED BY NUTRIENT RISK MANAGERS[161]

Information for Taking Action, by Source	
Source of information: risk assessor	**Source of information: risk manager**
• Nature of adverse health effects o Severity o Vulnerable age/gender/life stage subpopulations o Specification if risk is for all forms of nutrient/substance (i.e., total intake) or if for certain forms (e.g., folic acid supplements or food folate; preformed vitamin A or β-carotene) • Specification of UL for age/gender/life stage subpopulations and basis for UL (e.g., total intakes or particular nutrient form) • Identification of vulnerable subpopulations and their status relative to UL: o intake distributions of appropriate nutrient form relative to the UL: ▪ percentage exceeding the UL ▪ distribution approaching UL and at risk of exceeding UL with relatively small changes in intake o magnitude of intakes exceeding UL (level of intake compared with the UL; narrowness between intake and UL) • Other at-risk subpopulations (e.g., malnourished, persons using certain drugs or with certain diseases) and nature of their risk • If applicable, reasons why UL could not be established (e.g., insufficient data quality or quantity; risk present but not able to identify a threshold level) • Description of uncertainties involved in each of the above findings	• Additional data (e.g., manufacturing data, feasibility of change, existing regulatory authorities and limitations, cost) needed to clarify the immediacy of the need for action • As appropriate, risk managers ask risk assessors for a scientific evaluation of impact • For other subpopulations at risk (e.g., subpopulations with relevant diseases)[a]: o percentage exceeding UL or the appropriate risk intake level if different from the UL for the general population o magnitude of intakes exceeding UL (how close or far away from UL) o numbers of people in these subpopulations exceeding UL • If no UL because there is no threshold dose, identification of intake level at which adequacy is met[b] • Determination of implementation terminology as needed or as appropriate, vis-à-vis "tolerable upper level" or "safe upper level"

[161] From FAO/WHO (2006).

Information Used for Reducing the Level of a Nutrient Substance in the Food Supply, by Source	
Source of information: risk assessor	**Source of information: risk manager**
• Form of nutrient substance associated with risk: all forms (total intake) or specific forms • Role of bioavailability in risk and factors affecting bioavailability (e.g., nutrient substance form; interactions with other meal or food components) • Description of any nutrient–nutrient adverse interactions • Description of uncertainties involved in information provided	• Data needed to clarify outcomes of policy decisions such as the relative contribution of particular product types or classes to total daily intakes, or—if a staple product is the source of exposure—exploration of whether a substitute staple product that contains a smaller amount of the substance can be made available • Development of "what-if" scenarios, such as (i) the likely impact if amounts or types of nutrients were changed in specific types of foods, or (ii) the impact of using nutrient requirements (or some level thereof) as a starting point for setting limits on amounts in food so as to limit exposure to the degree possible; as appropriate or possible, request evaluation of scientific issues by risk assessor
Information Used Relative to Product Labelling, by Source	
Source of information: risk assessor	**Source of information: risk manager**
• Ability of individuals within subpopulations at risk to self-identify their risk • Use conditions likely to increase or decrease risk (e.g., consumption with or without meals, bolus or continual exposures) • Description of uncertainties involved in the information provided	• Evaluation of the likelihood that vulnerable subpopulations use food products containing the substance • Evaluation of the likelihood that vulnerable subpopulations are able to control conditions of use to decrease risk • Evaluation of the utility and understandability of label information by high-risk subpopulations
Information Used Relative to Education, by Source	
Source of information: risk assessor	**Source of information: risk manager**
• Ability of individuals within subpopulations at risk to identify their risk • Description of uncertainties involved in each of the information needs above	• Consumer studies on components and effectiveness of educational programs • Consultation with health professional and industry groups

[a] Because this information initially would have been outside the scope of that considered by risk assessors, the task may fall to risk managers. However, risk managers may consider options for engaging risk assessors in relevant scientific evaluations pertaining to such information.

[b] Because such data needs could not necessarily be anticipated prior to the risk assessment, the evaluation of the topic likely will take on an iterative aspect between nutrient risk managers and risk assessors.

[c] As appropriate, risk managers may engage risk assessors for scientific evaluation of such data.

APPENDIX 3: OTHER SPECIAL CHARACTERISTICS OF NUTRIENTS COMPARED WITH NONNUTRIENTS RELEVANT TO RISK ASSESSMENT

Homeostatic Mechanisms

Nutrients are subject to homeostatic mechanisms specific to each nutrient. This is in contrast to other substances, such as pesticides and other chemical contaminants, for which homeostatic mechanisms operate but are generally less specific. Nutrient homeostatic mechanisms ensure the maintenance of normal body functions in the presence of a variable "nutrition environment." It is likely that they evolved because of the unique dual risks that are posed by inadequate intake of an essential nutrient on one hand and by excessive intake of the substance on the other. The ability of the body to adjust to differences in intake for different nutrients must be taken into account during risk assessment. This underscores the importance of research programs targeted to obtaining such information.

Analysis Specific to Life Stage and Gender

Outcomes based on estimates of lifetime exposures or reflected as amounts consumed per unit of body weight are commonly used to express the results of risk assessments for nonnutrient substances. However, this is not usually an appropriate approach for considering either adequate intakes or upper levels of intake of nutrients. Physiological differences among age and gender groups and during certain stages of the life cycle (e.g., pregnancy or lactation) can result in different intake–response relationships and may at times result in different health effects for different groups. Moreover, differences in homeostatic mechanisms and requirements for growth among life stage groups may influence sensitivity to nutrient requirements or to toxicity. Therefore, nutrient risk assessment for DRIs is most meaningful if provided on the basis of life stage and gender. Basic research to better elucidate the differences in response to nutrient intake among the life stage and gender groups is needed.

Existence of "Background Level" of Exposure to Nutrients

Unlike many substances that are the subject of risk assessment, nutrients are routinely and actively sought as an "exposure." That is, normal diets provide a background level of nutrient intake; thus, avoiding exposure to nutrients is not an option, nor is it desirable. Although a level of intake to ensure adequacy is considered to pose no risk for the general healthy population, the potential for excessively high intakes with the increasing availability of fortified foods and dietary supplements means that risk managers often need to take into account background exposure (i.e., intake) and, in turn, safe ranges of intake.

Bioavailability/Bioequivalency/Biopotency[162]

Bioavailability and bioequivalency issues relate to risks associated with both inadequate and excessive intakes. However, the traditional adjustments for bioavailability or bioequivalency in the case of nutrients may need special scrutiny. As an example, the development of the EAR for iron involved adjusting for differences in bioavailability from food sources based on dietary intakes of heme and nonheme iron sources. It did not consider the need for different adjustments for iron added to the diets as fortificants or as supplements. With the increasing use of fortified foods and dietary supplements, a more appropriate bioavailability adjustment for iron may need to be developed, perhaps similar to that used for vitamin A, which specifies retinol equivalents. Similar issues may be relevant to other nutrients.

Consideration of different sources of nutrients as well as the matrix effects of the foods consumed with the nutrients offers special challenges. These can affect bioavailability or biopotency and therefore alter dose–response relationships. This makes for extremely complicated decisions when determining nutrient requirements and excessive nutrient intakes.

Terminology

Many terms used for risk assessment are appropriate for use with both nutrients and nonnutrients. However, because risk assessment evolved primarily within nonnutrient fields of study, some terms seem inappropriate or not relevant to nutritional applications. For instance, the term "exposure" seems to some to be incompatible with nutrients, since consuming nutrients is different from being exposed to an environmental contaminant. The term "intake" may be preferable. Further, the term "hazard" is not entirely applicable to all nutritional interests. The World Health Organization has defined hazard as "an inherent property of [a substance] ... having the potential to cause adverse effects."[163] Although this concept applies to harm associated with excessive nutrient intakes, it does not apply to risks associated with nutrient inadequacies, because an adverse effect associated with an inadequate nutrient intake is not due to an inherent property of that nutrient. Rather, it is because the substance of interest (the nutrient) is lacking in the diet. Therefore, an examination of such terms and developing an approach for modifying them as needed could be worthwhile.

[162] *Bioavailability* is defined as the degree and rate at which a substance is absorbed into a living system or is made available at the site of physiological activity. *Bioequivalency* is defined as the property wherein two drugs with identical active ingredients or two different dosage forms of the same drug possess similar bioavailability and produce the same effect at the site of physiological activity. *Biopotency* is defined as the strength of a chemical substance on the body, or how well or how far it can act on a biological system. Source: Merriam-Webster (available at http://www.merriam-webster.com/).
[163] IPCS (2004).

Nature of Available Data

A recognized challenge for nutrients is that the nature of the evidence available for evaluating nutrient effects is generally incomplete and difficult to use. Studies in the literature often fail to fully collect or report data on a full dose–response relationship, relying typically on one or two data points. Moreover, the wide range of potential adverse effects normally included in systematic safety studies, as might occur for food additives or pesticides, is not common in nutrition literature. Most nutrition-related animal and in vitro studies have not been designed to evaluate the safety of high nutrient intakes, but instead focus on evaluating beneficial effects or elucidating mechanisms. Focused research is needed.