Nutritional Risk Assessment: Perspectives, Methods, and Data Challenges, Workshop Summary

Carol West Suitor, Ann Yaktine, and Maria Oria, Rapporteurs, Food Forum

ISBN: 0-309-10872-1, 146 pages, 6 x 9, (2007)

NUTRITIONAL RISK ASSESSMENT

Perspectives, Methods, and Data Challenges

Workshop Summary

Carol West Suitor, Ann Yaktine, and Maria Oria
Rapporteurs

Food Forum

Food and Nutrition Board

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS • 500 Fifth Street, N.W. • Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This study was supported by Contract No. HHSF223200730582P between the National Academy of Sciences and the U.S. Department of Health and Human Services; the Interagency Risk Assessment Consortium; the U.S. Department of Agriculture; and the International Life Sciences Institute. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number 978-0-309-10871-3 (Book)
International Standard Book Number 978-0-309-10872-0 (PDF)

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

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Suggested citation: Institute of Medicine (IOM). 2007. *Nutritional risk assessment: Perspectives, methods, and data challenges, workshop summary.* Washington, DC: The National Academies Press.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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SUZANNE HARRIS, International Life Sciences Institute, Washington, DC

DAVID KLURFIELD, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, MD

KATHLEEN KOEHLER, Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services, Washington, DC

MOLLY KRETSCH, Agricultural Research Service, U.S. Department of Agriculture, Beltsville, MD

MICHAEL D. McELVAINE, Office of Risk Assessment and Cost–Benefit Analysis, U.S. Department of Agriculture, Washington, DC

MARIANNE MILIOTIS, Center for Food Safety and Applied Nutrition, Food and Drug Administration, U.S. Department of Health and Human Services, College Park, MD

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **A. Catharine Ross,** Department of Nutritional Sciences, Pennsylvania State University. Appointed by the Institute of Medicine, she was responsible for making certain that an independent

examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

Contents

Overview*

For more than two decades, the practice of risk assessment has been applied to human public health issues, and policy makers have used the results of risk assessments in their decision-making process. Approaches for risk assessment have been developed for nonnutrients such as drugs, food additives, and pesticides, but approaches for risk assessment have received less attention in the nutrition area. Some aspects of the risk assessment approach used for nonnutrients are applicable to the assessment of risks related to nutrition (called *nutritional risk assessment* in this workshop summary). The overall approach, however, must be adapted and modified to take into account the unique aspects of nutrients, including the fact that both high and low nutrient intakes are associated with risk. Experience with the application of a risk assessment process to the setting of upper levels of intake for essential nutrients, for example, has uncovered a number of challenges. Adapting and developing risk assessment strategies for application in nutrition science could lead to improved approaches to the development of dietary and nutritional recommendations and thus is a topic of considerable interest.

One nonscientific but overall challenge to nutritional risk assessment relates to increasing and improving communication among experts from key disciplines in ways that could inform the nutritional risk assessment process. Among these key disciplines are nutrition, toxicology, dietary exposure assessment, economics, risk analysis, and epidemiology. How can the perspectives and methods of these diverse fields be brought

*The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop.

together to develop more effective approaches for quantitative nutritional risk assessment? How can they be applied to a spectrum of topics related to food and nutrition—micronutrients, macronutrients, dietary supplements, whole foods, food groups, and dietary patterns? How can they help overcome the data challenges that confront nutritional risk assessors?

As a step toward improving the communication and sharing methods and information across disciplines, members of the Interagency Risk Assessment Consortium, the U.S. Health and Human Services Office of the Assistant Secretary for Planning and Evaluation, the Institute of Medicine's Food Forum, and the International Life Sciences Institute planned the Nutritional Risk Assessment Workshop. The workshop was held on February 28 and March 1, 2007, in Washington, D.C. This workshop, which was envisioned as one in a series, focused on opening a dialogue to explore the unique questions and challenges faced by nutritionists and the potential use of risk assessment methodologies to answer them.

Specifically, the workshop served as a forum for experts from various disciplines to

- discuss the strengths and challenges of using various risk assessment approaches to inform dietary and nutritional recommendations,
- explore the use of risk assessment approaches to evaluate standards for nutrient intake and the relationship of diet and nutrition to chronic disease risk, and
- identify next steps necessary to make progress in these areas.

After a brief introduction by Catherine E. Woteki and Robert L. Buchanan, panels of experts provided an overview of risk assessment as it relates to nutrition; explored ways to share risk assessment approaches used by different groups; addressed challenges related to dietary patterns and health outcomes; identified new developments and challenges related to genetics, dietary intake assessment, and food composition data; and listed numerous data gaps. Twenty-two experts from many fields gave formal presentations, and members of the audience broadened perspectives and added information during open discussion periods. The sessions were meant to offer an organized dialogue among the experts. With this in mind, various experts presented information on a range of methodological challenges of nutritional risk assessment and on approaches that might be used to address the challenges. Many speakers mentioned the

risk assessment process used to establish Tolerable Upper Intake Levels as part of the process for setting Dietary Reference Intakes. This risk assessment model appears in Figure O-1. During the wrap-up session, moderator Robert Buchanan and five other individuals—from the food industry; the federal government; and the risk assessment, consumer interest, and public health communities—provided their perspectives and highlighted challenges and potential solutions.

This report is a summary of the workshop presentations and discussions. The meeting transcripts and slides used during the presentations served as the basis for the summary. Some of the content was reorganized for improved clarity. Many of the topics addressed during open discussions were closely related to topics highlighted during the wrap-up session. Therefore, most of the relevant content from the open discussions appears in Chapter 6, Perspectives on Challenges and Solutions: Summary Remarks and Suggested Next Steps.

Chapter 6 also summarizes the topics identified during the presentation and discussion as meriting more attention. Among these topics were the following:

- expanding the application of risk assessment in the processes of setting Dietary Reference Intakes and of developing various nutrition guidelines,

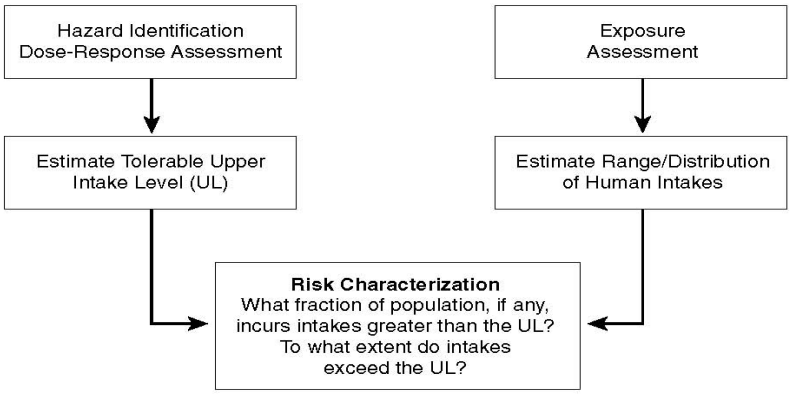

FIGURE O-1 Risk assessment model for nutrient toxicity.

- incorporating new dietary intake assessment methods and elements of the evidence-based review method into nutritional risk assessment,
- addressing uncertainties more explicitly,
- achieving a more complete separation between risk assessment and risk management,
- holding a workshop to test a risk assessment model for a nutrient,
- conducting methodological research related to nutritional risk assessment, and
- developing strategies for data collection related to nutritional risk assessment.

In addition, attention was directed to the need for improved communication targeted to consumers. Some presenters and discussants expressed strong viewpoints or made recommendations. Their viewpoints and recommendations should not be viewed as workshop conclusions or recommendations.

The agenda for the workshop appears in Appendix A, and Appendix B lists the workshop participants. Appendix C contains biographical sketches for the presenters, moderators, and discussants. Appendix D lists acronyms and abbreviations used throughout this workshop.

The workshop was supported jointly by the Department of Health and Human Services Office of the Assistant Secretary for Planning and Evaluation, the Interagency Risk Assessment Consortium, the International Life Sciences Institute Research Foundation, and the Institute of Medicine's Food and Nutrition Board's Food Forum. The following Interagency Risk Assessment Consortium members provided financial support: Department of Health and Human Services, Food and Drug Administration, U.S. Department of Agriculture (Agricultural Research Service and the Office of Risk Assessment and Cost–Benefit Analysis). In addition, the members of the Nutritional Risk Assessment Work Group of the Interagency Risk Assessment Consortium are acknowledged for their involvement.

1

Introduction

Presenters: Catherine E. Woteki and Robert L. Buchanan

CONTEXT

Risk assessment methods and their applications in food and nutrition have evolved considerably over the last 20 years. Concurrently, there have been important developments in approaches to assessing data sets, in statistical techniques, and in the fields of genetics, genomics, proteomics, and metabolomics. Many of these developments provide insights into how food affects human health. Risk assessment applications now occur in areas that originally were not considered to be in the risk assessment realm. Among these are applications of risk assessment to the microbiological safety of foods and human nutrition. This workshop was designed to bring together experts from many fields to consider what has been learned about the application of risk assessment to various food- and nutrition-related problems, to discuss the strengths and challenges in using risk assessment methods to inform the setting of dietary and nutritional recommendations and other forms of decision making, and to suggest next steps for making progress in these areas.

Catherine Woteki welcomed the group on behalf of the Food Forum, one of the cosponsors of the workshop. The Food Forum is a group of representatives from government agencies and academia and scientists from the food industry that operates under the auspices of the Food and Nutrition Board of the Institute of Medicine. The Food Forum discusses food-related topics ranging from risk assessment to aspects of consumer behavior. The activities in which the Food Forum is involved provide a venue for dialogue and for exploring the dimensions of different issues, but they do not result in recommendations.

Robert Buchanan described how this workshop grew out of a project undertaken as part of the Interagency Risk Assessment Consortium. This consortium is a group of 17 federal agencies and organizational units within those agencies that meet to find ways to enhance the application of risk assessment to food issues. Two years ago, the consortium recognized that work by the World Health Organization (Source: http://www.who.int/ipcs/methods/ew [accessed July 10, 2007]) and others would lead to increased interest in the application of risk assessment methods to nutritional questions. Thus, the consortium worked to help plan this workshop that was designed to provide a forum for the discussion of the potential of risk assessment approaches to inform diet- and nutrition-related recommendations and decisions. Buchanan acknowledged Laina Bush within the Office of the Assistant Secretary for Planning and Evaluation of the U.S. Department of Health and Human Services for her efforts and support.

Woteki expressed special thanks to the Interagency Risk Assessment Consortium for its instrumental role in planning the workshop. Woteki also expressed appreciation to the other cosponsors: the Food and Drug Administration; the Assistant Secretary for Planning and Evaluation of the U.S. Department of Health and Human Services; the Agricultural Research Service and the Office of Risk Assessment and Cost Benefit Analysis, both of the U.S. Department of Agriculture; and the International Life Sciences Foundation.

OBJECTIVES OF THE WORKSHOP

A major objective of the workshop was to introduce the nutrition and risk assessment communities to each other and foster their collaboration. The more specific objectives of the workshop follow:

1. Discuss the strengths and challenges of using various risk assessment approaches to inform dietary and nutritional recommendations.
2. Explore the use of risk assessment approaches to evaluate standards for nutrient intake and the relationship of diet and nutrition to chronic disease risk.
3. Identify next steps necessary to make progress in these areas.

2

Risk Assessment and Nutrition: Sharing Perspectives

Communication among members of different but related fields can be useful in addressing complex topics—in this case, nutritional risk assessment. This chapter addresses relationships between risk assessment and nutrition from the perspective of a risk assessor, a nutritional epidemiologist, a nutritionist in the food industry, and a physician working in prevention for the federal government. In particular, it addresses classical risk assessment processes and how they might be related to nutritional risk assessment, the questions and the challenges that nutrition poses for risk assessors, and selected applications of risk assessment in the food industry and the federal government.

A RISK ASSESSOR'S PERSPECTIVE: WHAT QUESTIONS CAN RISK ASSESSMENT ANSWER?

Presenter: Joseph Rodricks

Risk assessment is an activity that provides a crucial link between regulatory and public health policy decision making. It offers a highly systematic framework within which information can be organized and evaluated to serve the practical needs of decision makers. It provides information on what can and cannot be learned from the available research about threats to human health. Joseph Rodricks identified the focus of risk assessment, briefly described the risk assessment process, outlined

risk assessment questions related to the types of data, mentioned the application of risk assessment to nutritional risk, and identified topics for future efforts.

The Focus of Risk Assessment

According to Rodricks, two major questions are the focus of risk assessment:

1. What is the probability (preferably expressed quantitatively) that adverse health effects will occur in individuals exposed to an agent (whether it is a chemical, biological, or physical agent) or activity?
2. Under what conditions of exposure to an agent or activity are individuals unlikely to incur adverse health effects?

The use of risk management activities for risk assessment is inappropriate. Risk management activities include the identification of when risks become excessive or intolerable, the factors that should be considered in making decisions to reduce risks, and the means that should be used to reduce or manage risks.

The Risk Assessment Process

The process of risk assessment, which underwent its first major review by the National Research Council in 1983 (NRC, 1983), is a process that is still evolving. Figure 2-1 depicts the risk assessment process and features the key role of the decision-making context in designing a risk assessment.

Many years of experience have demonstrated that preservation of the integrity of the process requires the following:

- delineation of the problem to be addressed (the decision to be made),
- mechanisms to ensure interactive dialogues among all parties involved in risk assessment,
- clear identification of the questions to be addressed by risk assessment,

- the availability of the technical resources needed for risk assessment,
- protection of the integrity of the risk assessment process by ensuring that decision makers (the risk managers) and others cannot exert influence on the risk assessors,
- careful descriptions of the uncertainties involved in the risk assessment,
- complete coverage of the risk questions,
- adequate scientific peer review, and
- the clear presentation of results so that they may be understood by decision makers and other parties.

Although these points may seem obvious, they are often overlooked. In addition, with regard to the presentation of results, those who provide results from risk assessments need to recognize that many people do not understand probabilities.

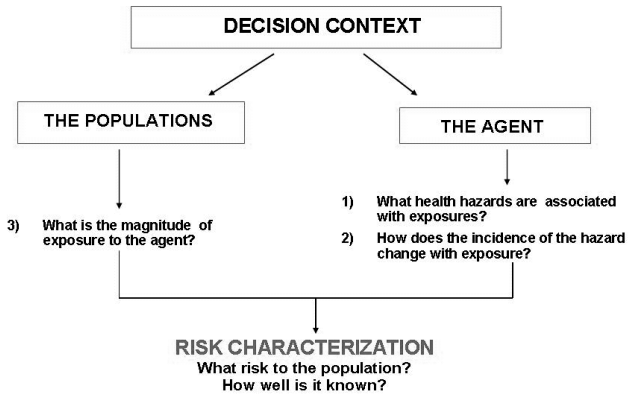

FIGURE 2-1 Steps in the risk assessment process. Note that hazard is an inherent property of the agent; it is not equivalent to risk.

Questions and Default Options Related to Types of Data

In risk assessment, the nature of the data leads to different types of questions. These questions are listed in Box 2-1.

The publication *Risk Assessment in the Federal Government* (NRC, 1983) notes that several default options may be available for addressing variability within populations, variability across species, and other factors that affect the findings of studies. Default options are policy judgments on how to accommodate uncertainties. That is, default options are used to make inferences in the absence of convincing evidence that indicates which of several competing methods or models is correct. An example of a default option is the scaling factor that is to be used to convert test responses in rodents to estimated responses in humans.

BOX 2-1
Risk Assessment Questions Related to Types of Data

Hazard and dose–response data

Derived from human studies

- What is the dose–response relationship?
- Is there a biological basis for a threshold?
- What is the probable threshold dose in the population that is the subject of the risk assessment? (This is a key question that requires the consideration of interindividual variability.)

Derived from animal studies

- Are the observed hazards relevant to humans?
- Is there an observed threshold dose?
- What is the probable threshold does in the human population that is the subject of the risk assessment?
  (These questions deal with problems of cross-species and interindividual variability.)

From several studies that report different findings

- How does one select among studies for the assessment of risk?

Exposure (dose) data

- How does one handle exposure data when the doses incurred by the relevant population are lower than the doses for which hazard data are available? (That is, how does one extrapolate data for exposures to high doses or to exposures to low doses?)
- How can negative data be used in defining risk?

Although the selection of default options introduces controversy, it ensures consistency and minimizes the possibility of the inappropriate manipulation of the findings from risk assessments. Default options tend to be cautious, potentially erring on the side of safety. In individual cases, a departure from the default may be allowed if it is well supported by the evidence (NRC, 1983).

Applying Risk Assessment Methods to Nutritional Risk Assessment

Although risk assessment cannot compensate for a lack of data and knowledge, it can guide research. There is a need for experimental models that can be used to study excessive nutrient intakes. Current thinking predicts a threshold for inadequate intakes, a threshold for excessive intakes, and a region between the two that is a condition of homeostasis. The extent to which the tails of the distribution of intakes for a nutrient fall outside the range of homeostasis provides a description of the nutrient intakes that may result in health risks.

Concluding Remarks

Rodricks identified five important topics for future efforts:

1. development of consensus guidelines for the extrapolation of the findings and data from previous studies and other default options for future risk assessments;
2. determination of the certainty of evidence supporting homeostasis;
3. examination of how the range of homeostasis varies among individuals, including the consideration of people who differ by life stage (growth, development, reproductive state, aging), nutritional status, and, perhaps, health status;
4. useful ways to describe individual and population risks given the variabilities mentioned above; and
5. improved methods for describing scientific uncertainties to decision makers and others.

A NUTRITIONAL EPIDEMIOLOGIST'S PERSPECTIVE: RELEVANT ISSUES IN NUTRITIONAL RISK ASSESSMENT

Presenter: Shiriki Kumanyika

Given that food is a human need and a universal exposure, dietary intakes can be evaluated as positive, negative, or neutral for health. Shiriki Kumanyika addressed the kinds of questions that are pertinent to nutritional risk assessment and the methods used to quantify nutritional risk. She then identified challenges to the assessment of nutritional risk.

Framing the Questions

In the United States, many different groups pose questions about nutritional risk. These groups include the Institute of Medicine's Food and Nutrition Board; various agencies of the federal government that address health, food safety, and food regulation; the Dietary Guidelines Advisory Committee; disease-focused organizations, such as the American Heart Association and the American Cancer Society; life-stage interest groups, such as the American Academy of Pediatrics and the March of Dimes; the food industry; and consumers. The nature of the questions reflects the group's interest or responsibility. Consumers' perceptions of risk, however, often do not match the risks identified by other groups.

Types of Risk

In nutrition, risk may take a number of forms, including

- the adequacy–toxicity continuum as it relates to the direct effects of essential nutrients;
- food-borne illnesses, including allergies; and
- the broad areas of the effects of diet on health as they relate to the prevention and management of chronic diseases.

Population Considerations

Risks vary within populations. Population considerations that are important in assessments of nutritional risk include life stage, genetics, environmental stressors, behaviors (such as smoking) that influence nutrient requirements and metabolic vulnerability, and health status. Ethnic differences may need to be considered for some nutrients, such as sodium, potassium, and calcium.

Food and Nutrition Variables

A wide range of dietary substances may pose risks. These substances include proteins, fats, carbohydrates, fiber, vitamins, and minerals that occur naturally in foods or that are added to foods or taken as supplements; other naturally occurring food constituents; contaminants; toxins; mutagens; botanicals; other nonnutrient dietary supplements; and alcohol. The category "other naturally occurring food constituents" includes an array of substances ranging from anthocyanins to sulfides (allium) (Van Duyn and Pivonka, 2000). In addition to individual food components and supplements, other food and nutrition variables may affect risk either positively or negatively. These variables include specific foods; food processing and preparation methods; and entire dietary patterns, which entail interactions within the mix of nutrients and foods consumed. The complexity that is integral to the food supply and dietary patterns adds to the complexity of risk assessment.

Outcomes

Physiological indicators of the effects of diet on health include changes related to growth; adipose tissue; musculoskeletal tissue; metabolism; cognitive function; and the gastrointestinal, cardiovascular, reproductive, immunological, and neurological systems (Task Force on Community Preventive Services, 2005). Health outcomes of major public health importance for assessing the effects of diet include cardiovascular diseases, different types of cancers, type 2 diabetes mellitus, obesity, dental caries, and osteoporosis (WHO, 2003). Each of these diseases has subcategories. Many reversible intermediates (e.g., hypertension and elevated low-density lipoprotein cholesterol concentrations) occur be-

tween dietary intakes and possible morbidity and mortality outcomes. Multiple pathways and multiple targets also add to the complexity of risk assessment.

The effects of a single nutrient substance may involve many different pathways (Blumberg, 1997). For example, many nutrients and food variables could affect the risk of the same disease, but in different ways. For example, increased intakes of soluble fiber and vitamin B_6 could help prevent cardiovascular disease, whereas increased intakes of saturated fat and sodium could increase the risk (Blumberg, 1997; Esrey, et al., 1996). Another element of the complexity is that many of the cellular and biochemical mechanisms that play a role in the pathogenesis of major chronic diseases appear to be interrelated (Deckelbaum et al., 1999).

Quantification of Nutritional Risks

The quantification of nutritional risks informs guidance to the public about diet and supplement intake. Two major groups have worked to quantify nutritional risks in the United States: (1) the Food and Nutrition Board of the Institute of Medicine, which developed the Dietary Reference Intakes (DRIs), and (2) the Dietary Guidelines Advisory Committee (advising the U.S. Department of Health and Human Services and the U.S. Department of Agriculture, which jointly publish the *Dietary Guidelines for Americans*).

Published DRIs include values for Estimated Average Requirements (EARs), Adequate Intakes, Recommended Dietary Allowances (RDAs), and Tolerable Upper Intake Levels (ULs) for 45 nutrients or nutrient categories (IOM, 2006). In some cases, EARs and ULs were not set because of a lack of data. The *2005 Dietary Guidelines for Americans* (DHHS/USDA, 2005) provide nine focus areas, ranging from adequate nutrients within calorie needs to food safety. Themes in the *2005 Dietary Guidelines for Americans* include calories needed to achieve desirable weight; limits on total and saturated fat and cholesterol intakes; the consumption of a variety of foods, with an emphasis on plant sources; moderate sugar and salt intakes; and alcohol consumption in moderation, if used. The advisory committee that encouraged these themes considered adequacy, the avoidance of excess or toxic amounts of nutrients, and the prevention of chronic illness (DGAC, 2005).

Concluding Remarks

Kumanyika identified the need to address the following challenging topics:

- inconclusive or absent data;
- adverse effects (e.g., on chronic diseases, within the range of nutrient intakes that falls between the extremes of adequacy and toxicity);
- the various effects (i.e., sometimes beneficial and sometimes harmful) of a given nutrient or diet pattern, depending on the level consumed or, perhaps, on the interactions between nutrients or food constituents;
- the safety risks of recommended foods, such as fish; and
- paradigms that are appropriate for the examination of evidence related to chronic disease outcomes and to risks that the consumption of single foods or dietary patterns may pose, as such paradigms may differ from those used to address other types of outcomes or exposures (IOM, 2002).

A number of the research needs identified by the 2005 Dietary Guidelines Advisory Committee (DGAC, 2005) are also relevant to the area of nutritional risk assessment. A major challenge rests with addressing the complexity of assessing nutritional risk in an acceptable manner. Current risk assessment approaches address questions relating to the direct effects of single or relatively specific and selective exposures. However, there are many types of nutritional risk, many variables, many endpoints, and many interactions. The result is a set of very complex questions, and the applicability of current methods to addressing complex exposures and multiple possible endpoints is unclear.

AN INDUSTRY PERSPECTIVE: HOW THE FOOD INDUSTRY USES RESULTS FROM RISK ASSESSMENT

Presenter: Kathryn Wiemer

The food industry actively applies risk management principles in a variety of areas, including food safety and nutrition. Kathryn Wiemer provided a brief overview of food fortification and illustrated how Gen-

eral Mills applies risk management principles to discretionary food fortification decisions. The application of risk management principles involves, in part, the use of findings from nutritional risk assessments.

Milestones in Fortification History

The food industry informs consumers about food fortification by means of the nutrition label. Figure 2-2 depicts milestones in food fortification history beginning in 1973, when the FDA established U.S. Recommended *Daily* Allowances (U.S. RDAs) for labeling foods, and projected to about 2012. The U.S. RDAs differ from the Recommended *Dietary* Allowances (RDAs) mentioned earlier in this chapter. In particular, the U.S. RDAs were based on the 1968 Recommended Dietary Allowances set by the National Research Council. Beginning in 1993, the FDA called for Daily Values (DVs) to replace the U.S. RDAs on nutrition labels, but, despite revisions of the Recommended Dietary Allowances after 1968, the DVs were also based on the 1968 values.

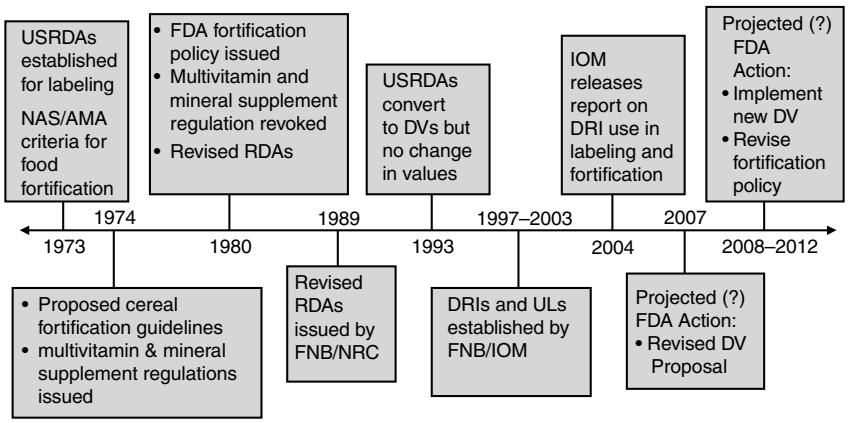

FIGURE 2-2 Milestones in food fortification history.
NOTE: AMA = American Medical Association; DRI = Dietary Reference Intake; DV = Daily Value; FDA = Food and Drug Administration: FNB = Food and Nutrition Board; NAS = National Academy of Sciences: RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level; US RDA = U.S. Recommended Daily Allowance.

Discretionary Fortification

Discretionary fortification refers to the addition of nutrients to food, excluding cases in which the food product is formulated to meet a standard of identity promulgated by the FDA, such as for enriched flour.

Principles

The FDA's fortification policy (FDA, 1980) outlines principles for the addition of nutrients to foods. Although this policy is not a regulation, it provides guidance to the food industry. More recently, the report *Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification* (IOM, 2003) presented guiding principles related to the discretionary fortification of foods (Figure 2-3). The guiding principles address topics related to risk assessment, such as the distribution of usual intakes in the population, how the discretionary fortification would alter the dietary intake of the nutrient in question, and, if applicable, the severity of the adverse effect on which the UL for the nutrient is based. Although these guidelines and recommendations were designed to assist regulatory agencies that oversee fortification, the food industry considers them as well; and they pose a number of challenges. In particular, when

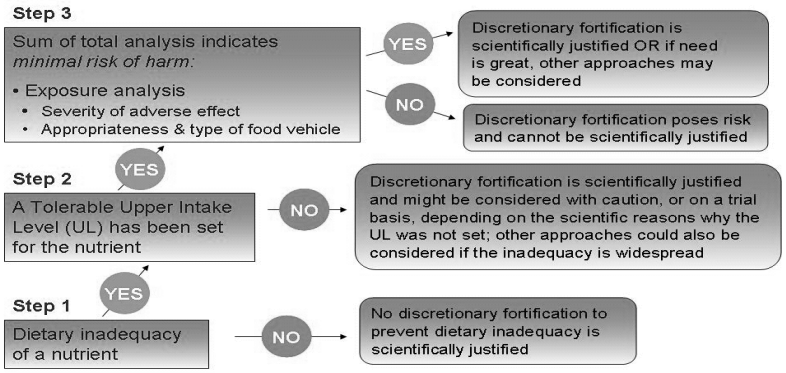

FIGURE 2-3 Decision tree for the discretionary fortification of foods.
SOURCE: IOM (2003).

making discretionary fortification decisions, the food industry must consider FDA's fortification policy, ULs for nutrients, the findings in the report *Dietary Reference Intakes: Applications in Dietary Assessment* (IOM, 2001a), public policy on health, including Dietary Guidelines, and evolving scientific nutrient research.

General Mills's Approach

General Mills's approach to discretionary fortification uses FDA's fortification policy (FDA, 1980) as the framework and DRI reports as the core. The approach includes the steps shown in Box 2-2.

BOX 2-2
General Mills's Approach to Discretionary Fortification

1. Initial assessment
    a. Is the food an appropriate vehicle for fortification?
        i. Is it widely consumed?
        ii. Are added nutrients distributed uniformly in the food?
        iii. Are the nutrients stable in the food?
    b. Is there a public health need?
        i. What are typical intakes of the nutrient by the target population?
        ii. What are typical intakes of the food by the target population?
    c. What level of fortification should be considered?
        i. Are there concerns about possible overconsumption?
        ii. What is the bioavailability of the nutrient form?
    d. What is the current regulatory and health policy environment?
2. Ongoing assessment and monitoring
    a. DRI nutrient reports (IOM, 1997, 1998, 2000, 2001b, 2002/2005, 2004)
    b. The DRI report on dietary assessment (IOM, 2001a)
    c. New scientific research pertaining to nutrients
    d. Nutrient intake and biochemical data
    e. Nutrition and health policy
    f. Marketplace assessment
    g. Consumer research
3. Periodic detailed reviews of new scientific research to determine whether or not to recommend changes to the nutrient contents of the company's products
4. Support and collaboration from internal groups (product research and development, manufacturing, and marketing)

One current issue involves the overlap among DVs, Recommended Dietary Allowances (RDAs), and ULs, especially since the DVs do not change for different age groups whereas RDAs and ULs do. The DV for several nutrients is higher than the UL for certain age groups. Wiemer directed attention to zinc: the DV is 15 milligrams (mg), but the UL for children ages 1 to 3 years (7 mg) is much lower than the DV, and the UL for children ages 4 to 8 years (12 mg) is somewhat lower than the DV. Meat, fish, and poultry; ready-to-eat cereals; other grain products; and milk are the main sources of zinc in the U.S. diet and account for well over 67 percent of the total average zinc intake.

Further analysis of dietary intake data shows that, compared with the percentage of people whose zinc intakes are greater than the UL, a higher percentage of people are not meeting the EAR for zinc. Estimates indicate that reducing the amount of zinc in cereal would decrease but not eliminate the occurrence of intakes by children that exceed the UL for zinc.

Wiemer took the position that industry can and should play a role in addressing nutrient intake shortfalls, pointing out several shortfalls identified in the *Dietary Guidelines for Americans* (DHHS/USDA, 2005): calcium, magnesium, and vitamin D for bone health; whole grains and fiber for heart and digestive health; and healthy fats (omega-3 fatty acids) and potassium for heart health.

Concluding Remarks

In summary, Wiemer posed several challenging questions:

1. What is the best approach for interpreting and applying the DRI values to discretionary fortification?
   a. Should all UL values have equal weight? (Consider vitamin A and zinc.)
   b. What approach is appropriate when UL values for children are lower than the current DV or the RDA or EAR for adults?
2. How can the benefit of fortification for one subpopulation be balanced against the potential risk of adverse effects for another subpopulation?

3. What approach will be used to develop ULs for nutrients that are being added to foods but for which no UL has been set (for example, omega-3 fatty acids)?

A PUBLIC POLICY PERSPECTIVE: LIMITATIONS OF CURRENT RISK ASSESSMENT METHODS FOR DECISION MAKING

Presenter: William Dietz[1]

The presentation addressed the limitations of current methods for assessing the risk of obesity, the consideration of specific foods and food behaviors (rather than nutrients) as risk factors for obesity, and the risk of high folic acid intakes to certain subpopulations. William Dietz's perspective is that of a person who is involved in prevention and, therefore, in helping make decisions based on the available data.

Limitations of Current Methods for Assessing the Risk of Obesity

Uncertainties exist about the use of body mass index (BMI) as a predictor of risk. Moreover, two of the proximal determinants of BMI—energy expenditure and energy intake—have limitations. Because these two factors are interrelated and can not be examined independently of one another, there may not be a threshold effect for either of them in terms of the risk for obesity.

Energy Expenditure Measurements

Cross-sectional data indicate that obese individuals are less active than those who are not overweight. An important meta-analysis (Fogelholm and Kukkonen-Harjula, 2000), however, concluded that the findings are very mixed from prospective studies of the impact of baseline physical activity on changes in body fat levels. Using doubly labeled water, Bandini and colleagues (1990) found that the total energy expen-

[1]Dr. Dietz made it clear that the views expressed in this presentation were his own and should not be construed to represent any agency determination or policy.

diture of obese adolescents exceeds that of nonobese youth. As a group, the nonresting energy expenditure among preadolescent girls did not predict changes in body fat levels over about a 5-year period. Moreover, the physical activity level, which is the ratio of total energy expenditure to the resting metabolic rate, is similar between obese and nonobese individuals (Bandini et al., 1990). The type of energy expenditure that is most promising as a predictor of weight gain is based on the amount of nonexercise type of energy expenditure, such as fidgeting, that an individual engages in. However, good measurement techniques are not yet available for determining this type of energy expenditure (Dietz et al., 1994).

Energy Intake Measurements

Bandini and colleagues (1990) found that self-reported metabolizable energy intake was substantially lower than measured total energy expenditure in adolescents, and the degree of underreporting tended to increase with increases in BMI. This limitation of self-reported intake data (obtained by using diet records or diet recalls) has been confirmed in many other studies. Moreover, Subar and colleagues (2003) demonstrated that estimates of energy and protein intakes from food frequency questionnaires have very low correlations with the estimates obtained by multiple 24-hour recalls. Thus, estimates of energy intake are not good determinants of the risk of becoming obese.

Foods and Behaviors as Risk Factors for Obesity

Because neither measures of energy expenditure nor energy intake serve as good determinants of the risk of developing obesity, some investigators are examining data on foods and food behaviors as risk factors for obesity. The consumption of sugar-sweetened beverages is one example of a potential risk factor for obesity. Observational studies have found a positive relationship between the consumption of sugar-sweetened beverages and weight change (Berkey et al., 2004; Ludwig et al., 2001; Phillips et al., 2004; Striegel-Moore et al., 2006; Welsh et al., 2005). The evidence has been consistent, with some studies showing that there is a dose–response relationship and that sugar-sweetened beverage intake relates temporally to changes in body weight.

Fructose—the major source of which is sugar-sweetened beverages—may be a potential contributor to obesity. There is no insulin response to this monosaccharide (in contrast to the insulin response obtained when fructose is delivered in the form of the disaccharide sucrose). Studies also implicate fructose consumption as a risk factor for hypertriglyceridemia, hepatic and adipose insulin resistance, a small increase in plasma glucose concentration, and mild gastrointestinal distress or irritable bowel syndrome. One problem in examining the relationship between fructose intake and the development of obesity is a lack of data that can be used to examine changes in fructose intake over time. Dietz underscored the need for intervention studies, especially ones involving sugar-sweetened beverages, to learn more about the potential contribution of suspect foods or nutrients to various disease outcomes.

Other dietary variables potentially related to the development of obesity include the energy density of food, portion sizes, meal patterns, binge eating, restrained eating, nighttime eating syndrome, the glycemic index of food, and macronutrient ratios.

The Risk of High Folic Acid Intakes to Certain Groups

In the United States, the fortification of enriched cereal grains with folic acid has resulted in a marked decline in the incidence of pregnancies affected by neural tube defects. Nonetheless, it appears that subsets of the population with the TT gene sequence variant of the methylene tetrahydrofolate reductase enzyme may be at increased risk of low plasma folate concentrations (R. J. Berry, National Center for Birth Defects and Developmental Disabilities, personal communication, February 14, 2007). This raises concern that a folate intake high enough to achieve the desired plasma folate concentrations in this subgroup may approach the UL. In part because an estimated 38 percent of people of Chinese descent and 20 to 25 percent of the Hispanic population have this gene variant, this topic merits consideration. The potential adverse effects of high folic acid intake include interactions with other B vitamins, effects such as hypermethylation, seizure thresholds, and an incomplete conversion of folic acid to its active form. At present, there is a limited capacity to measure the outcomes. Moreover, Rosenberg (2005) pointed out that there is no clear assignment of the responsibility to monitor the population for adverse effects of folic acid fortification.

Concluding Remarks

The three examples given—energy balance and obesity, foods and food-related behaviors and obesity, and folic acid and its potential adverse effects—illustrate selected limitations of current methods of risk assessment and point out challenges for the future.

OPEN DISCUSSION

During the open discussion, the workshop participants raised a number of points relating to discretionary fortification. Among the topics addressed were the following:

- the influence of nutrient bioavailability on discretionary fortification decisions,
- the influence of labeling requirements for portion size on the nutrient profile that appears on the label of fortified cereal,
- the extent to which food companies consider information about the fortification of other companies' food products as a part of their discretionary fortification decisions,
- concern about iodization policies in the face of both the increased consumption of prepared foods made with noniodized salt and the decreased use of iodized table salt, and
- ways to handle the effects of increased folic acid consumption on vitamin B_{12} status and its health effects.

Other topics that were discussed during the open discussion have been incorporated into Chapter 6, Perspectives on Challenges and Solutions: Summary Remarks and Suggested Next Steps.

3

An Examination of Current and Potential Nutritional Risk Assessment Methods

Information gained from classical and nutritional risk assessments has led to new questions and possible new approaches to nutritional risk assessment. This chapter covers the perspectives of several nutritional scientists and risk assessment experts on various aspects of risk assessment. Robert Russell, an expert in human metabolism of retinoids and carotenoids, addressed how different groups have used risk assessment methods to establish upper intake levels for nutrients and identifies data gaps that impede the assessment of risk related to excessive nutrient intakes. Suzanne Murphy, an expert in dietary assessment methodology, covered potential connections between the establishment of nutrient requirements and Tolerable Upper Intake Levels (ULs). Christine Taylor, an expert in nutrition policy, pointed out lessons learned from an international workshop on the topic of upper levels for nutrients. Barbara Petersen, a risk assessment expert, provided background information on nutritional risk assessment and then introduced a method that could be used to consider both the risks and the benefits of nutrient intake as a function of that intake. Gregory Paoli, another risk assessment expert, distinguished safety-based standard setting from risk assessment and reviewed the rationale for formal risk assessment and the elements for risk-based advice. The chapter ends with a brief summary of the points raised during the commentary by Sanford Miller, whose expertise includes food safety.

THE INSTITUTE OF MEDICINE PROCESS TO ESTABLISH TOLERABLE UPPER INTAKE LEVELS: MODEL AND DATA NEEDS

Presenter: Robert M. Russell

The Institute of Medicine's (IOM's) conceptual model for the UL (see Figure O-1 in the Overview) involves determination of the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. Robert Russell provided a brief review of the derivation of a UL and the sources of uncertainty and then focused on how three different expert groups arrived at different conclusions when they determined the upper levels[1] for vitamin A, beta carotene, vitamin B6, and zinc. He concluded his presentation with a list of the kinds of data needed to improve the determination of upper levels for these four nutrients.

Brief Overview

The process of deriving an upper level typically involves the identification of a critical data set; the identification of a critical toxic effect (the endpoint, a no-observed-adverse-effect level [NOAEL] or a lowest-observed-adverse-effect level [LOAEL]); and the derivation of an uncertainty factor, which typically is less than 10 for nutritional risk assessment. By using this approach, the upper level is obtained by the following formula:

$$\text{Upper level} = \frac{\text{NOAEL or LOAEL}}{\text{Uncertainty Factor}}$$

Therefore, the larger that the uncertainty factor is, the lower that the value of the upper level is.

The process of assigning an uncertainty factor has been somewhat subjective. Factors that have contributed to assigning a larger uncertainty factor include extrapolation of the findings of studies with animals to

[1]The general term "upper level" is used when applicable because the expert committees in different parts of the work had slightly different definitions for the value that was determined.

humans, evaluation of the effects of short-term rather than long-term exposures, the use of small numbers of subjects in experimental studies, the greater severity of the hazard, and the use of a LOAEL rather than a NOAEL.

Selected Results from Different Expert Groups That Set Upper Levels for Nutrients

In preparation for this workshop, Russell examined reports by expert groups from three parts of the world: (1) IOM for the United States and Canada, (2) Expert Group on Vitamins and Minerals for the United Kingdom, and (3) Scientific Committee on Food for the European Union. He focused on the establishment of upper levels for vitamin A (EVM, 2003; IOM, 2001; SCF, 2002), beta carotene (EVM, 2003; IOM, 2000a; Rothman et al., 1995), vitamin B_6 (EVM, 2003; IOM, 1998a; SCF, 2000), and zinc (EVM, 2003; IOM 2001; SCF, 2003). Russell found that the expert groups came to different conclusions, largely because of differences in the adverse effect identified or differences in the uncertainty factor used, as briefly described below.

Vitamin A

IOM set the UL for women of reproductive age by using a NOAEL for teratogenicity and an uncertainty factor of 1.5 (for a resultant UL of 3,000 micrograms per day [μg/day]). For all other adults, IOM set the UL by using a LOAEL for liver toxicity of 14,000 μg/day, based on case reports, and an uncertainty factor of 5. Among the other adverse effects considered were risks of bone mineral density changes, hip fracture, and bulging fontanel (for infants). The available data on the risk of hip fracture were not used because the findings were inconsistent (Freudenheim et al., 1986; HoutKooper et al., 1995; Melhus et al., 1998; Feskanich et al., 2002). More recent studies on the association of vitamin A with the risk of low bone mineral density (Ballew et al., 2001; Promislow et al., 2002; Rejnmark et al., 2004), hip fracture (Opotansky and Bilezikian, 2004; Rejnmark et al., 2004), and osteoporosis (Maggio et al., 2003; Penniston et al., 2006) remain inconclusive.

The expert group in the United Kingdom considered the evidence base to be inadequate to establish an upper level, indicating that the study

on teratogenicity by Rothman and colleagues (1995), which IOM used to establish the UL for women of reproductive age, was biased. The report did indicate, however, that vitamin A intakes greater than 1,500 μg/day may be inappropriate, mainly on the basis of studies by Melhus et al. (1998) and Feskanich et al. (2002), and advised women not to take vitamin A supplements if they were pregnant.

The Scientific Committee on Food used the study by Rothman et al. (1995), identified a LOAEL rather than a NOAEL, used no uncertainty factor, and set an upper level identical to that set by IOM. This expert group reported that it did not use an uncertainty factor because other studies show that the true threshold for risk is probably higher. The upper level set by the Scientific Committee on Food was considered to cover the risk of hepatotoxicity.

The vitamin A UL of 600 retinol activity equivalents (RAE)/day that IOM set for infants (IOM, 2001) is based on the vitamin A content of breast milk. An intake of 600 RAE/day is lower than the estimated amount of vitamin A consumed by 56 percent of the 4- to 5-month-old infants participating in the Supplemental Nutrition Program for Women, Infants, and Children (WIC), suggesting that the UL value for infants may need to be reexamined.

Beta-Carotene

The example of beta-carotene also illustrates that different groups examining the same data may come to very different conclusions. Neither IOM nor the EU Scientific Committee on Food set an upper level for beta-carotene. The reasons that both expert groups gave for not setting an upper level were similar (IOM, 2000b; EC, 2000): no dose–response data were available, the data were conflicting, or different formulations had been used in different studies. By contrast, the United Kingdom's expert committee set an upper level of 7 milligrams per day (mg/day) (EVM, 2003), an amount that is close to what some vegetarians ordinarily ingest. They used data from the Alpha-Tocopherol Beta-Carotene Study to establish a NOAEL of 20 mg (that study had also been reviewed by IOM and the group from the European Union). The United Kingdom's expert committee used supportive data from a study of ferrets exposed to a dose of beta-carotene that would be comparable to the dose for humans. Even when the ferrets that were exposed to the beta-carotene were not exposed to cigarette smoke, they still developed squamous metaplasias. Further

investigation has demonstrated that dose matters: giving ferrets that had been exposed to cigarette smoke a beta-carotene dose comparable to 6 mg/day in humans did not result in metaplasia.

Vitamin B_6

The expert groups from North America, the United Kingdom, and the European Union relied on data from different studies and set very different upper levels for vitamin B_6. IOM used the study by Bernstein and Lobitz (1988) to set the NOAEL for vitamin B_6 and used a small amount of data on doses under 200 mg to set a UF of 2 (IOM, 1998b). This resulted in a UL of 100 mg/day when vitamin B_6 is consumed as pyridoxine. In the United Kingdom, the upper level of 10 mg/day was set by using data on ataxia in dogs (Phillips et al., 1978) and using a large uncertainty factor (300) based on the use of a LOAEL, interspecies variation, and interindividual variation (EVM, 2003). In the European Union, the upper level of 25 mg/day was set by using data from Dalton and Dalton (1987), and an uncertainty factor of 4 was selected because of deficiencies of the data in the research database (SCF, 2000).

Zinc

The three expert groups differed in their establishment of upper levels for zinc as well. IOM and the Expert Group on Vitamins and Minerals used the same key study (Yadrick et al., 1989), but they derived different LOAELs and used different uncertainty factors. The Scientific Committee on Vitamins and Minerals disregarded the study by Yadrick et al. (1989) and used two different studies instead: those of Davis et al. (2000) and Milne et al. (2001). The resulting upper levels were as follows:

- IOM = 40 mg/day
- United Kingdom = 25 mg/day
- European Union = 25 mg/day

Despite the use of very different methods in the United Kingdom and the European Union, the result was the establishment of identical upper levels.

Concluding Remarks

To provide a more reliable and valid basis for establishing upper levels for the four nutrients discussed here, there is a need to obtain more complete data on the following:

- defined critical endpoints associated with nutritional status (for vitamin A),
- the biomarkers to be used to define chronic disease (for beta-carotene),
- vitamin B_6 intakes from long-term studies,
- systems that dysfunction with nutrient excess (for zinc), and
- dose–response (for all four nutrients).

The use of experimental animal models could be helpful in obtaining much of this information. In addition, uniform rules are needed for the application of uncertainty factors (for all four nutrients), and the use of a common approach to the establishment of upper levels could be helpful.

POTENTIAL CONNECTIONS BETWEEN ESTABLISHING NUTRIENT REQUIREMENTS AND TOLERABLE UPPER INTAKE LEVELS

Presenter: Suzanne P. Murphy

Although adverse health effects are associated with both nutrient inadequacy and nutrient excess, expert groups use very different approaches to set nutrient requirements and upper levels. Suzanne Murphy suggested that the term "nutritional risk assessment" can apply equally to the processes of determining requirements for nutrients and the establishment of upper levels for nutrients. Murphy described the two approaches, examined why different approaches are used, and explored whether risk assessment methods are applicable to both approaches and how the use of different approaches limits the use of the Dietary Reference Intakes (DRIs).

Why Are Different Approaches Used to Set Nutrient Requirements and Upper Levels?

Overview of the Two Approaches

To set nutrient requirements, the DRI expert panels were asked to estimate the average requirement (the Estimated Average Requirement [EAR]) and its standard deviation. They computed the Recommended Dietary Allowance (RDA) as the EAR plus two standard deviations of the requirement (IOM, 2006a). To set a UL, the UL expert group was asked to use a risk assessment approach that involves hazard identification, dose–response assessment, intake (exposure) assessment, and risk characterization (refer to Figure O-1 in the Overview). In both cases, the expert groups were asked to identify a functional outcome and to conduct a dose–response assessment, an intake assessment, and a risk characterization. The approaches and the terminology used differed, however.

Possible Reasons to Question the Use of Different Approaches

One might view too little of a nutrient to be a hazard, in the same way that too much of the nutrient would be a hazard. By the definition of *nutrient*, long-term inadequacy leads to the deterioration of health and, eventually, death. The concepts appear to be comparable: both can be viewed as distributions. The EAR concept describes a distribution of requirements. On the other hand, the UL concept describes a threshold, that is, the beginning of the risk of an adverse effect. Figure 3-1 depicts hypothetical distributions for requirements and adverse effects. If a person's usual intake were at the amount indicated, the person would be at some risk from excessive intake. Indeed, Murphy argued that there could be a very low (nearly zero) risk of excessive intake in the homeostasis area of intake (see "Applying Risk Assessment Methods to Nutritional Risk Assessment" in Chapter 2), just as there could be a very low risk of inadequate intake in that area.

Because the UL is not defined with a mean and a distribution, Murphy noted that a complete description of the risk is problematic.

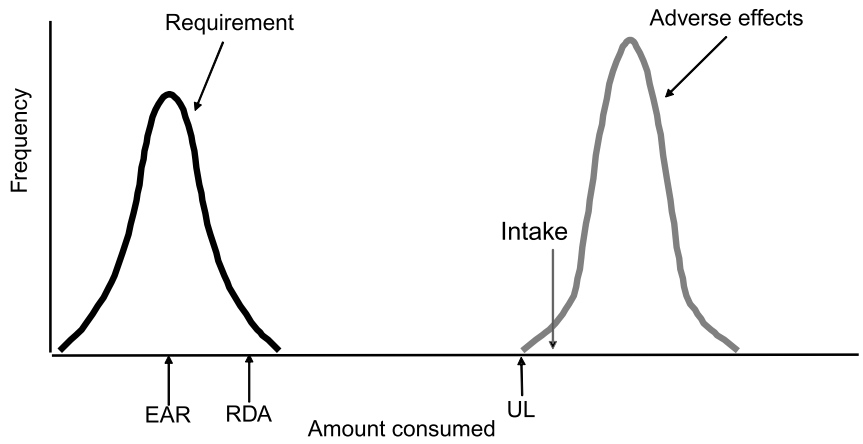

FIGURE 3-1 Hypothetical distributions of nutrient requirements and adverse effects. Intake at the amount indicated by the intake arrow would pose some risk, but without knowing the actual distribution, further interpretation would be problematic.
NOTE: EAR = Estimated Average Requirement; RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level.

Without a distribution, no method is available that can be used to interpret the prevalence of intakes above the UL. It would be desirable to be able to provide a quantification of the risk of an adverse effect rather than being limited to a statement that a certain percentage of the population has intakes above the UL.

Are Some Risk Assessment Methods Applicable to Both Nutrient Requirements and Upper Levels?

Murphy posed several questions about risk assessment methods that might be applicable to both nutrient requirements and upper levels:

- Does the concept of a NOAEL apply to nutrient requirements? If so, the value would need to be at an intake higher than the RDA, which has an estimated 2 to 3 percent risk of inadequacy.
- Are there similarities between a NOAEL and an Adequate Intake (AI)? For example, since the AI serves as a threshold, in some

cases it might be comparable to a NOAEL; that is, intakes above this threshold would not pose a risk of inadequacy.

- Should uncertainty factors be used when nutrient requirements are set? The distribution around the EAR expresses uncertainty; but, perhaps, other uncertainties should be addressed more explicitly, such as extrapolations of requirements from one age or sex group to another.

How Do the Different Approaches Limit the Uses of the DRIs?

Knowing the distribution of requirements for a nutrient allows the estimation of the prevalence of inadequacy. The situation is somewhat different for adverse effects. In particular, knowing a threshold for adverse effects allows estimation of the proportion of the population at risk of adverse effects, not the proportion experiencing adverse effects.

The WIC population provides an example of differences in the usefulness of the EAR and the UL. In a study conducted to evaluate the potential benefits and risks of revising the WIC food packages (IOM, 2006b), benefit was defined as a reduction in the prevalence of inadequate nutrient intake (intakes less than the EAR), or a reduction in the prevalence of excessive nutrient intake (intakes greater than the UL), or both. Risk was defined as an increase in either of these. The analysis predicted that the revised food package would lead to a reduction in the prevalence of inadequate iron intakes, which should be measurable as a decrease in the prevalence of women with poor iron status. In contrast, despite the predicted substantial reduction in the prevalence of excessive vitamin A intakes by formula-fed infants ages 6 to 12 months, it is unclear whether a reduction in adverse effects (anorexia, hyperirritability, skin lesions) would be expected as a result of the changes in the food package.

Concluding Remarks

To identify commonalities and to align the methods better, Murphy recommended a review of the models that have been used to set nutrient requirements and ULs. She suggested that a more consistent approach to the various methods for the establishment of the DRIs could increase

their scientific credibility and their usefulness in assessing and planning intakes.

LESSONS ABOUT NUTRITIONAL RISK ASSESSMENT LEARNED FROM THE FOOD AND AGRICULTURE ORGANIZATION/WORLD HEALTH ORGANIZATION TECHNICAL WORKSHOP

Presenter: Christine L. Taylor

In her presentation, Christine Taylor provided an overview of the work carried out during a technical workshop on nutritional risk assessment from the perspective of lessons that may be relevant to this Food Forum Workshop on Nutritional Risk Assessment. She also identified special considerations that call for multidisciplinary expertise and made closing remarks.

Overview of the Workshop in Geneva

In May 2005, 18 international scientists with a range of expertise met in Geneva, Switzerland, for the Food and Agriculture Organization/World Health Organization (FAO/WHO) Technical Workshop on Nutrient Risk Assessment. The participants examined the long-standing scientific principles of risk assessment that had been established for nonnutrient substances, and taking into account the principles of nutrition science, they worked to adapt them for nutrient substances. The resulting publication, *A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances: Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment* (FAO/WHO, 2005), is available at http://www.who.int/ipcs/methods/nra/en/index.html.

Nutritional Risk Assessment Requires Adaptations of Classical Risk Assessment

From the beginning of that project, it was clear that the classical risk assessment approaches, which have been well established for nonnutrients, are useful for nutritional risk assessment but are not always directly

applicable to nutrients. They must be adapted to take into consideration a range of factors. These factors include the specific homeostatic mechanisms unique to nutrients; the metabolic and physiological differences among nutrients by age, sex, and life stage; and the need to provide nutritional risk assessment in the face of limited data. Another very important factor that distinguishes nutrients from nonnutrients is that nutrients are associated with two types of risk (dual risks) rather than just one type of risk. That is, nutrients may demonstrate a risk because of too little intake as well as because of too much intake, as shown in Figure 3-2. The interest is in estimating and characterizing both types of risk. Different data sets are used to produce the two risk curves. Despite the appearance of Figure 3-2, the curves are unlikely to be symmetrical.

Nutritional Risk Assessment Needs a Multidisciplinary Perspective

During the FAO/WHO technical workshop, it was noted that a range of expertise is essential to adapt risk assessment approaches to nutrient substances and to carry out the assessments appropriately. Bailar and

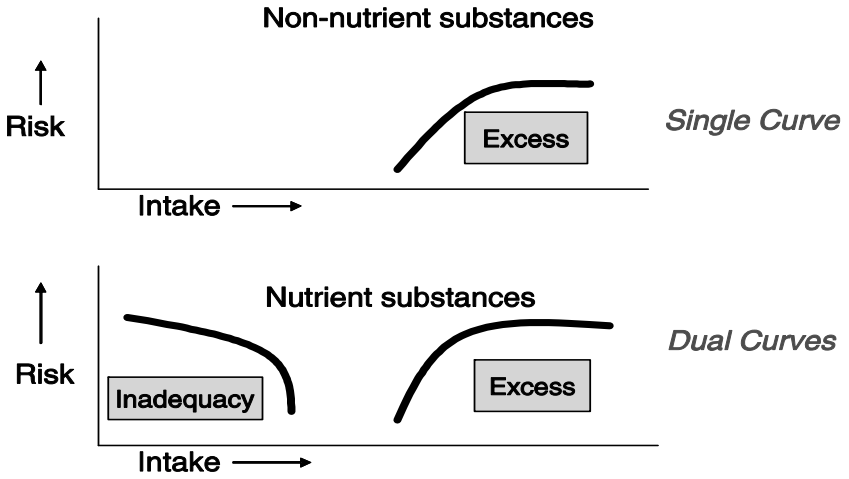

FIGURE 3-2 Comparison of the relationship between intake and risk for nonnutrient and nutrient substances. Nutrients differ from nonnutrients in that nutrients present dual risk curves (that is, risk curves for both inadequacy and excess).

Bailer (1999) referred to risk assessment as "the mother of all uncertainties." Uncertainty is inherent because of the limited nature of the data, an incomplete understanding of the process, and the different ways of viewing the questions. An expert's disciplinary background is likely to influence the way in which that expert views and discusses uncertainty, including variability.

Thus, nutritional risk assessment needs to include and to give mutual respect and equal weight to a wide range of experts: risk assessors, nutritionists, clinicians, physiologists, pathologists, epidemiologists, biochemists, food scientists, statisticians, and, perhaps, others. Furthermore, trained experts in risk assessment inform and facilitate the general decision-making process. As the discipline of risk assessment gains experience, the models and approaches available may evolve. For instance, in nonnutritional risk assessment, there is now some movement away from cut-point, qualitative, or policy models and toward probabilistic or quantitative models. Quantitative models portray risk as a distribution (such models require considerable data). Nutritional risk assessors may need to consider these newer models in the future.

Key Aspects of Nutritional Risk Assessment That Call for Multidisciplinary Expertise

Specific Homeostatic Mechanisms

Specific homeostatic mechanisms allow the maintenance of normal body functions in the presence of various intakes of essential nutrients. Examples include the following:

- changes in iron stores lead to increases or decreases in the absorption of iron, as appropriate;
- the blood calcium concentration acts in the regulation of the renal conversion of vitamin D to the active vitamin D hormone;
- the renal excretion of calcium occurs when the concentration of the mineral in blood exceeds a threshold;
- the liver stores excess vitamin C until the capacity of the liver is exceeded.

Appropriate multidisciplinary expertise allows careful consideration of such mechanisms in nutritional risk assessment.

Age, Sex, and Life Stage

Risk assessment for nonnutrients often considers lifetime exposures, and the risk is expressed on the basis of body weight. When nutritional risk is assessed, special consideration must be given to a person's age, sex, and life stage. The nutrient-related metabolic and physiological states differ depending upon such factors, and these factors can result in different intake–response relationships and different adverse effects. Multidisciplinary expertise helps make it possible to address such factors appropriately.

Extrapolation or Scaling

When data on the relationship between intake and response are lacking for some age and sex groups or for people at certain life stages, extrapolation or scaling is an approach that uses data from one group to make estimates for another group. Extrapolation for nonnutrients often uses body weight as the basis; but for nutrients this approach may have drawbacks because it does not take into account intermediary metabolic rates, energy intake, or the basal metabolic rate. More appropriate approaches may use surface area or energy requirements as the basis for extrapolation. The basis used for extrapolation can have substantial effects on the estimates that are made. Multidisciplinary expertise may help with the selection of the best approach to extrapolation and scaling.

Intake Assessments

Uncertainties associated with intake assessments often play a minor role in classical risk assessment. To be conservative on the side of safety, classical risk assessment may use large correction factors (called default options in Chapter 2). When the correction factors are large, the biases or errors associated with intake estimates are less relevant. In the case of nutrients, however, the use of large safety or correction factors is seldom an option because they could lead to an upper level that is too low to ensure an adequate intake. Therefore, in nutritional risk assessment, careful

attention should be directed to the nonsystematic bias, errors, and variability associated with intake estimates. Moreover, to obtain an estimate of total intake, it may be necessary to combine intake data from different sources, thereby introducing additional challenges. Such challenges call for the nutritional risk assessment team to include individuals with various types of expertise.

Other

In general, data have not been systematically generated for nutritional risk assessment. Instead, nutritional risk assessors must usually rely on secondary data obtained from studies of the benefits or mechanisms of action of nutrients. The guidance and criteria needed for decision making in the face of limited data call for the use of a multidisciplinary approach to nutritional risk assessment. Because concerns about protection of the public's health may drive the final decisions that are made about nutritional risk, the inclusion of individuals with a diversity of expertise helps ensure that the most appropriate questions will form the basis for a systematic review of the data.

Terminology also presents a challenge. Terms such as "hazard," "dose," and "exposure" have different meanings or may be troubling or perplexing to experts from different disciplines. The milieu of a multidisciplinary approach helps overcome this challenge.

Concluding Remarks

In her closing comments, Taylor pointed out that the need to view nutritional risk assessment through a number of perspectives is underscored by the Hindu parable about six blind men who went to see the elephant. Each man was certain that he knew the nature of the elephant, but in fact, each had touched only a part of the animal. Therefore, each man was partly correct and partly incorrect in his assessment. One of the most important lessons learned during the Geneva workshop was that nutritional risk assessment requires the involvement of experts from many fields and the establishment of an environment that respects and gives equal weight to each one.

EXPANDING METHODS USED IN NUTRITIONAL RISK ASSESSMENTS

Presenter: Barbara Petersen[2]

Nutrient intake by consumers is undergoing change. In the past, huge swings in the intakes of some nutrients occurred seasonally, diets may not have been adequate for optimal health, and the focus of assessment was on deficient intakes of a relatively small number of nutrients. Today, however, there is reason for concern about both excess and deficient intakes, interest in the wide array of beneficial components of food has grown, there are fewer seasonal differences in food patterns, consumers want improved foods without adverse effects on the taste of the foods or on health, and food processors can readily modify foods. Such changes call for a review of assessment methods. Barbara Petersen provided an overview of current assessment methods, described a tool (the Beneficial Utility Index) that is being designed to quantify the relationships between benefits and risks at different intake levels, and summarized the reasons for the use of such an index.

Overview of Current Assessment Methods

Some background information is helpful in understanding the extent to which classical risk assessment paradigms are useful in nutritional and functional food evaluations, whether they are holding back progress (and if so, how), and unique aspects of safety assessments for nutrients.

Classical Risk Assessment Methods

Classical risk assessment methods incorporate many variables and assumptions to quantify exposures and risks. The methods, with some modification, should be useful for evaluating nutrients. A quick look at the differences in methods used for toxic substances and pharmaceuticals will help guide the selection of the best method for nutrients.

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[2]Barbara Petersen acknowledged her coworkers who helped with the development of the Beneficial Utility Index and named Nga Tran and Layla Barraj, who attended this workshop.

Toxic substances Because toxic substances are presumed to offer no benefit to consumers, interest in the public health outcomes of exposure to toxic substances calls for the substances to pose no risk to the consumer. The results of tests conducted in animals predominate in assessments of the risk of potentially toxic substances. Thus, the risk assessment process is designed to be very conservative (erring on the side of safety) and to use worst-case scenarios for potential toxic responses. In addition, standardization of the assessment methods is important so that policy decisions are consistent.

Pharmaceuticals Because pharmaceuticals are presumed to provide consumer benefit, some adverse effects may be acceptable. Testing of the substance is done in both animals and humans. Human studies are essential for assessment of the potential risks of pharmaceuticals. Risk assessments are less conservative, and information about the benefits and the risks is communicated to consumers.

Safety Assessments

Typically, safety assessments involve a simple comparison of an Acceptable Daily Intake (ADI), which is estimated using animal toxicology or human studies and expressed per kilogram of body weight per day, with an Estimated Daily Intake (EDI), which is determined per kilogram of body weight per day. If the ADI is greater than the EDI, the substance is acceptable. If the ADI is less than the EDI, either the substance is unacceptable or further research is required.

Nutritional Assessments

Nutritional assessments are more complicated than classical risk assessments because they try to balance benefits and risks. Various mechanisms affect the absorption, metabolism, storage, and excretion of nutrients. The risks and benefits may differ according to the underlying biochemical mechanisms, the time frames of exposure, and the subpopulations who consume the nutrient. Because of potential adverse outcomes to the health of the public, attention must be directed to the quality of nutrient intake estimates: What are the effects of overestimating or underestimating intakes? How can the estimates be improved? How can

descriptions of the quality of the intake estimates be improved? Other questions related to nutritional risk assessments include whether nutrients should be treated more like toxic compounds or like pharmaceuticals and how to consider both the benefits and risks that nutrient intake may pose.

Many, if not all, nutrients are essential and also potentially toxic; they pose risks (e.g., nutrient deficiency) at low intake as well as at high intakes (e.g., nutrient toxicity). Typical plots of these dual risks, as in Figure 3-2, have a number of limitations. In particular, they

- do not address the degree of variability in dietary intakes,
- do not balance the severity of the adverse effects of selected intakes of a nutrient against the biological benefits of the nutrient, and
- do not help describe the benefits and adverse effects that operate over very different time scales or by different biochemical mechanisms.

Beneficial Utility Index

The Beneficial Utility Index (BUI) is a tool proposed for use for quantification of the relationship between the benefits and the risks of nutrient intake under different intake scenarios.[3] The tool is intended to be useful in addressing two desired public health outcomes both in the short term and over a lifetime: (1) maximizing efficacy (benefits) and (2) minimizing toxicity (harm). The tool would also help provide an understanding of situations that affect the ratio of benefit to harm.

Data and Models Used

The BUI is designed for use with populations and not individuals. It incorporates dose–response curves for benefits (for example, the impact of either reducing a nutrient deficiency or improving nutritional status), dose–response curves for harm, and weighting factors. The most important or the most sensitive effects (markers) to be included in the model must be prioritized. Examples of markers for the benefits of increasing

[3]The approach was adapted from research for evaluating pharmaceuticals conducted by J. Venitz at Virginia Commonwealth University.

the intake of a food component include the concentrations of nutrients in the blood**,** enzyme activities, antioxidant function, and platelet status.

The BUI considers sources of variability, such as short-term and long-term dietary practices (including those affecting the bioavailability of the nutrient) and differences in individual requirements for the nutrient.

Beneficial Utility Index Curves

Two curves are used to develop the BUI: (1) the benefit–efficacy distribution curve, which is a distribution of the probability of the occurrence of the defined benefit at different intake levels, and (2) the toxicity distribution curve, which shows the distribution of the probability of the occurrence of negative consequences. These curves are combined mathematically to compute the BUI, which is depicted in Figure 3-3.

The next step is weighting the BUI to reflect the severity of the outcomes that result from a deficiency of a nutrient (that is, the degree of potential benefit of improving nutritional status), the severity of the toxic effects from the nutrient, the amount of uncertainty in the data, the biological variability in the population, and the variability in intake of the nutrient.

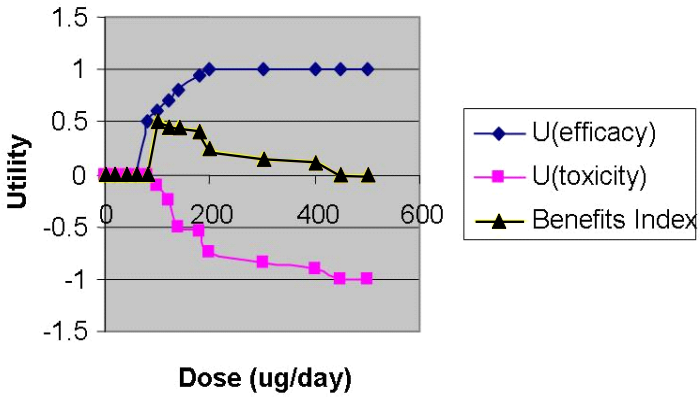

FIGURE 3-3 Beneficial Utility Index. U = utility.

Hypothetical Example Using a Beneficial Utility Index

Petersen presented an example in which hypothetical nutrient GYX had been shown to improve brain development in children and to be essentially free of adverse effects except for an occasional skin rash that is reversible with a decreased intake of GYX. In this example, a literature review revealed that a similar hypothetical compound, GYZ, causes diarrhea at elevated doses, which is a reason for concern. Data regarding GYZ could be used to derive weighting factors at different doses, which could be applied to the index. Methods can be used to incorporate uncertainty into the efficacy and toxicity curves and, thus, into the BUI, as depicted in Figure 3-4.

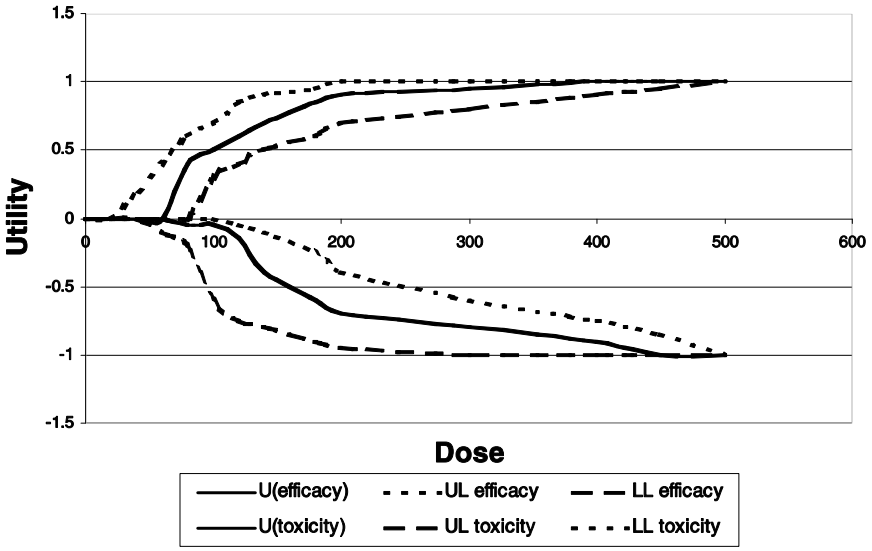

FIGURE 3-4 Impact of the BUI: Incorporating the uncertainty into the efficacy and toxicity curves: example of the impact on the BUI by using hypothetical nutrient GYX. U = utility; LL = lower limit; UL = upper limit.

Concluding Remarks

Petersen took the position that nutrients and other beneficial components of food need their own tool for use in the evaluation of their risks and benefits. The tool needs to include both benefits and risks (likelihood and severity) and to allow an understanding of the dose–response, the timing of consumption, differential mechanisms of action, and consumer compliance with dietary guidance. The potential advantages of a utility index include the ability to (1) quantify the relationship between benefits and risks, (2) understand uncertainty and variability more completely, and (3) incorporate additional factors to weight the results.

KEY CHALLENGES IN RISK-BASED APPROACHES TO NUTRITION POLICY

Presenter: Gregory Paoli

Risk assessment is a processing tool. Risk assessors process evidence to generate statements of the probability of individual events. They combine these probabilities to determine the probability of an adverse outcome of interest. According to Gregory Paoli, the primary value of risk assessment lies in its ability to infer the probability of adverse outcomes by appropriately combining a formal representation of the risk-generating system with the rules of inferring probability. He also noted that the approach used to set the EAR, which uses distributions of inadequacy, involves elements of risk assessment.

Risk-Based Advice

Risk-based advice may be based on a formal risk assessment or on a safety assessment.

Formal Risk Assessment

Formal risk assessments may be conducted on the basis of two rationales: a practical rationale or a public policy rationale.

Practical rationale Two features provide a practical rationale for conducting formal risk assessment: the process (1) allows the management of problems of overwhelming complexity and (2) provides links to appropriate tools. The complexity relates to multiple hazards, multiple pathways, multiple agents, multiple outcomes, and cascading events, all in the face of much uncertainty. Probability provides a multidisciplinary language. This makes it possible to use the tested tools of the decision sciences and of the risk and reliability sciences to help address the problem.

On the other hand, risk assessment may require too much time and too many resources to solve a problem. It may prevent decisions from being made.

Public policy rationale In matters of public health, there is a desire for the use of a rationale that calls for decisions to meet a standard of reasonableness. What one is accountable for may determine whether a risk assessment or a safety assessment is the preferred approach.

Safety-Based Standard Setting

Safety-based standard setting differs substantially from risk assessment. The safety-based standard setting approach includes no estimate of the probability of harm and ordinarily includes no exposure assessment. One cannot use the safety assessment approach to predict risk, even when an exposure assessment has been completed. ULs represent the values set by using safety-based standard setting. The UL value (for example, 2 grams of a certain nutrient per day for adults) includes uncertainty, variability, uncertainty about the variability, and value judgments. It can be an adequate risk management tool, but it does not represent the outcome of a risk assessment.

Basic Elements for Risk-Based Advice

According to Paoli, three elements are necessary for use of the term *risk-based advice*:

1. Decisions are based on explicit knowledge and a description of the full risk-generating system, including hazards, pathways, and outcomes.
2. The process includes measurements on the dimensions of likelihood and the magnitude of consequences.
3. Decisions are based on their capacity to reduce risk at reasonable cost.

Such advice is needed for complex situations involving a variety of risks, for example, the multiple risks facing a certain group of people, such as the Inuits of northern Quebec, Canada.

Disability-Adjusted Life Years

The concept of disability-adjusted life years attempts to describe the burden of disease by considering the duration and the severity of health outcomes. This concept can be combined with data on the frequency of occurrence of the specific disease to become a useful part of risk assessment. Paoli encouraged the use of this approach.

Risk Communication

Risk management may result in a communication product (the analogy that Paoli gave was an air quality health index) that results in behavioral change. When risk is mitigated through a communication product, it would be useful to extend the risk assessment paradigm to include an estimate of the amount of risk reduction that results from communication of the risk.

Concluding Remarks

Reasonableness is a complex combination of the evidentiary, managerial, and obligatory aspects of decision-making processes. Risk assessment provides a structure for providing these elements in a defensible way. Risk assessment also opens a large multidisciplinary tool kit for analysis, clear and succinct presentation of the knowledge, and decision making.

COMMENTARY

Discussant: Sanford A. Miller

In his brief commentary, Sanford Miller highlighted a few of the challenges facing nutritional risk assessment and proposed several steps for addressing the challenges.

Challenges for Nutritional Risk Assessment

Classical risk assessors address the risks associated with single very small events and thus tend to think in terms of precision and to have models with high specificities. In contrast, those who assess the risks of nutrient substances must take into account the fact that the substance may affect multiple systems or organs. How can risk assessors factor the multiple effects into a risk assessment? In addition, how can they address both the risk and the benefit of the same substance? Many of the default decisions made in nutritional risk assessment have been made on an ad hoc basis, differing from substance to substance, dose to dose, and expert group to expert group.

Clearly, the inclusion of a variety of individuals with diverse skills is important in nutritional risk assessment. It can be challenging, however, to gather all the experts needed to conduct an appropriate risk assessment. Moreover, it often is difficult for the experts to understand each other.

Possible Steps to Address the Challenges

Among the steps that Miller proposed are the following:

- Agree on a set of criteria for the selection of outcomes to be used in a nutritional risk assessment.
- Agree on default options to be used to address uncertainties.
- Develop training programs in the area of nutritional risk assessment. Such academic programs would need to cover all or most of the areas that are used in the risk assessment process.

OPEN DISCUSSION

Moderator: Molly Kretsch

The key points that were raised in the open discussion have been incorporated into Chapter 6, Perspectives on Challenges and Solutions: Summary Remarks and Suggested Next Steps.

4

Establishing Relationships Between Dietary Patterns and Health Outcomes

The complexities of diet and of diet-related diseases complicate nutritional risk assessment. This chapter covers information on the challenges in establishing relationships between food patterns and health outcomes, the use of evidence-based reviews for linking dietary factors with chronic disease outcomes, and the use of evidence-based reviews for evaluating health claims for use on food labels.

In introducing the session, Michael Doyle commented on risk assessments of *Listeria monocytogenes*, a microbial pathogen. Those risk assessments made it possible to prioritize the types of foods that are most important as vehicles for *Listeria* and that are thus targets for action to improve the public's health. He expressed the hope that eventual outcomes of this workshop will be the ranking of risks and the engagement in other opportunities for advancing the nutritional aspects of food that could improve the public's health.

CHALLENGES IN ESTABLISHING RELATIONSHIPS BETWEEN FOOD PATTERNS AND HEALTH OUTCOMES

Presenter: Julie Mares

The relationships between diet and chronic disease differ in character from the relationships between diet and deficiency or between diet and acute disease, but the techniques available for evaluating them often do not reflect this. Using examples from her research on age-related macular degeneration (AMD), Julie Mares highlighted common and often overlooked sources of uncertainty that bias the interpretation of relationships

between diet and chronic disease and that often lead to the drawing of wrong conclusions. These involve (1) the complex and slowly developing nature of chronic disease, (2) the timing and broad nature of dietary influences on the development of chronic disease, and (3) the bias imposed by limitations inherent in specific study designs. Mares also suggested strategies that could be used to reduce the impacts of these biases to improve the interpretation of the long-term and complex relationships of diet to chronic disease. Delgado-Rodrigous and Llorca (2004) provide comprehensive coverage of the issues related to the internal validity of studies.

Relevant Features of Chronic Diseases

Chronic diseases typically develop in several stages, over long time periods, and in people who live a long time. Such diseases are multifactorial. Typically, they involve a number of pathogenic mechanisms; are influenced by one's environment, lifestyle, and genetic attributes; and are associated with comorbid conditions.

In addition, the effects of nutrients may differ at different stages of a disease. In cancer, for example, the effects may differ during the initiation, promotion, and progression of the cancer. In AMD, the potential for a person to obtain the beneficial effects from the carotenoid lutein appears to relate to the stage of the disease. The current evidence that lutein and zeaxanthin (another carotenoid) reduce the risk of disease progression is stronger for the later stages of AMD than for the earlier stages.

Chronic diseases develop over decades, as shown in Figure 4-1. Among people exposed to conditions that increase the risk, however, relative risks for many chronic diseases decrease with age. This apparent decrease in risk could reflect two factors: (1) the changing nature of the surviving cohort and (2) selective mortality bias. For diseases that strongly increase in prevalence with age (such as AMD) these two factors can reduce the apparent influence of protective factors.

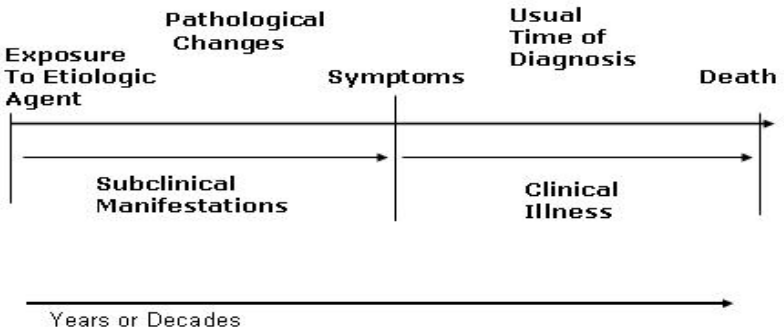

FIGURE 4-1 Chronic diseases develop over decades.

Addressing Uncertainties Relating to the Influence of Diet

Investigators have used a variety of markers of dietary intake, including both external and internal markers. A number of factors may influence these markers, as shown in Figure 4-2. Mares called for the use of dietary intake as the anchor of all markers because it provides the opportunity to study many aspects of diet concurrently and because dietary intake estimates facilitate comparisons across studies.

Biomarker data are useful complements to the dietary data. Biomarker data can be used to circumvent errors in nutrient databases and inaccuracies in people's reports of what they eat. Such data reflect influences on the absorption and turnover of a food component. A typical biomarker, such as the blood concentration of a nutrient or metabolite, reflects a single dietary constituent. Increasing evidence suggests, however, that the intake of other nutrients can modify the influence of any single nutrient. Therefore, the use of biomarker data to evaluate the relationship of diet to chronic disease is useful only when such data are complemented with measures of broad aspects of the diet, which can be obtained from detailed food frequency questionnaires.

Biomarkers reflect intake over a short time. Using data that reflect a few weeks of intake imposes a large error when relating the intake to a condition that develops over decades. The random error is compounded with bias in studies of middle-aged and older adults whose intakes change with time and also change in response to the presence of other chronic diseases that may increase risk for the disease being studied. (Cardiovascular disease, for example, may lead to dietary change and it

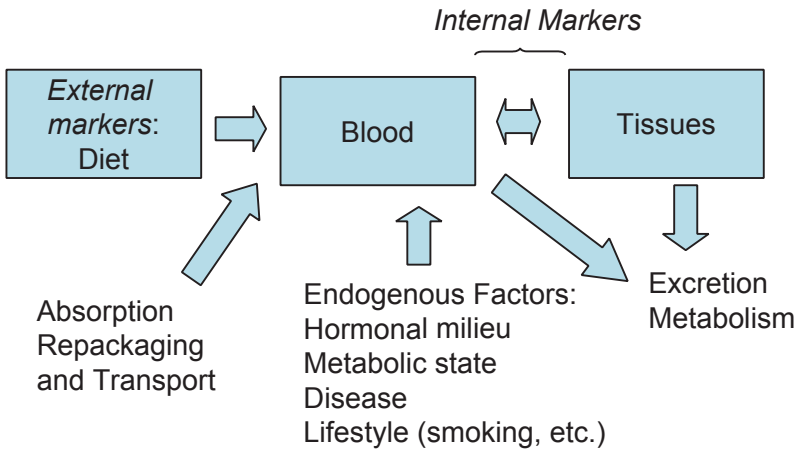

FIGURE 4-2 Types of markers of dietary intake and the factors affecting them.

increases the risk of AMD.) The result may be an apparent deleterious association between blood concentrations of a nutrient and the disease when, in fact, the nutrient is protective. That is, the analysis produces a completely wrong answer.

Diet–Time Period Relationships

The period during which diet is measured may have more of an impact on the precision of the estimate than the method used to measure the diet. Thus, the period covered by the measurement may bias the results. In estimating the odds ratios for the prevalence of AMD according to whether a person's diet was high or low in saturated fat, for example, Mares-Perlman and colleagues (1995) observed that dietary assessment at the baseline gave odds ratio estimates very different from those obtained from retrospective estimates of the diet consumed 10 years earlier. For this reason, it is optimal to obtain multiple estimates of dietary intake over the time period that is expected to influence the development of the disease being studied. When this is not possible, it is better to collect retrospective estimates of dietary intake than to ignore the past diet altogether. Others have demonstrated that people's recall of the diet that they

consumed a decade earlier is a better reflection of what they actually ate than their more recently recalled diet (Byers et al., 1987).

Changes in diet over time may introduce additional uncertainty. More than half of the population over the age of 65 years has three or more chronic diseases. Since chronic disease often influences diet, current dietary intake of older people may not reflect their diet over most of their adult lives. In a study that collected dietary data for two different periods, Moeller and coworkers (2006) computed multivariate-adjusted odds ratios for intermediate AMD among women whose diets were high and low in lutein and zeaxanthin. When the investigators compared women of all ages, they found lower odds ratios if they excluded women with unstable diets.

Other Factors That Affect the Influence of Diet on Disease

Other risk factors may modify the influence of diet. For example, people with poor diets may be lost from the cohorts being studied. In addition, the proportion of people who are susceptible to the influence of diet may change. For example, Ogren and colleagues (1996) found that among men born in 1914, 26 percent of smokers and 31 percent of those with hypertension at age 55 years died before the age of 68 years. Thus, the proportion of a surviving cohort with long-term chronic conditions can decrease with increasing age in a study sample.

Strategies to Enhance the Study of Diet and Chronic Disease

Both the splitting and the lumping of data can be useful in enhancing the study of diet and chronic disease, as described below.

Splitting of data Subgroup analyses, which involve the splitting of data, are important both within and across studies. Such analyses need to reflect the stage of the disease in the natural history of the disease, the time period in the natural history of the disease, the absence or presence of other risk factors, and the age of the individual or the presence of comorbid conditions. To evaluate these potential biases, one can evaluate the risk ratios across strata defined by age, disease severity, and the presence of other risk factors. This approach provides valuable information even if one does not detect statistically significant interactions of the

primary association. Mares calls for more attention to this issue in the publication of epidemiological associations in samples of people over 50 years of age.

Lumping of data The lumping (grouping) of data can be useful for assessment of the dietary attributes that influence similar pathogenic mechanisms. It can also be useful and efficient to lump several outcomes in each study.

Contributions of Different Study Designs

As depicted in Figure 4-3 and briefly discussed below, studies of different types can make a valuable contribution to the body of evidence used in nutritional risk assessment. Differences in findings from different types of studies offer an opportunity to find the reasons for those differences.

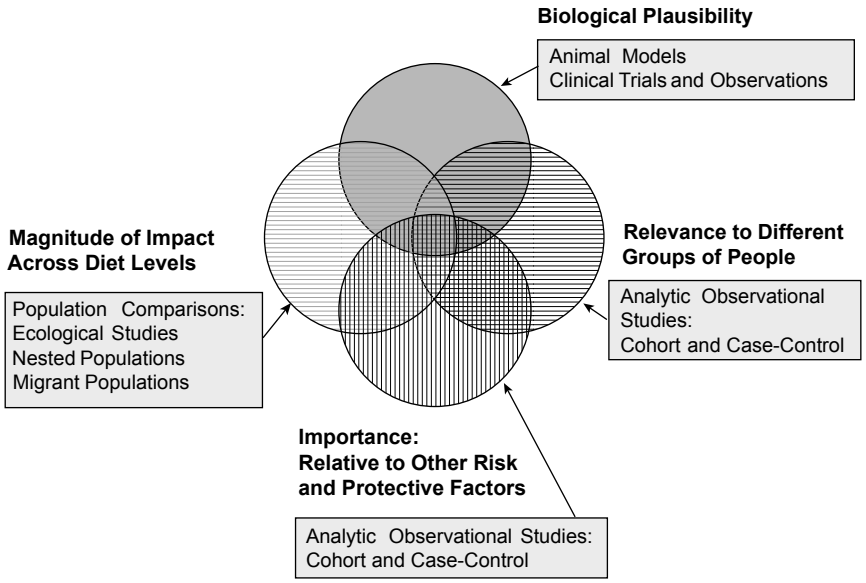

FIGURE 4-3 Uses of different types of studies in examining the body of evidence. The results of studies with different designs can contribute unique insights. The ability to make inferences about the causal influences of dietary attributes or patterns in the development of chronic disease is strengthened when all types of evidence point in the same direction.

Animal Models for Age-Related Chronic Diseases

Animal models for chronic disease either do not exist or are very limited. The models that are available often do not reflect various aspects of human disease, such as the natural history of the disease and environmental, medical, and dietary influences. Thus, investigators mainly rely on human studies to evaluate the impact of diet on human disease. Nevertheless, animal models may be useful for examining the biological plausibility of effects of particular dietary components or the synergy between two dietary components.

Observational Studies

Cohort and case–control study designs provide useful information about the relationships of diet to health, including the importance of diet relative to the importance of other risk- and protective factors among large groups of people. Other population comparisons and ecologic studies provide information about the impacts of a wide range of diets and conditions.

Randomized Clinical Trials

Clinical trials are useful for determining biological mechanisms and plausibility. Mares views randomized clinical trials as part of a toolbox rather than the "gold standard" for the collection of evidence. The applicability of the conclusions from such trials are often limited to single nutrients or groups of nutrients, the doses of the nutrient(s) given, the form of the nutrient(s) tested, the duration of treatment, and the characteristics (e.g., high or low risk) of the study population. Loss to follow-up can bias the findings of a study, and investigators often do not adequately evaluate this problem. Cost factors may preclude the testing of modifying factors, such as other aspects of the diet and a person's genetic makeup, physical activity, lifestyle, and medical history.

Clinical trials complement results of observational studies. For example, the Rotterdam Eye Study showed that diets rich in the components of the supplements used in the Age-Related Macular Degeneration Study reduced the incidence of intermediate AMD by 35 percent (Van Leeuwen et al., 2005).

Mares listed several ways to improve the utility of clinical trials in the understanding of diet and disease, namely (1) the use of shorter, intermediary endpoints, especially those common to the development of many chronic conditions; (2) studies of the natural history of the disease; and (3) broader studies that address multiple dietary attributes. Examples of such studies include the Dietary Approaches to Stop Hypertension (Sachs, 2001) and the Mediterranean Diet used in the Lyon Heart Study (De Longeril, 1999).

Concluding Remarks

In closing, Mares encouraged investigators to take a bird's eye view by observing more and by broadening trials:

- Observe more by using multiple study designs, large or pooled data sets, diet estimation complemented with biomarkers, and subgroup analyses, with less concern about the statistical significance of interactions.
- Broaden trials so that they study a variety of disease outcomes, especially intermediate stages that reflect biological mechanisms, and a variety of dietary attributes.

EVIDENCE-BASED REVIEW PROCESS TO LINK DIETARY FACTORS WITH CHRONIC DISEASE

Presenter: Alice H. Lichtenstein

The application of the evidence-based review process to matters of public health importance has been expanding. Alice Lichtenstein provided an overview of the evidence-based systematic review process and used omega-3 fatty acids to illustrate how this process can be a useful tool for addressing nutrition-related issues. The example, omega-3 fatty acids and cardiovascular disease (CVD), came from work conducted at Tufts-New England Medical Center under the auspices of the Agency for Healthcare Research and Quality (AHRQ). AHRQ evidence reports and summaries are available at http://www/ahrq.gov/clinic/epcquick.htm.

Steps in the Evidence-Based Review Process

Many steps occur in the evidence-based review process, as summarized below:

- Form a technical expert panel that includes stakeholders and the key people to guide the group.
- Refine the key questions. This is the most important step in the process.
- Identify search terms, using enough terms to identify all the relevant literature while minimizing extraneous articles.
- Develop the inclusion and the exclusion criteria. Examples of such criteria include the minimum and maximum doses, the minimum number of subjects per study, the minimum information on the intervention required, and the basic criteria used for the study design.
- Conduct the literature search by using predefined databases. This includes examination of the reference lists of reviews and primary articles and contact with domain experts to identify relevant articles missed by the database searches.
- Screen abstracts for potentially relevant articles.
- Retrieve the full articles selected.
- Review the articles according to the predetermined criteria.
- Extract data from the articles that meet the criteria. The PICO approach is useful for this step. It involves focusing on the population (P), the intervention (I), the comparator group (C), and the outcome (O).
- Grade the studies for their methodological quality and applicability.
- Develop data tables. These typically include (1) summary tables that present data on sample size, intervention, duration, results, and quality and (2) summary matrices that place studies in a grid based on methodological quality and applicability.
- Perform additional analyses (e.g., a meta-analysis), as appropriate.
- Draft the report.
- Send the report out for peer review.
- Revise the report as needed.

Overview of an Evidence-Based Review: Omega-3 Fatty Acids and CVD

Two of the specific questions asked in the review of omega-3 fatty acids and CVD were:

1. What is the efficacy or association of omega-3 fatty acids in preventing incident CVD outcomes in people without known CVD (primary prevention) and with known CVD (secondary prevention)?
2. What adverse events related to omega-3 fatty acid dietary supplements are reported in studies of CVD outcomes and markers?

The PICO approach was used to address these questions, as follows:

- The populations (P) covered subjects in studies of both primary prevention and secondary prevention.
- The interventions (I) included alpha-linoleic acid in addition to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
- The comparators (C) were diets and other oils (e.g., an oil in the placebo capsules, which might be an oil that could affect the results).
- The outcomes (O) were all-cause mortality, myocardial infarction, stroke, and sudden death.

Among the inclusion criteria that were used were experimental or observational studies of at least 1-year duration with at least five human subjects, with reported original CVD outcome data, and with all sources of omega-3 fatty acid intakes evaluated.

In this evidence-based review, the possible ratings for methodological quality were as follows: least bias, the results are valid (rating of A); susceptible to some bias but not sufficient to invalidate the results (rating of B); and significant bias, may invalidate the results (rating of C). The following ratings were used for applicability: the sample is representative of the target population (rating of I), the sample is representative of a relevant subgroup of the target population but not the entire population (rating of II), and the sample is representative of a narrow subgroup of subjects only and is of limited applicability to other subgroups (rating of III). The possible ratings of the overall effect were as follows: a clinically meaningful benefit was demonstrated (rating of ++), a clinically

meaningful beneficial trend exists but is not conclusive (rating of +), a clinically meaningful effect is not demonstrated or is unlikely (rating of 0), and a harmful effect is demonstrated or is likely (rating of –).

The overall conclusions were that the intake of omega-3 fatty acids (EPA and DHA) from fish or fish oil supplements reduces the incidence of all-cause mortality and cardiac and sudden deaths but not stroke. The benefits of fish oil supplementation were greater in the secondary prevention studies than in the primary prevention studies. The adverse effects appeared to be minor, but data were limited and incomplete. That is, most studies either did not report on adverse effects or did not describe the tabulation method used.

Concluding Remarks

The conclusions drawn from systematic evidence-based reviews of relationships between dietary factors and chronic disease may differ. Divergences likely result from differences in the specific questions asked, the inclusion and exclusion criteria used, the statistical model used for analysis, and the quality rating system used. The process is challenging, in part because of the limited data available in the field of nutrition and human outcomes.

EVIDENCE-BASED REVIEW FOR HEALTH CLAIMS: A CASE STUDY

Presenter: Kathleen C. Ellwood

The Food and Drug Administration (FDA) is using an evidence-based review process as a basis for health claim language on food labels. Kathleen Ellwood provided background information on nutrition labeling and health claims, described the process for reviewing the scientific evidence, and summarized results from selected evidence-based reviews.

Background Information on Nutrition Labeling and Health Claims

The Nutrition Labeling and Education Act of 1990 serves as the basis for the current food labels, including the provisions that allow voluntary nutrition claims on food labels; and it covers health claims when they are authorized by the FDA. Health claims on food labels serve as a way to inform consumers about the relationships between the substances (food or component in food) and a disease. The U.S. Congress set "significant scientific agreement"[1] as the standard for substantiating health claims. As a result of court challenges under the First Amendment to the Constitution, the FDA was directed to provide for health claims that did not meet the significant scientific agreement standard. *Qualified health claims* are based on scientific evidence that is credible but that does not meet the higher standard.

Health claims are voluntary statements that address a causal relationship between a substance and either a disease or a health-related condition for the general U.S. population or for a subpopulation, such as women or the elderly population. The substance is to be able to reduce the risk of disease, not treat, prevent, cure, or mitigate a disease (*Whitaker v. Thompson*, 2004).

Process for Reviewing the Scientific Evidence

The process for reviewing the evidence for significant scientific agreement health claims and qualified health claims is the same; the level of supportive evidence distinguishes the two. In particular, the process involves the following steps (FDA/CFSAN, 2003b):

1. Define the substance–disease relationship.
2. Identify relevant studies.
3. Classify relevant studies.
4. Rate the relevant studies for quality.
5. Rate the studies for the strength of the body of evidence.
6. Report the rank.

[1]Abbreviated in FDA publications as SSA.

Definition of Substance–Disease Relationship

The *substance* means a specific food or a specific component of a food in a conventional food or a dietary supplement (FDA, 2006a). The *disease or health-related condition* means "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease) or a state of health leading to such dysfunctioning (e.g., hypertension" [FDA, 2006b]).

Identification of Relevant Studies

Relevant studies include intervention and observational studies that involve healthy people and that measure the risk of the disease or health-related condition named in the claim. Animal and in vitro studies, review articles, meta-analyses, and book chapters are not relied upon. The last three types of sources, however, may be used to identify additional relevant studies. Intervention and observational studies with fatal flaws are excluded. Examples of such flaws are the lack of a control group or a nonvalidated surrogate endpoint in an intervention study and the exclusion of key confounders of risk in an observational study.

Classification of Relevant Studies

FDA considers intervention studies to be the "gold standard" and uses intervention studies that measure modifiable risk factors. Among the observational studies, prospective cohort studies are considered more reliable than case–control studies and cross-sectional studies. Two key elements of such studies are the measurement of the intake of the substance and the handling of factors (such as age and weight) that could confound the results.

Rating of Quality

The factors considered in rating the studies for quality include the study design and the inclusion and exclusion criteria used, the balance of population characteristics, verification of compliance, and the statistical methods used.

Rating of Strength of the Evidence

The factors used to rate the strength of the body of evidence include the types, quality, and quantity of studies; the study sample size; the consistency of the findings; replication of the findings; and relevance to the general population or target subgroup.

Ranking

Different levels of scientific evidence result in different qualifying language, as shown in Box 4-1. The qualifying language provided in the task force report (FDA/FSAN, 2003a) provides examples only; the language may vary depending on the specific circumstances of each case.

Results from Selected Evidence-Based Reviews

Lycopene/Tomatoes and Cancer

In 2004, FDA received two petitions requesting a large number of health claims for tomatoes, tomato products, and the carotenoid lycopene in relation to reduction in the risk of cancer. The petitions cited a large number of publications and websites. Through a literature search, the FDA identified additional publications. None of the intervention studies identified were credible because all evaluated the *treatment* of men diagnosed with prostate cancer. A review of the observational studies eliminated many studies. Of the 13 relevant observational studies evaluating the relationship between tomatoes or tomato products and prostate cancer, 6 indicated a reduction in risk and 7 reported no association. The prostate cancer claim language statement for food labeling is, "Very limited and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer." FDA concludes that there is little scientific evidence supporting the claim.

BOX 4-1
INTERIM EVIDENCE-BASED RANKING SYSTEM FOR HEALTH CLAIMS[a]

Significant Scientific Agreement Health Claim: high level of comfort (A)
". . . may reduce the risk of . . . "

Qualified Health Claims
- Moderate/good level of comfort (B)
  " . . . not conclusive."
- Low level of comfort (C)
  " . . . limited and not conclusive."
- Extremely low level of comfort (D)
  " . . . Very limited and preliminary scientific research . . . ."

[a]The precise language used by the agency in exercising enforcement discretion may vary depending on the specific circumstances of each case.

SOURCE: FDA/CFSAN, 2003a.

Chromium Picolinate and Type 2 Diabetes

A review of the evidence identified five credible intervention studies of chromium picolinate intake and the risk of type 2 diabetes (T2D). Four of these studies showed no effect of chromium picolinate on blood sugar levels, and a single study showed a beneficial effect of chromium picolinate on insulin resistance. Qualifying health claim language in this case includes "a relationship between chromium picolinate and either insulin resistance or T2D is highly uncertain."

Green Tea and Breast Cancer

A review of the evidence identified three credible observational studies relating green tea intake to the risk of breast cancer. Two of these were prospective cohort studies that showed no relationship, and one was a case–control study that showed a beneficial relationship. Qualifying health claim language in this case includes "it is highly unlikely that green tea reduces the risk of breast cancer."

Concluding Remarks

Kathleen Ellwood encouraged participants to visit the FDA website for more detailed information on this topic.

OPEN DISCUSSION

Moderator: Michael Doyle

The key points made during the open discussion have been incorporated into Chapter 6, Perspectives on Challenges and Solutions: Summary Remarks and Suggested Next Steps.

5

New Developments in and Challenges to Nutritional Risk Assessment

A number of new developments can have an impact on nutritional risk assessment. In this session, moderated by Robert L. Buchanan, John Milner addressed the roles of nutrigenomics and population variability in nutritional risk assessment and challenges that these factors present; Amy Subar reviewed dietary intake assessment methods, and described innovative methods to collect and analyze food and nutrient intake data; and Joanne Holden described the major U.S. source of food composition data, the expansion of these data, and uncertainties and data needs. No open discussion occurred at the end of the session.

ROLES OF NUTRIGENOMICS AND POPULATION VARIABILITY IN NUTRITIONAL RISK ASSESSMENT

Presenter: John Milner[1]

John Milner described nutrigenomics as a three-phased prong that involves nutrigenetics, nutritional epigenetics, and nutritional transcriptomics (Figure 5-1). In his presentation, Milner focused on genomics, the very wide variability among individuals seen in study results, other complicating factors, and the potential value of genetic information.

[1]John Milner stated that the opinions that he expressed are his own and not necessarily those of the National Cancer Institute.

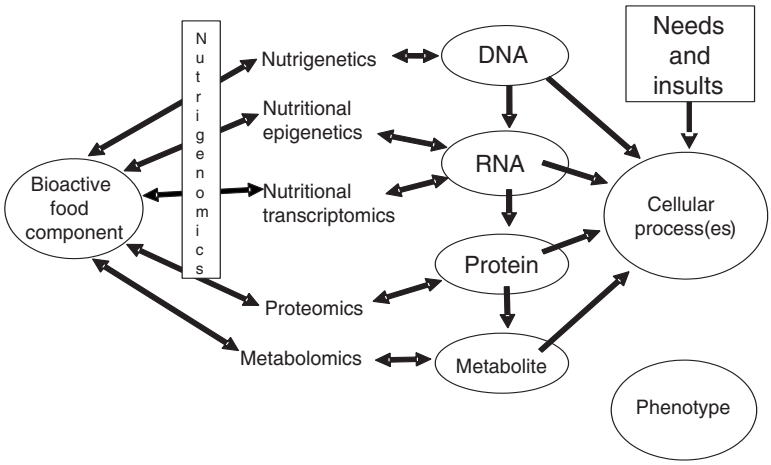

FIGURE 5-1 Interrelationships of bioactive food components, nutrigenomics, and other factors that influence cellular processes.

Genomics and Variability

Genomics is an exceedingly complex topic, in part because there are approximately 30,000 genes and 8 million to 10 million single-nucleotide polymorphisms (SNPs). Few intervention studies, however, have truly tested the importance of SNPs to gene expression. Most of the evidence about the effects of diet as an environmental stimulus on gene expression comes from observational studies of differences in the patterns of deoxyribonucleic acid (DNA) methylation in response to folate intake. Issa et al. (2001), for example, showed a 300-fold variation in the methylation pattern among individuals.

An individual's response to dietary interventions will depend in part on his or her genetic background (nutrigenetic effects), the cumulative effects of food components on genetic expression profiles (nutritional transcriptomic and nutritional epigenomic effects), the occurrence and activities of proteins (nutritional proteomic effects), and the dose and temporal changes in cellular low-molecular-weight compounds (metabolomic effects).

The examination of epidemiological data from studies on the relationships of food or food components to health outcomes reveals much variability in outcomes both among studies and within single studies. Examples include studies that have addressed the influence of soy on the

relative risk of breast cancer, the influence of tomato intake or plasma lycopene concentration (a potentially useful biomarker) on the relative risk of prostate cancer, and the influence of tomato and tomato product intake on serum lycopene concentrations. The wide variability in outcomes suggests that a number of factors may be involved, such as the region of the world where the study was conducted, the inclusion of both premenopausal and postmenopausal women, the form in which the product was consumed, and genetic differences among the subjects. Milner suggested that a solution may result from an increased understanding of genomics and of the associated genetic processes and how they affect the overall phenotype of an individual.

Other Complicating Factors

The Complex Nature of Food

Approximately 25,000 bioactive food components exist in the overall food supply. This leads to the question, "Which of the many dietary components are the most important for evaluating nutritional risk?" Candidates include essential nutrients but also many types of nonessential food components:

- phytochemicals, such as carotenoids and isothiocyanates;
- zoochemicals, such as conjugated linoleic acid and omega-3 fatty acids;
- fungochemicals, especially compounds with biological activity that are found in mushrooms; and
- bacteriochemicals, which are products formed during fermentation and compounds resulting from the action of the intestinal flora.

The prioritization of dietary variables poses a substantial challenge.

Microbes

Microbes account for about 9 percent of the cells in the human body, but ordinarily they are overlooked in studies. Mammalian genes can af-

fect the actions of some microbes that grow in the gastrointestinal tract. Among a large percentage of individuals of Asian descent, for example, gastrointestinal microbes metabolize soybeans to form equol, a substance that possesses anticancer properties (Decroos et al., 2005, 2006); but the occurrence of equol production varies widely among individuals and populations (Setchell and Cole, 2006).

Amounts and Times of Administration of a Food Component

In an intervention trial, Duffield-Lillico and colleagues (2002) found that the response to supplemental selenium differed by baseline selenium status. If the time of dietary exposure differs—before or after age 55 years, for example, in the study by Limburg et al. (2005)—the dietary exposure may create a different response among individuals. Moreover, a study by Swami and colleagues (2005) suggests that dynamic interactions among different food components may influence the quantity of a substance needed for a response.

Potential Value of Genetic Information

Genetic information may assist the nutritional risk assessment process in a number of ways, including the following:

1. the identification of people who must achieve minimum nutrient intakes to reduce their risk (e.g., see Wong et al., 2003);
2. the identification of those people who would benefit the most and those who would benefit the least from dietary change (e.g., see Ordovas et al., 2002);
3. the identification of those at risk of a specific adverse effect (e.g., see Rapuri et al., 2001);
4. the formulation of appropriate interventions; and
5. improved interpretation of study results (e.g., see Yang et al., 2001).

For people with specific genetic polymorphisms, a study by Ahn and colleagues (2004) suggests that the benefits of the intake of fruits and vegetables may appear once a threshold intake is exceeded. Ordovas and

coworkers (2002) reported that setting an intake goal may decrease the risk in some individuals but increase the risk in others.

Concluding Remarks

In conclusion, Milner stressed that (1) understanding nutrigenomics is fundamental to establishing sensitive and reliable biomarkers that will be useful in assessing risk, (2) effective communication is needed so that consumers can understand the relevance of their own genetics to protecting their health, and (3) a bioethical framework must be upheld to prevent discrimination.

MEASURING USUAL DIETARY INTAKE FOR RISK ASSESSMENT

Presenter: Amy F. Subar

The precision of any dietary risk assessment depends on the strength of the intake assessment. Amy Subar addressed the strengths and the limitations of major dietary intake assessment methods and introduced some innovative methods for the collection and analysis of data.

Major Intake Assessment Methods Used in Population Studies and Their Strengths and Limitations

The major intake assessment methods include food records or diaries, 24-hour dietary recalls, and food frequency questionnaires (FFQs). Subar also mentioned methods that use biomarkers.

Food Records or Diaries

Food records or diaries require the subject to record all foods that he or she consumed, including their amounts. The methods used to obtain food records or diaries vary considerably. For example, investigators may or may not train the respondents, conduct a detailed review of the

records, or use highly standardized coding rules. Some investigators have developed electronic methods involving personal digital assistants or cell phones.

Strengths Food records and diaries provide detailed, quantified information about intake that could be relatively accurate. The data are rich with regard to information about nutrient intake, cooking practices, and meal and eating frequencies.

Limitations A major limitation of food records or diaries is that the process of recording food intakes influences the diet and may thus introduce bias. Moreover, the method requires literacy, imposes a large burden on both the respondent and the investigator, and is subject to sample selection bias. Recording becomes even less complete over time, and underreporting is typical, especially for overweight or obese respondents.

Twenty-Four-Hour Dietary Recalls

The 24-hour dietary recall method is widely used in dietary surveillance. The interviewer asks the respondent questions to obtain information on the types and the amounts of all foods that the respondent consumed during a defined 24-hour period. Variations in the approach used to obtain 24-hour recalls include the extent of the training of the interviewers, the standardization of probing questions, the method of administration, and the use of aids to estimate portion size.

Strengths The strengths of 24-hour recalls are similar to those of food records or diaries, with two additions: the recalls (1) do not affect eating behavior and (2) are subject to less sample selection bias than are food records or diaries.

Limitations A key limitation of the 24-hour recall method is that subjects have imperfect knowledge and memory of their food consumption. Recalls are costly to administer, and a single day's recall is insufficient to estimate one's usual intake (the theoretical long-run average daily intake) of a dietary component. As with food records, reporting may be less complete with subsequent recalls, and underreporting is typical.

Food Frequency Questionnaires

FFQs address the need for a feasible method to collect dietary intake data in large studies. FFQs vary in the foods that they include, the methods of addressing portion size and food preparation, the period covered, and other characteristics. Different methods are used to develop the food list and the corresponding nutrient database. The food list and database may be developed with a specific population subgroup in mind.

Strengths The strengths of FFQs include their low respondent burden, their attention to the usual individual intake of foods with one administration of the FFQ, the low cost of administration and processing of the FFQ, and the lack of an effect on eating behavior.

Limitations FFQs lack detail, require literacy, are cognitively complex, and are subject to severe measurement error. Different FFQs may perform differently, and different populations may respond differently to the same FFQ.

Biomarkers

If the presence of a biological compound had a strong relationship to the intake of a nutrient, it could provide the basis for a useful method to assess the intake of that nutrient. A *recovery biomarker* is one that represents a one-to-one relationship. (Doubly labeled water and urinary nitrogen are two examples of a recovery biomarker.) A *concentration biomarker* reflects the biological response to the intake of a nutrient in terms of a complex metabolism. (Serum selenium and serum ferritin are examples of concentration biomarkers.) Concentration biomarkers cannot be used to assess the amount of a nutrient consumed, but they do correlate with the amount consumed. Some forms of nutrients in the body have no relationship to nutrient intake at all because their concentration is closely regulated by physiological processes.

Innovative Methods of Collecting and Analyzing Intake Data

Investigators are exploring the automation of instruments to simplify and reduce the costs of data collection. Such instruments include World Wide Web-based FFQs and 24-hour diet recalls. In addition, the National Cancer Institute (NCI) has developed an approach that combines dietary assessment methods to improve overall estimates of population intake distributions and individual intakes. With the NCI method of analyzing intake data, the strengths of the two methods may be complementary.

Automated Methods of Data Collection

Subar described the NCI's prototype for an automated self-administered 24-hour recall (ASA24). It is intended to be user-friendly. For example, it allows the user to search and browse for foods, includes pictures for the identification of foods and the estimation of portion size, lists all the selections made, and asks questions. NCI's vision is that ASA24 will be a complete system for probing, coding, and analysis that can be updated easily and that is publicly available on the Web. It would also be adaptable to other languages. Modeled after the dietary surveillance system in the National Health and Nutrition Examination Survey, it would allow the collection of multiple 24-hour recalls at a minimal cost. Among the next steps in the development of ASA24 are cognitive testing and validation against interviewer-administered recalls.

National Cancer Institute Method to Estimate Usual Intake

To estimate the proportion of the population with intakes above or below a particular cutoff point, one needs to estimate the usual intake distribution for the population. To do this, investigators have used data from 24-hour recalls or from food records and statistical modeling (typically, the National Research Council method [NRC, 1986] or the Iowa State University method [Nusser et al., 1996]). These statistical methods are well established for most nutrients and for foods consumed daily by nearly everyone. The methods are less useful for estimation of the usual intake of foods consumed episodically, especially because of the large number of zero intakes.

In response to the challenge, the NCI method decomposes usual intake as follows:

Usual intake = consumption probability × intake on consumption day

The relative frequency of nonzero 24-hour recalls provides information about the consumption probability. Because the amounts consumed on consumption days are always positive, standard statistical methods can provide the distribution of the usual intakes on the consumption day. Combining both distributions produces an estimate of the distribution of usual intake.

The NCI method for foods uses a two-part nonlinear mixed model to correlate the intake probability and the intake amount. The use of covariates allows direct evaluation of the effects of covariates on usual intake and helps correct for measurement error. The Food Propensity Questionnaire, an FFQ that asks about the long-term frequency of intake but not about portion sizes, could be used as a covariate in the NCI model. This use of the Food Propensity Questionnaire in conjunction with the 24-hour recall removes concerns about the bias introduced by FFQs when they are used to estimate absolute intake. Moreover, combining data from the 24-hour recalls and the Food Propensity Questionnaire may substantially improve the estimates. Further information on these methods is published in *The Journal of the American Dietetic Association* (Dodd et al., 2006; Subar et al., 2006; Tooze et al., 2006).

Concluding Remarks

Subar concluded by emphasizing that good estimates of usual intakes are necessary for risk assessment and that good models with which to make such estimates are available. Continued research on methods and analytical techniques for estimating intakes is needed to improve nutritional risk assessment.

NUTRIENTS AND FOOD COMPOSITION: DATA NEEDS

Presenter: Joanne M. Holden

The assessment of the intake of dietary components requires information on the composition of foods and of supplements. Sources of food composition data include the U.S. Department of Agriculture (USDA), the food industry, developers of secondary databases, databases in other nations and regions, the scientific literature, and limited food analyses conducted for specific studies. Joanne Holden described the work of USDA's Agricultural Research Service in relation to food composition data, highlighted the collaborative nature of the National Food and Nutrient Analysis Program (NFNAP), and concluded by identifying data and resource needs.

Current Status of USDA's Food Composition Data

As shown in Figure 5-2, data flow into the USDA nutrient databank from many sources. After the data that are received undergo review, evaluation, and estimation, USDA releases the information in a number of different forms. The most notable of these forms is the National Nutrient Database for Standard Reference (SR), which is the authoritative source of food composition data for the United States. This database covers a wide array of foods (more than 7,200), including agricultural commodities, processed and prepared foods, formulated foods, selected brand name foods and fast foods, candies, and beverages. The 19th edition of the database (SR19) includes both original analytical data and calculated data, giving values for up to 140 nutritional components. The nutrient composition of each food is presented for various weights and measures (e.g., 100 grams, one-half cup, one medium piece [of a specified weight] of the food). Recently, the nutrient units used (e.g., dietary folate equivalents) have been harmonized with those used for the Dietary Reference Intakes. The data are available at www.ars.usda.gov/nutrientdata.

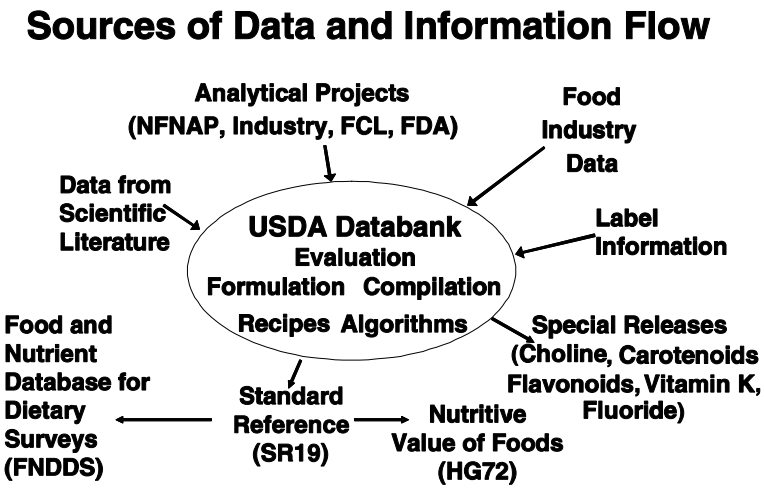

FIGURE 5-2 Sources of data and information flow for the U.S. Department of Agriculture's nutrient databank. NOTE: FCL = Food Composition Laboratory, FDA = Food and Drug Administration, NFNAP = National Food and Nutrient Analysis Program, USDA = U.S. Department of Agriculture.

The databank is expanding to include nonnutrients, new sources of information about traditional nutrients, specific forms of food components (e.g., the carotenoid lutein), and compounds used in large amounts in foods or dietary supplements. Among the substances added over the past few years are five subclasses of flavonoids, *trans*-fatty acid, choline, proanthocyanidins, added sugars, and fluoride. Some of these substances appear in special-interest databases. Extensive product reformulations (such as in response to concerns and regulations related to *trans*-fatty acids) sometimes require time-consuming updates.

Efforts are under way to develop fast and accurate high-capacity nutrient profiling methods that use food extracts. Intended uses include the categorization of foods, the identification of food components, and the quantification of the amounts of selected components.

The goal is for the SR data to be representative of the nutrient profile of the national food supply and to be applicable to populations and various subpopulations and to clinical and metabolic studies. USDA makes the data available in several electronic forms, which provide numerous advantages over printed volumes.

National Food and Nutrient Analysis Program

The NFNAP is a cooperative effort that is supported by many institutes of the National Institutes of Health (NIH); the Food and Drug Administration; and a number of other partners from the U.S. Department of Health and Human Services, USDA, the food industry, and universities. The NFNAP effort includes the identification of key foods and nutrients for analysis, the evaluation of the quality of existing data, the development and implementation of a plan for the nationally based sampling of foods, the analysis of sampled foods using valid methods and rigorous quality control procedures, and the compilation and dissemination of representative estimates, including variability estimates.

Key foods are defined as the list of foods that provide about 75 percent of the dietary intake of a specific food component. Some foods are key foods for several nutrients. Examples of key foods include fluid milk (both milk with 3.25 percent milk fat and milk with 2 percent milk fat), whole chicken eggs, and pizza. The dynamic nature of the U.S. food supply calls for periodic updates of key foods. For example, recent work on the selenium content of ground beef found that the variation in selenium content by geographic region was less than expected. Currently, work is under way through NFNAP to sample and update the information on 105 foods.

Uncertainties Regarding the Composition of Foods and Supplements

The variance in the composition of foods is a function of the variance of components inherent to the food and of the variance associated with the method used to analyze the food. Important issues related to the compositions of foods and supplements include the statistical bias that occurs with changes in the food or supplement formulation, the variability in composition, the validity of the analytical methods, the actual fortification levels, and the specificities of the descriptions of the reported foods. The assessment of the composition of selected fortified foods has revealed some rather large discrepancies between label claims and the actual content determined on analysis.

USDA, the Office of Dietary Supplements at NIH, and others are conducting pilot research on the compositions of dietary supplements. They are developing a dietary supplements ingredients database with

selected analytical verification of the data in the database. It will become available on the Web and initially will include data on the ingredients in vitamin and mineral preparations, amino acid preparations, fortified foods, and beverages. Later, it will include data on the ingredients in herbal and other botanical products.

Concluding Remarks

Holden's closing remarks focused on food composition data needs and the need for resources. Key data needs include the following:

- new food composition data to match changing food consumption patterns,
- estimates of the contents of food components that are important to the public's health,
- estimates of variability in foods (such as foods of different cultivars or from different geographical locations), and
- more specific data for brand-name products.

In addition, there is a need for valid and robust analytical methods and for reference materials for quality control. Sustained federal funding, especially from USDA but also from NIH and other federal departments and agencies, is critical to support the acquisition, compilation, and analysis of food composition data. Continued collaboration with the food industry is needed to obtain current data about the compositions of products, support for sampling and analysis, and support for the dissemination of the data.

6

Perspectives on Challenges and Solutions: Summary Remarks and Suggested Next Steps[1]

During the final session, moderated by Robert L. Buchanan, representatives of five sectors summarized key points from their perspectives, as follows: Catherine E. Woteki, industry; Barbara O. Schneeman, government; Gregory Paoli, risk assessment; Darlene Adkins, consumers; and Laina Busch, public health. The meeting ended with a lively open discussion involving many individuals, as did three of the earlier sessions. To capture the richness of the final presentations and of the open discussions throughout the meeting, this chapter organizes the points made under two major categories: the risk assessment process and consumer perspectives.

THE RISK ASSESSMENT PROCESS

Several participants described risk assessment as a systematic process for organizing and evaluating existing knowledge and its limitations. The workshop presenters pointed out the complexity of the process and issues of uncertainty that need to be addressed. Gregory Paoli emphasized that risk assessment is a tool that can be used to manage both uncertainty and complexity. Risk managers find the product of a well-

[1]Special thanks were given to Kathleen Koehler of the Office of the Assistant Secretary for Planning and Evaluation of the U.S. Department of Health and Human Services, Marianne Miliotis of the Food and Drug Administration, Michael D. McElvaine of the Office of Risk Assessment and Cost–Benefit Analysis of the U.S. Department of Agriculture, Suzanne Harris and Stephen Olin of the International Life Sciences Institute, and Maria Oria of the Institute of Medicine's Food and Nutrition Board for their work in helping to organize the workshop.

conducted risk assessment useful in their decision making: the process lays out the evidence, the assumptions that have been made, and the limitations of the evidence.

The Dietary Reference Intake (DRI) process introduced the use of the risk assessment model for assessing nutritional risk in the United States and Canada. According to Barbara Schneeman, the work on DRIs demonstrated benefits to the use of the risk assessment model for nutrition and the potential value of improving the process. Catherine Woteki indicated that much can be learned from the DRI process, from recent applications of risk assessment to microbiological risks, and from work on the evidence-based review process—each of which evolved over the past decade.

Ways of Thinking About Risk

The workshop presenters examined aspects of different types of risk. Fundamental questions related to the use of nutritional risk assessment in setting DRIs include, How do you state the problem? and What are the endpoints? Among the possible endpoints of a nutritional risk assessment are the prevention of nutrient deficiency diseases, the maintenance of the body pool or of body stores of nutrients, the maintenance of body function, the reduction of risk factors for chronic diseases, chronic disease prevention, and the prevention of toxicity.

One challenge may be defining the context for risk: To whom does the risk or benefit apply? How do genotypes fit in? Another challenge is addressing the risk (and the benefit) for the population as a whole. Should a nutrient risk assessment weight a public health issue more heavily than a nutrient shortfall that is identified on the basis of a biochemical parameter? How does one risk trade off from another? Well-conducted nutritional risk assessments can provide key information to risk managers who need to develop policies related to food fortification and dietary supplements.

What are the challenges and opportunities for risk assessments that involve dietary patterns rather than a single nutrient? Alice Lichtenstein suggested that a model that captures dietary behavior combined with one or two validated biomarkers might be a useful approach to addressing the risks associated with dietary patterns.

Participants raised many other questions, such as the following: Does a probability of benefit (as is implied by health claims on food products)

create other types of risk by implying that one food should be eaten in place of another? Instead of addressing each topic in isolation, how can the full range of options be understood and presented to enable the full impact of proposed policies to be considered by risk managers? Joseph Rodricks indicated that there are tools for examining the risks of excess together with the risks of inadequacy. Several participants emphasized that the process of finding answers for many of these questions is only in the early stage.

Considerable discussion focused on distinctions between risk–risk assessments and risk–benefit assessments. Barbara Petersen considered the differences in the two approaches to be semantic. A number of participants stated that a risk–risk approach is essential to nutrient risk assessment; others indicated that communication that uses a risk–risk terminology can be very problematic to consumers because consumers think in terms of risk and benefit.

Expanding Applications of Risk Assessment in Setting Dietary Reference Intakes

Suzanne Murphy challenged the group to consider the extent to which risk assessment approaches would be applicable to establishing nutrient intake recommendations. Is it appropriate to use one method to set Estimated Average Requirements (EARs) and an entirely different method to set Tolerable Upper Intake Levels (ULs)? In particular, could some aspects of models of risk assessment be used to set EARs, and could some aspects of setting requirements be used to set ULs? Barbara Schneeman and Gregory Paoli both noted that the approach used to set EARs incorporates elements of risk assessment. Schneeman pointed out that the provisional definition of nutritional risk developed by the Codex Committee for Nutrition and Foods for Special Dietary Use incorporates the probability of an adverse health effect associated with either the excessive or the inadequate intake of a nutrient or some other food component.

Considering the obstacles to studies involving high doses of substances, several participants pointed out the need for further work in developing models for estimating the distributions of risk. Richard Forshee suggested that priority be given to nutrients for which the difference between the amount specified for the Recommended Dietary Allowance and the amount specified for the UL is small. Sanford Miller suggested

that Barbara Petersen's Beneficial Utility Index model merits a closer look for use for nutritional risk assessment that addresses both low and high intakes of a nutrient.

Using Tools in Nutritional Risk Assessment

Among the nutritional risk assessment tools discussed were biomarkers, methods for collecting dietary data, and evidence-based reviews.

Biomarkers

The term *biomarkers* actually covers three concepts for different types of indicators: (1) biomarkers for nutrient intake, (2) biomarkers for susceptibility to disease, and (3) biomarkers of effect (biomarkers that indicate a causal relationship between intake of the nutrient and the occurrence of the disease).

Dietary Data Collection Methods

New tools are in development for the collection of accurate dietary data and their appropriate analysis. The U.S. Department of Agriculture has an ongoing program for updating and expanding food composition data. Considerable concern was raised that bias is likely to be present in estimates of dietary intakes (including supplement intakes) and that the bias could affect estimates of the percentage of the population with inadequate or excessive intakes. Major sources of bias include (1) the underreporting of dietary intakes and (2) overages in the labeled contents of supplements and fortified foods, especially for labile nutrients such as vitamin C. For both folate and vitamin A, estimates from U.S. dietary data indicate that large proportions of the population have inadequate intakes, but laboratory data do not support that finding.

From a different perspective, dietary data may be the most accurate data available to risk assessors. Information on the accuracy of the reporting of supplement use is not yet available. To understand dietary data better, Barbara Petersen suggested the examination of data from consum-

ers with reported high nutrient intakes and the use of scaling methods once estimates of the extent of the bias are available.

Evidence-Based Reviews

Alice Lichtenstein expressed the view that finding ways to apply the evidence-based review approach to the DRI process would require considerable work. Challenges include data limitations and the extensive resources needed for such reviews. In the establishment of DRIs, a major role for evidence-based review may be to frame the nutritional risk assessment questions and identify whether the evidence for answering the questions exists. Evidence-based reviews set criteria in advance and clearly define the process for examining the scientific literature.

Using Data from Observational Studies Versus Data from Randomized Controlled Trials

The workshop speakers and other participants expressed different points of view regarding the value of data obtained from observational studies in comparison with data from randomized controlled trials. For example, Alice Lichtenstein noted the discordance between data from the two types of studies, whereas Julie Mares expressed the view that the interpretation of the observational data may have been in error. It is inappropriate to use findings from observational studies of food–disease relationships to draw conclusions regarding supplements, for example.

Addressing Uncertainty

The handling of uncertainty was a topic of considerable discussion among the workshop participants. Scientific uncertainty usually represents variability around a point estimate. Several participants stated that the uncertainty factors used in the DRI process to set ULs do not reflect scientific uncertainty. Instead, the uncertainty factors are more like safety factors, in that they consider the severity of the effect or they attempt to provide a way to extrapolate from one type of data to another. A number of participants expressed concern that bias and risk management decisions entered into the setting of the uncertainty factors. These par-

ticipants called for a reexamination of the use of the uncertainty factor in setting ULs.

Several participants noted the importance of addressing uncertainty more explicitly with regard to setting both the EAR and the UL. Barbara Petersen's method of expressing uncertainty by the addition of upper and lower limits to her efficacy and toxicity curves (Figure 3-4 in Chapter 3) serves as one example of how to do this. Joseph Rodricks mentioned that there are some formal tools for weighing uncertainties and the knowledge of adverse effects versus other considerations.

Maintaining Appropriate Separation Between Risk Assessment and Risk Management

Several participants underscored the importance of clear communication between risk assessors and risk managers at the problem formulation stage, before the risk assessment begins. Laina Bush argued that the economists and other social scientists involved in regulatory impact analysis should also be involved in the problem formulation step. Risk assessors need to understand what kinds of information the risk managers require for their decision making.

The development of probabilistic models of the distribution of risk instead of determination of a cutoff point might help address concerns about the inappropriate incorporation of risk management decisions into the risk assessment. Robert Buchanan suggested that the risk assessment entail a clear description of the relationship between exposure and risk and that a second group (the risk managers) decide the level of intake that is safe. That is, given a distribution of risk and other relevant information, the risk manager would decide the point on the distribution curve that should be targeted. The report *Dietary Reference Intakes: Applications in Dietary Planning* (IOM, 2003) gives an example of this approach with regard to deciding what point to target on the distribution around the EAR.

Catherine Woteki pointed out that federal agencies make risk management decisions using information provided by the DRI process, an approach that is somewhat analogous to the separation of risk management and risk assessment. Numerous participants emphasized that value judgments that occur in the risk assessment process need to be clearly identified.

Possible Next Steps

Workshop to Explore the Risk Assessment Model

Catherine Woteki suggested that holding a workshop of several days' duration, as briefly described below, could serve as a useful next step:

- Conduct a trial risk assessment of a single nutrient.
- Select a nutrient and a risk assessment model or models in advance.
- Explore the application of the model(s) to the nutrient: define questions and endpoints, identify available and needed data, and identify the assumptions to be used.
- Evaluate the results.
- Determine data and resource needs.
- Address the appropriateness of the risk assessment model or models to nutrition in terms of biology and public health.

Several participants supported the potential value of such an approach.

Methodological Research and Data Collection

Methods Gregory Paoli emphasized that there is a great need for methodological research—that is, research on the mathematical properties of the problem conducted with hypothetical data. Such research would allow one to learn, for example, how important it is to have data on the standard deviation and the tails of the distribution. Are such data really needed to obtain a robust estimate of risk? Risk assessors can use this knowledge to guide the selection of the data to be collected. Economists have developed methods that can be used to compare different outcomes, and these could be informative for the nutritional risk assessment process.

Other potentially useful methods include (1) the exploratory analysis of large data sets on supplements to search for toxic effects and (2) the use of pharmacokinetic or toxicokinetic modeling with animal studies and in vitro data. Joseph Rodricks stated that, in the chemical area, toxicokinetics can be especially helpful in providing a basis for methods to extrapolate across species and across doses and an understanding of vari-

ability in populations. Thus, he suggested that toxicokinetic methods be considered for use with nutritional risk assessment. Several participants emphasized the importance of developing and using animal models more extensively, with the ferret–carotene model given as an example of how one can obtain valuable information on dose–response. The use of such models would require research on methods for the extrapolation of the findings from those studies to humans.

The Beneficial Utility Index described by Barbara Petersen was viewed as a promising new model by some, especially if it can adequately incorporate susceptibility, duration of exposure, and delayed response. Joseph Rodricks suggested the exploration of methods that consider quality-of-life factors, such as the disability-adjusted life years method, to find useful quantitative approaches to the comparison of different health endpoints in nutritional risk assessment.

Gregory Paoli pointed out that, in other fields of study, considerable time and effort are expended on characterizing and testing risk assessment methods before they are used as a basis for decision making. Several participants called for the development of more robust methods before a crisis arises.

Data collection Several presenters and other participants noted the urgent need for data, including data that could be useful for methodological research. Much emphasis was placed on the need for dose–response data. *Dietary Reference Intakes Research Synthesis, Workshop Summary* (IOM, 2007), is a useful source of information on data needs.

Some participants called for the purposeful collection of data on the adverse effects of nutrients and other food components and for investigators to build plans for the collections of such data into their applications for federal funding. Robert Buchanan suggested a two-part plan: (1) the development of a framework that would allow data from different studies to be combined for analytical purposes and (2) action to convince a group of researchers to collect their data using that framework. A challenge in grant applications would be the incorporation of a consistent framework for data collection while leaving room for individual creativity in experimental design. Consideration would need to be given to the length of the observation period needed to obtain an accurate assessment of adverse events.

CONSUMER PERSPECTIVES

Darlene Adkins expanded on comments made during the discussions, underscoring the point that uncertainties and complexities that challenge risk assessors and managers lead to challenges to consumers as well. Consumers find it difficult to make sense of the glut of nutrition information that they receive—information that comes from a very wide range of sources, with much of it unsolicited. Kathy Wiemer, for example, noted that even nutrition professionals tend to perceive, incorrectly, that any intake that is above the UL is dangerous. John Milner and Darlene Adkins pointed out that individuals vary in their responsiveness to the benefits or the risks from dietary changes and that this needs to be considered in consumer education efforts.

Communicators need to provide consumers with messages that are credible, reliable, objective, and unbiased. Ways need to be found to present the complexities in an understandable manner—one that allows the consumer to make sound decisions that consider the facts in the light of the consumer's own situation. In particular, Darlene Adkins called for a reassessment of the nutrition label, an exploration of how consumers can be equipped to handle more complete nutrition information, and ways to provide useful nutrition information about food consumed at food establishments. To accomplish these tasks more effectively, both Darlene Adkins and Laina Bush called for research on consumer behavior and factors that influence their decision making.

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A

Workshop Agenda

Nutritional Risk Assessment:
Bridging Perspectives, Sharing Methodologies,
Identifying Data Challenges

The National Academies
2100 C Street, NW
Washington, D.C.

February 28–March 1, 2007

Objective: The workshop will serve as a forum for experts on various disciplines to:

- **discuss the strengths and challenges in using risk assessment tools to inform dietary and nutritional recommendations,**
- **explore the use of risk assessment tools to evaluate standards for nutrient intake and the relationship of diet and nutrition to chronic disease risk, and**
- **identify next steps necessary to advance in these areas.**

DAY 1—NAS AUDITORIUM

8:00–9:00 am **Registration**

INTRODUCTION

9:00 am **Welcome from Food Forum**
Catherine Woteki, Mars Inc.

Objectives of the Meeting
Robert Buchanan, Food and Drug Administration

SESSION 1
RISK ASSESSMENT AND NUTRITION: BUILDING PERSPECTIVES

Moderator
Laina Bush, U.S. Department of Health and Human Services

9:30 am	**Overview of Risk Assessment: What Are the Questions That Risk Assessments Tools Can Answer? How Might This Relate to Nutrition Risk Assessment?** *Joseph Rodricks, ENVIRON International Corporation*
10:00 am	**Overview of Current Issues in Nutrition: What Are the Questions and Challenges in Nutrition? How Might Risk Assessment Help to Address Nutrition Questions?** *Shiriki Kumanyika, University of Pennsylvania*
10:30–11:00 am	**BREAK**
	Discussants:
11:00 am	**a. Industry Perspective: How Does the Food Industry Use Risk Assessment Tools?** *Kathryn Wiemer, General Mills*
11:20 am	**b. Public Policy/Government Perspective: How Does the Government Use Risk Assessment Tools?** *William Dietz, Centers for Disease Control and Prevention*
11:40 am	**Open Discussion**
12:15–1:30 pm	**LUNCH**

SESSION 2
SHARING METHODOLOGIES:
CURRENT USES OF NUTRITIONAL RISK ASSESSMENT

Questions:
1. How have different groups used risk assessment methodologies to establish upper intake levels?
2. What are the data gaps to assess risk from excess nutrient intakes and establish better upper nutrient intake levels?
3. Can risk assessment tools help in establishing nutrient requirments? If so, what tools would be useful?

Moderator: Molly Kretsch, USDA

1:30 pm	**The IOM Process to Establish Tolerable Upper Intake Levels: Model and Data Needs** *Robert Russell, Tufts University*
2:00 pm	**Potential Connections Between Establishing Nutrient Requirements and Tolerable Upper Intake Levels** *Suzanne Murphy, University of Hawaii*
2:30 pm	**Nutrient Risk Assessment: Lessons Learned from the FAO/WHO Technical Workshop** *Christine Taylor, Institute of Medicine*
3:00 pm	**BREAK**
3:30 pm	**Implications of Using Conservative Assumptions in Nutritional Risk Assessments** *Barbara Petersen, Exponent*
4:00 pm	**Commentary** *Sanford Miller, University of Maryland*
4:10 pm	**Open Discussion**
5:00 pm	**Adjourn**

DAY 2—Lecture Room

8:00–9:00 am **Registration**

9:00 am **Welcome**
Michael Doyle, University of Georgia
Food Forum Chair

SESSION 3
SHARING METHODOLOGIES: DIET/FOOD PATTERNS AND HEALTH OUTCOMES

Questions:
4. What are the challenges encountered when establishing relationships between diet/food consumption patterns and health or risk of disease?
5. What approaches are currently used to establish diet/food consumption patterns and health or risk of disease relationships?
6. What kind of risk assessment tools and models could be best used or adapted for evaluating associations between nutrition and health or disease risks?
7. How should nutritional studies be designed in order to provide information and data useful for nutritional risk assessments?

Moderator: Michael Doyle

9:15 am **Challenges in Establishing Relationships Between Diet Patterns and Health Outcomes**
Julie Mares, University of Wisconsin

9:45 am **Evaluation of Health Claims in Nutrition Labeling**
Kathleen C. Ellwood, Food and Drug Administration

10:15–10:45 am **BREAK**

10:45 am **Evidence-based Review Process to Link Dietary Factors with Chronic Disease: Heart Disease and Diet as a Case Study**
Alice Lichtenstein, Tufts University

11:15 am **Key Challenges in Risk-Based Approaches to Nutrition Policy**
Gregory Paoli, Decisionalysis Risk Consultants

11:45 am **Open Discussion**

12:15–1:30 pm **LUNCH**

SESSION 4
IDENTIFYING DATA NEEDS AND OVERCOMING CHALLENGES

Questions:

- What is the future potential contribution to nutrition risk assessment of new methods for describing population variability with regard to nutrient bioavailability, and physiological and or genomic responses to nutrients and food components?
- What is the future potential contribution to nutrition risk assessment of new methods for quantitatively describing population variability regarding food and nutrient intake levels?
- What are the current status and future needs for food composition data to meet the challenges of nutrition risk assessment?

Moderator: Bob Buchanan, FDA

1:30 pm **The Role of Nutrigenomics and Population Variability in Nutritional Risk Assessment**
John Milner, National Cancer Institute
National Institutes of Health

2:00 pm **Dietary Intake and Exposure Assessment in Nutritional Risk Assessment**
Amy Subar, National Cancer Institute
National Institutes of Health

2:30 pm **Nutrients and Food Composition: Data Needs**
Joanne Holden, Agricultural Research Service
U.S. Department of Agriculture

3:00–3:30 pm **BREAK**

SESSION 5
WRAP-UP: PERSPECTIVES ON CHALLENGES AND SOLUTIONS

Moderator: Bob Buchanan, Food and Drug Administration

3:30 pm **What Did We Hear and What Are the Next Steps?**
Industry: Catherine Woteki, Mars, Inc
Government: Barbara Schneeman, Food and Drug Administration
Risk Assessor: Gregory Paoli, Decisionalysis Risk Consultants
Consumer: Darlene Adkins, National Consumers League
Public Health: Laina Bush, U.S. Department of Health and Human Services

4:20 pm **Open Discussion**

5: 00 pm **Adjourn**

B
Workshop Participants

Eyassu Abegaz, PhD
Ajinomoto Corporate Services, LLC
Washington, DC

Darlene Adkins Kerr
Child Labor Coalition
Washington, DC

James Astwood, PhD
ConAgra Foods
Omaha, NE

Leila Barraj, DSc
Exponent
Washington, DC

Nicole Bender
Greer, Mitchell, Margolis, Burns
Washington, DC

Donna Blum-Kemelor, MS, RD
U.S. Department of Agriculture
Alexandria, VA

P. Michael Bolger, PhD
Food and Drug Administration
College Park, MD

Susan Borra, RD
International Food Information Council Foundation
Washington, DC

Ann Bouchoux
International Food Information Council
Washington, DC

Robert Brackett, PhD
Food and Drug Administration
College Park, MD

Mary Brandt, PhD
Food and Drug Administration
College Park, MD

Ronette Briefel, DrPH, RD
Mathematica Policy Research, Inc.
Washington, DC

Trish Britten, PhD
U.S. Department of Agriculture
Alexandria, VA

Danielle Brulé, PhD, RD
Health Canada
Ottawa, Ontario, Canada

Robert L. Buchanan
Food and Drug Administration
College Park, MD

Robert Bursey
Ajinomoto Corporate Services, LLC
Washington, DC

Vicki Burt, ScM
National Center for Health Statistics
Hyattsville, MD

Laina M. Bush, MBA
U.S. Department of Health and Human Services
Washington, DC

Frank Busta, PhD
University of Minnesota
St. Paul, MN

Barbara Buyske, MS, RD
Wyoming WIC Program
Cheyenne, WY

Heather Carter, MS, MPH
Centers for Disease Control and Prevention
Atlanta, GA

Julie A. Caswell, PhD
University of Massachusetts
Amherst, MA

Christine Chaisson, PhD
The Life Line Group
Annandale, VA

Yuhuan Chen, PhD
Grocery Manufacturers Association
Food Products Association
Washington, DC

Ei Cho, PhD
Food and Drug Administration
College Park, MD

Tae Chong, MHC
National WIC Association
Washington, DC

David Cockram, MS, RD, LD
Ross Products Division of Abbott Laboratories
Columbus, OH

Ian Coulter, PhD
Samueli Institute
Corona Del Mar, CA

John Courtney, PhD
American Society for Nutrition
Bethesda, MD

Nancy Crane, MPH, MS
Food and Drug Administration
College Park, MD

Darla Danford, MPH, DSc
National Heart, Lung, and Blood Institute
Bethesda, MD

Cindy Davis, PhD
National Cancer Institute
Rockville, MD

Sheila Davis, MD
W. Montague Cobb/NMA Health Institute
Washington, DC

Fabiana De Moura, PhD
University of California at Davis
Germantown, MD

Kerry Dearfield, PhD
U.S. Department of Agriculture
Washington, DC

Rita Deng, MHS
Rockville, MD

William Dietz, MD, PhD
Centers for Disease Control and Prevention
Atlanta, GA

Lorelei DiSogra, EdD, RD
United Fresh Produce Association
Washington, DC

Diana Doell, PhD
Food and Drug Administration
College Park, MD

Joyce Donohue, PhD
U.S. Environmental Protection Agency
Washington, DC

Michael P. Doyle, PhD
University of Georgia
Griffin, GA

Johanna T. Dwyer, DSc, RD
National Institutes of Health
Bethesda, MD

Robert Earl, MPH, RD
Grocery Manufacturers Association
Food Products Association
Washington, DC

Allison Edwards, PhD
Food and Drug Administration
College Park, MD

Katie Egan, BS, RD
Food and Drug Administration
College Park, MD

Kathleen C. Ellwood, PhD
Food and Drug Administration
College Park, MD

Nancy Emenaker, PhD, RD
National Cancer Institute
Rockville, MD

Jody Engel, MA, RD
National Institutes of Health
Bethesda, MD

Cecilia Wilkinson Enns, MS, RD, LN
U.S. Department of Agriculture
Beltsville, MD

Krista Esslinger
Health Canada
Quebec, Canada

Michael Falk, PhD
Life Sciences Research Office
Bethesda, MD

Hamed Faridi, PhD
McCormick & Company, Inc.
Hunt Valley, MD

Eileen Ferruggiaro, PhD, RD
U.S. Department of Agriculture
Alexandria, VA

Peter Fischer, PhD
Health Canada
Ottawa, Ontario, Canada

Daniel Folmer, PhD
Food and Drug Administration
College Park, MD

Richard Forshee, PhD
University of Maryland
College Park, MD

Elizabeth Frazao, PhD
U.S. Department of Agriculture
Washington, DC

Andrew Freedman, PhD
National Cancer Institute
Bethesda, MD

Pavlette Gaynor, PhD
Food and Drug Administration
College Park, MD

Shirley Gerrior, PhD, RD, LD
U.S. Department of Agriculture
Washington, DC

Marcia Greenblum, MS, RD
Nutrition and Foods Safety Education
Egg Nutrition Center
Washington, DC

Peter Greenwald, MD
National Cancer Institute
Rockville, MD

Edward Groth III, PhD
Groth Consulting Services
Pelham, NY

Joanne Guthrie, PhD, MPH
U.S. Department of Agriculture
Washington, DC

Mary Hager, PhD, RD
American Dietetic Association
Washington, DC

Brenda Halbrook, MS, RD
U.S. Department of Agriculture
Alexandria, VA

Rosemary Hall, MS
U.S. Environmental Protection Agency
Washington, DC

Suzanne Harris, PhD
ILSI Research Foundation
Washington, DC

Kazuo Hasegawam, DVM
Ajinomoto Corporate Services, LLC
Washington, DC

John Hathcock, PhD
Council for Responsible Nutrition
Washington, DC

Rachel Hayes-Bohn, MPH, RD
U.S. Department of Agriculture
Alexandria, VA

Carrie Hendrickson, PhD
Food and Drug Administration
College Park, MD

Donna Hines, MA
U.S. Department of Agriculture
Alexandria, VA

James Hodges
American Meat Institute Foundation
Washington, DC

Joanne M. Holden, MS
U.S. Department of Agriculture
Beltsville, MD

Answorth Honore, MPH
Cedars Medical Center
Miami, FL

Barry Hooberman, MPH, PhD
Food and Drug Administration
Rockville, MD

Ebony Horry, MS
U.S. Department of Agriculture
Alexandria, VA

Van Hubbard, MD, PhD
National Institutes of Health
Bethesda, MD

Jayne Hurley, BS, RD
The Center for Science in the Public Interest
Washington, DC

Hasan Hutchinson, PhD, ND
Institute of Nutrition, Metabolism and Diabetes
Canada

Karen Jackson, RD, FADA
Area Agency on Aging 1-B
Southfield, MI

Yvonne Jackson, PhD
Administration on Aging
Washington, DC

Jayasri Janakiram, MA
Children's Hospital
Washington, DC

Clifford Johnson, MPH
National Center for Health Statistics
Hyattsville, MD

Wen Yen Juan, PhD
U.S. Department of Agriculture
Alexandria, VA

Christle Kaefer, MBA, RD
National Cancer Institute
Bethesda, MD

Claudine Kavanaugh, PhD
Food and Drug Administration
College Park, MD

Marta Kealey, RD
U.S. Department of Agriculture
Alexandria, VA

Jillonne Kevala, PhD
Center for Food Safety and Applied Nutrition
College Park, MD

Abu Khan, PhD
Food and Drug Administration
College Park, MD

Cho-il Kim, PhD
Center for Nutrition Policy and Promotion
Korea Health Industry Development Institute
Seoul, Korea

Catherine Klein, PhD, RD
Life Sciences Research Office
Bethesda, MD

David M. Klurfeld, PhD
U.S. Department of Agriculture
Beltsville, MD

Kathleen Koehler, PhD, MPH
U.S. Department of Health and Human Services
Washington, DC

Phillip Kott, PhD
National Agricultural Statistics Service
Fairfax, VA

Molly Kretsch, PhD
U.S. Department of Agriculture
Beltsville, MD

Shiriki Kumanyika, PhD, MPH
University of Pennsylvania
Philadelphia, PA

Connye Kuratko, PhD
Martek Biosciences
Columbia, MD

Michael Landa, J.D.
Food and Drug Administration
College Park, MD

Jennifer Layne, M.S., C.S.C.S.
Tufts University
Boston, MA

Haeng Shin Lee, PhD
Korea Health Industry Development Institute
Seoul, Korea

Hyoung Lee, PhD
Food and Drug Administration
College Park, MD

Elyse Levine, PhD, RD
N. Chapman Associates
Washington, DC

Dan D. Levy, PhD
Food and Drug Administration
College Park, MD

Janine Lewis
World Health Organization
Switzerland

Alice Lichtenstein, DSc
Tufts University
Boston, MA

Jean Lloyd, MS
U.S. Administration on Aging
Washington, DC

Wes Long, PhD
Food and Drug Administration
College Park, MD

Ronald Lorentzen, PhD
Food and Drug Administration
College Park, MD

Dorothy Mackerras, MPH, PhD
Food Standards Australia New Zealand
Canberra, BC, Australia

Bernadene Magnuson, PhD
University of Maryland
College Park, MD

Julie Mares, PhD
University of Wisconsin
Madison, WI

Karen Matsuoka, PhD
Office of Management and Budget
Washington, DC

Antonia Mattia, PhD
Food and Drug Administration
College Park, MD

Michael D. McElvaine, DVM, MPH
U.S. Department of Agriculture
Washington, DC

Donald J. McNamara, PhD
Egg Nutrition Center
Washington, DC

Linda D. Meyers, PhD
Institute of Medicine
Washington, DC

Marianne Miliotis, PhD
Food and Drug Administration
College Park, MD

Clare Miller, MS, RD
U.S. Department of Agriculture
Alexandria, VA

Sanford A. Miller, PhD
University of Maryland
College Park, MD

John A. Milner, PhD
National Cancer Institute
Rockville, MD

David Mitchell
Greer, Mitchell, Margolis, Burns (GMMB)
Washington, DC

Veta Mitchell, MS
Pennsylvania Department of Health
Harrisburg, PA

Tina Moore, MS
U.S. Environmental Protection Agency
Washington, DC

Julie Moss, PhD
Food and Drug Administration
College Park, MD

Joe Mulinare, MD, MSPH
Centers for Disease Control and Prevention
Atlanta, GA

Suzanne P. Murphy, PhD, RD
University of Hawaii
Honolulu, HI

Jill Nicholls, PhD
National Dairy Council
Rosemont, IL

Canice Nolan, PhD
European Commission Delegation
Washington, DC

Stephen Olin, PhD
International Life Sciences Institute
Washington, DC

Maria P. Oria, PhD
Institute of Medicine
Washington, DC

Gregory M. Paoli, BASC, MASC
Decisionalysis Risk Consultants
Ottawa, Ontario, Canada

Deepali Patel
Institute of Medicine
Washington, DC

Kathleen Pellechia, RD
U.S. Department of Agriculture
Beltsville, MD

Barbara Petersen, PhD, MPH
Exponent
Washington, DC

Christine Pfeiffer, PhD
Centers for Disease Control and Prevention
Atlanta, GA

Janet Phoenix, MD, MPH
National Research Center for Women and Families
Washington, DC

Susan Pitman, MA, RD
FoodMinds
Washington, DC

Donna Porter, PhD, RD
Library of Congress
Washington, DC

Diane Radler, PhD, RD
University of Medicine and Dentistry of New Jersey
Newark, NJ

Crystal Rasnake, MS
Food and Drug Administration
College Park, MD

Lin Rayshiang, MS
Pennsylvania Department of Health
Harrisburg, PA

Elizabeth Resek, MS
U.S. Environmental Protection Agency
Washington, DC

Cecilia Richardson, MS, RD, LD
National WIC Association
Washington, DC

Donna Robie, PhD
Food and Drug Administration
College Park, MD

Joseph V. Rodricks, PhD
ENVIRON International Corporation
Arlington, VA

Sharon Ross, PhD
National Cancer Institute
Rockville, MD

Robert Russell, MD
Tufts University
Boston, MA

Nadine Sahyoun, PhD, RD
University of Maryland
College Park, MD

Leila Saldanha, PhD
NutrlQ LLC

Etta Saltos, PhD
U.S. Department of Agriculture
Washington, DC

James Schaub, PhD
U.S. Department of Agriculture
Washington, DC

Priscilla Samuel, PhD
Mead Johnson Nutritionals/Bristol-Myers Squibb Company
Evansville, IN

Sandra Schlicker, PhD, CNS, LN
Consultant
Washington, DC

Barbara Schneeman, PhD
Food and Drug Administration
College Park, MD

Andrew Shao, PhD
Council for Responsible Nutrition
Washington, DC

Tomoko Shimakawa, DSc
Food and Drug Administration
College Park, MD

Kaniz Shireen, MS
Food and Drug Administration
College Park, MD

Kathleen Smith, RD
Consultant
Annandale, VA

Christine Spain, MA, MS
President's Council on Physical Fitness and Sports
Washington, DC

Keisha Stafford, RD, LDN
Washington Adventist Hospital
Takoma Park, MD

Desire Stapley, MED, RD
Food and Nutrition Information Center
Beltsville, MD

Pamela Starke-Reed, PhD
National Institutes of Health
Bethesda, MD

Kimberly Stitzel, MS, RD
American Heart Association
Washington, DC

Amy Subar, PhD, MPH, RD
National Cancer Institute
Bethesda, MD

William Sveum, PhD
Kraft Foods
Glenview, IL

Shirley S.H. Tao, PhD
Food and Drug Administration
College Park, MD

Christine L. Taylor, PhD
Institute of Medicine
Washington, DC

Susan Thompson, PhD
Food and Drug Administration
College Park, MD

Nga Tran, DrPH
Exponent
Washington, DC

Lisa Troy, MA
Food and Nutrition Board
Washington, DC

Elaine Trujillo, MS, RD
National Cancer Institute
Rockville, MD

Paula Trumbo, PhD
Food and Drug Administration
College Park, MD

Moraima Ramos Valle
U.S. Department of Food and Drug
College Park, MD

Brian Wansink, PhD
Cornell University
Ithaca, NY

Kurtria Watson, RD
U.S. Department of Agriculture
Alexandria, VA

Jennifer Weber, RD, MPH
American Dietetic Association
Washington, DC

Jane White, PhD, RD
University of Tennessee
Knoxville, TN

Kathy Wiemer, MS, RD, LD
General Mills
Minneapolis, MN

Richard A. Williams, PhD
Food and Drug Administration
College Park, MD

Carl Winter, PhD
University of California
Davis, CA

Catherine E. Woteki, PhD
Mars, Incorporated
McLean, VA

Essie Yamini, PhD
Food and Drug Administration
College Park, MD

Ann Yaktine, PhD
Institute of Medicine
Washington, DC

Allison Yates, PhD
U.S. Department of Agriculture
Beltsville, MD

Linda Youngman, PhD
Food and Drug Administration
Rockville, MD

C

Speaker, Moderator, and Discussant Biographies

Darlene Adkins Kerr is vice president of public policy at the National Consumers League (NCL). Ms. Adkins has been with the League since 1991 and is responsible for League policy, activities, public education, and publications related to nutrition/health issues, labor standards, and financial services.

Ms. Adkins' projects have included a variety of nutrition/health issues, such as asthma, nutrition labeling, and obesity. She serves on the Advisory Council of the Joint Institute for Food Safety and Applied Nutrition (JIFSAN).

She has also written financial education materials on issues such as trial offers, debit and credit cards, and credit reports/personal budgets. Ms. Adkins coordinates the Child Labor Coalition for NCL, managing numerous advocacy campaigns, projects, and grants. She is the North American Coordinator and sits on the International Council of the Global March Against Child Labor.

Robert L. Buchanan, Ph.D., is currently Senior Science Advisor and Director of the Office of Science, Center for Food Safety and Applied Nutrition at the Food and Drug Administration. Dr. Buchanan received his B.S, M.S., M.Phil, and Ph.D. degrees in Food Science from Rutgers University, and post-doctoral training in mycotoxicology at the University of Georgia. Since then he has 30 years experience teaching and conducting research in food safety, first in academia, then with the USDA Agricultural Research Service, and most recently with the FDA. His scientific interests are diverse, and include extensive experience in predictive microbiology, quantitative microbial risk assessment, microbial

physiology, mycotoxicology, and HACCP systems. He has published approximately 300 manuscripts, book chapters, and abstracts on a wide range of subjects related to food safety, and is one of the co-developers of the widely used USDA Pathogen Modeling Program. He also has an ongoing interest in the development of science-based public health policy. In addition to currently serving as the FDA CFSAN Senior Science Advisor, he has served as Deputy Administrator for Science with the USDA Food Safety and Inspection Service, and is the U.S. Delegate to the Codex Alimentarius Commission Committee on Food Hygiene. Dr. Buchanan serves on the editorial boards of several journals, and is a member of the International Commission on Microbiological Specification for Foods. He has also served as a member of the National Academy of Science's Institute of Medicine Committee on Emerging Microbial Threats and the National Advisory Committee on Microbiological Criteria for Foods.

Laina Bush, M.B.A., is Team Leader for Science Policy within the Office of the Science and Data Policy of the Office of the Assistant Secretary for Planning and Evaluation at the Department of Health and Human Services (HHS). As Team Leader, she serves as senior policy analyst, advisor, and supervisor with major responsibility for policy research, analysis, evaluation, leadership, and planning related to activities of the science based agencies in HHS (FDA, NIH, and CDC) as well as public health science policy issues generally.

Ms. Bush has previously worked at the FDA and at the Office of Management and Budget's Office of Information and Regulatory Affairs.

Some of her research projects have included examinations of best practices within industry and state governments to manage costs of prescription drugs, international drug price comparisons, food labeling and weight management, medical and public health issues related to mercury, and the impacts of direct to consumer advertising of pharmaceuticals.

She has served on many work groups and task forces including the 2005 Dietary Guidelines for Americans drafting committee, Toxics and Risk Subcommittee, Interagency Working Group on Mercury, Interagency Working Group on Dioxin, Katrina Environmental Impacts and Cleanup Workgroup, Women's Health Committee on Breastfeeding, and the President's Council for Food Safety Strategic Planning Task Force.

William Dietz, M.D., Ph.D., is the director of the Division of Nutrition and Physical Activity in the National Center for Chronic Disease Preven-

tion and Health Promotion at the Centers for Disease Control and Prevention (CDC). Prior to his appointment to the CDC, he was a professor of pediatrics at the Tufts University School of Medicine, and director of clinical nutrition at the Floating Hospital of New England Medical Center Hospitals. He received his B.A. from Wesleyan University in 1966 and his M.D. from the University of Pennsylvania in 1970. Following an internship at Children's Hospital of Philadelphia, he spent 3 years in the Middle America Research Unit of the National Institute of Allergy and Infectious Disease in Panama studying insect-borne viruses. After the completion of his residency at Upstate Medical Center, he received a Ph.D. in Nutritional Biochemistry from Massachusetts Institute of Technology.

In addition to his academic responsibilities in Boston, Dr. Dietz was a principal research scientist at the MIT/Harvard Division of Health Science and Technology, associate director of the Clinical Research Center at the Massachusetts Institute of Technology, and director of the Boston Obesity/Nutrition Research Center funded by NIDDK. He has been a counselor of the American Society for Clinical Nutrition, and past president of the North American Association for the Study of Obesity. In 1995 he received the John Stalker Award from the American School Food Service Association for his efforts to improve school lunches. Dr. Dietz served on the 1995 Dietary Guidelines Advisory Committee. He is a past member of the NIDDK Task Force on Obesity and President-elect of the American Society for Clinical Nutrition. In 1998, Dr. Dietz was elected to the Institute of Medicine of the National Academy of Sciences. He is the author of over 100 publications in the scientific literature.

Michael P. Doyle, Ph.D., is Regents Professor of Food Microbiology and director of the University of Georgia Center for Food Safety. Previously, he was Distinguished Professor of Food Microbiology and Toxicology at the University of Wisconsin. Dr. Doyle's research program promotes collaboration among the food industry, the university, and federal and state agencies. His research focuses on developing methods to detect and control foodborne bacterial pathogens at all levels of the food continuum, from the farm to the table. He is internationally acknowledged as a leading authority on foodborne pathogens, especially *Escherichia coli* O157:H7. His National Academies service includes chairmanship of the Committee on the Review of the USDA E. coli 0157:H7 Farm-to-Table Process Risk Assessment and participation in the 2004 *US-Iranian Workshop on Food Safety*, the NRC Committee on Na-

tional Needs for Research in Veterinary Science, and the IOM/NRC Committee to Ensure Safe Food from Production to Consumption. He currently chairs the Food and Nutrition Board's Food Forum. He was elected to the IOM in 2003.

Kathleen Ellwood, Ph.D., is the Director of the Division of Nutrition Programs and Labeling, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, at the Food and Drug Administration. This Division is responsible for the development of policies, regulations, position papers, regulatory guidelines, and advisory opinions on issues related to nutrition and nutrition labeling (primarily health claims and nutrient content claims), dietary recommendations, food fortification, and related nutrition science issues. She was the National Program Leader for Human Nutrition with the USDA Agricultural Research Service (ARS) from 1999 to 2002. In this position she provided strategic planning and guidance for the ARS human nutrition research program. Prior to joining ARS, Dr. Ellwood was the Director of the Human Nutrition and the Food Safety competitive grant programs for USDA's Cooperative State Research, Education, and Extension Service (CSREES). Dr. Ellwood has held research positions at FDA, CFSAN, and USDA, ARS. She received her Ph.D. in nutritional biochemistry from the University of Maryland. Dr. Ellwood is a member of several professional societies and has numerous publications.

Joanne M. Holden, M.S., received her M.S. in Human Nutrition from the University of Maryland. She joined the Beltsville Human Nutrition Research Center, ARS, USDA as a support scientist in the Carbohydrate Metabolism Laboratory where she conducted research on the effects of carbohydrate intake and metabolism. Then, Ms. Holden worked as a Research Nutritionist in the Food Composition Laboratory, Beltsville Human Nutrition Research Center for 20 years before joining the Nutrient Data Laboratory (NDL) as Research Leader in 1995. Her research interests include food sampling and the evaluation of data quality. As Research Leader of the NDL, Ms. Holden provides leadership in the acquisition, evaluation, compilation, and dissemination of food composition data and related research efforts. She has served as the Co-Director of the International Postgraduate Course for the Production, Management, and Use of Food Composition Data since 1994. The course which has been held in Wageningen, The Netherlands, and various regions around the world has trained more than 350 scientists from 50 countries

since 1992. The NDL is one of seven units in the Beltsville Human Nutrition Research Center of the ARS in Beltsville, Maryland, USA. The primary responsibility of the NDL is to provide authoritative food composition data on foods available in the United States. The USDA National Nutrient Database for Standard Reference (SR) is the primary product of the NDL. The current release of the USDA National Nutrient Database for Standard Reference (SR19) contains data on over 7,200 food items. It is the standard reference source for food composition data in the U.S. and provides the core data for most public and private sector databases. In addition, NDL develops and releases other Special Interest Databases, including carotenoids, choline, isoflavones, flavonoids, and fluoride databases, each containing data for 125-400 major food sources of these components. These various databases are available free of charge to all Internet users at NDL's website (www.ars.usda.gov/nutrient data). Also, NDL releases data at a reasonable cost on a CD-ROM. SR is updated, in part, and re-released annually. To support the development of these database products NDL conducts research on sampling, sample handling, and data compilation. NDL has established the National Food and Nutrient Analysis Program to generate original analytical data and to support food composition research and estimation. NDL staff collaborates with analytical laboratories and with other national and regional database groups to keep abreast of new developments in analytical methodology and quality assurance, areas essential to the development of accurate and representative values.

Shiriki K. Kumanyika, Ph.D., M.P.H., is Associate Dean for Health Promotion and Disease Prevention at the University of Pennsylvania School of Medicine and professor of epidemiology in the Department of Biostatistics and Epidemiology. Before coming to the University of Pennsylvania, Dr. Kumanyika was professor of nutrition and epidemiology and head of the Department of Human Nutrition and Dietetics at the University of Illinois at Chicago. She has also held prior positions on the nutrition and epidemiology faculties of the Pennsylvania State University, Johns Hopkins University, and Cornell University. Her publications reflect over 20 years of research related to cardiovascular diseases, obesity, nutritional epidemiology, and the health of minority populations, older populations, and women. Dr. Kumanyika was a member of the IOM Committee on Understanding the Biology of Sex and Gender Differences and of the Committee on Legal and Ethical Issues in the Inclusion of Women in Clinical Studies. She served on the IOM Committee

on Prevention of Obesity in Children and Youth and currently serves on the IOM Committee on Progress in Preventing Childhood Obesity. She is currently a member of the Advisory Council of the NIH's National Heart, Lung and Blood Institute. She earned an M.S. in social work from Columbia University, a Ph.D. in human nutrition from Cornell University, and an M.P.H. from Johns Hopkins University.

Alice H. Lichtenstein, Ph.D., is the Stanley N. Gershoff Professor of Nutrition Science and Policy in the Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy at Tufts University and Senior Scientist and Director of the Cardiovascular Nutrition Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging. Dr. Lichtenstein holds a secondary appointment as Professor of Family Medicine and Community Health at Tufts University School of Medicine. Dr. Lichtenstein completed her undergraduate work at Cornell University in Nutrition. She earned her masters and doctoral degrees in nutrition from Harvard University. Dr. Lichtenstein received her post-doctoral training in the field of lipid metabolism at the Cardiovascular Institute at Boston University School of Medicine. Dr. Lichtenstein's research is focused on assessing the interplay of diet and heart disease risk factors. Current studies focus on *trans*–fatty acids, soy protein and isoflavones, sterol/stanol esters, genetically modified/selectively bred oils and glycemic index in postmenopausal females and older males.

Dr. Lichtenstein is a member of the American Society for Nutrition; and the Arteriosclerosis, Thrombosis and Vascular Biology, as well as the Nutrition, Physical Activity and Metabolism Councils of the American Heart Association. She is immediate past-chair of the American Heart Association Nutrition Committee. She has served on the USDA/HHS 2000 Dietary Guidelines Advisory Committee and the Dietary Reference Intake Macronutrient Panel of the National Academy of Sciences, Institute of Medicine, Food and Nutrition Board.

Julie Mares, Ph.D., is a Professor of Ophthalmology and Visual Sciences at the University of Wisconsin-Madison and part of Interdepartmental Faculty in Nutritional Sciences and Population Health. Dr. Mares earned a Ph.D. from the University of Wisconsin in Nutritional Sciences in 1987, an M.S. in Public Health from the University of Illinois, School of Public Health in 1980 and a B.S. in Foods and Nutrition from the University of Illinois in 1976. She is a member of several professional organizations, including the American Society for Nutritional Sciences and

the Association for Research in Vision and Ophthalmology and the International Carotenoid Society. Over the past eighteen years, she and her research team have published over 60 manuscripts and book chapters that describe relationships of nutrition to common age-related chronic diseases of the eye to clinicians, scientists and the general public. Her epidemiologic research team has used several techniques to assess diet and nutritional status and has used them to investigate relationships of these to age-related macular degeneration and cataract and to diabetic retinopathy in several large populations. Her current research focuses on measuring carotenoids in the retina and examining relationships with levels in the diet and blood and with the occurrence of age-related cataract and macular degeneration.

Linda D. Meyers, Ph.D., is the Director of the IOM's Food and Nutrition Board. She has also served as FNB Deputy Director and as a Senior Program Officer. Prior to joining the IOM in 2001, she worked for 15 years in the Office of Disease Prevention and Health Promotion in the U.S. Department of Health and Human Services (DHHS) where she was a Senior Nutrition Advisor, Deputy Director, and Acting Director. Dr. Meyers has received a number of awards for her contributions to public health, including the Secretary's Distinguished Service Award for *Healthy People 2010* and the Surgeon General's Medallion. Her research interests include indicators of nutrition in populations, nutrition monitoring, and nutrition policy. Dr. Meyers has a B.A. in health and physical education from Goshen College in Indiana, M.S. in food and nutrition from Colorado State University, and Ph.D. in nutritional sciences from Cornell University.

Sanford A. Miller, Ph.D., is currently a Senior Fellow at the Center for Food, Nutrition, and Agriculture Policy in College Park, MD, and was named Professor and Dean Emeritus of The Graduate School of Biomedical Sciences at The University of Texas Health Science Center at San Antonio (UTHSCSA) in December 2000. From 1987-2000, Dr. Miller was the Dean of the Graduate School of Biomedical Sciences and Professor in the Departments of Biochemistry and Medicine at the UTHSCSA. He is the former Director of the Center for Food Safety and Applied Nutrition at the FDA. Previously, he was a Professor of Nutritional Biochemistry at the Massachusetts Institute of Technology. Dr. Miller has served on many national and international government and professional society advisory committees, including the Federation of

American Societies for Experimental Biology (FASEB) Expert Committee on GRAS Substances, the National Advisory Environmental Health Sciences Council of NIH, the Institute of Medicine's Food and Nutrition Board and the Food Forum, the Joint WHO/FAO Expert Advisory Panel on Food Safety (Chairman), and the Steering Committees of several WHO/FAO panels. He has served as a member of the Food and Nutrition Board's Committee on Dietary Reference Intakes and Subcommittee on Upper Reference Levels of Nutrients. In 1998, Dr. Miller was elected a Fellow of The American Society for Nutritional Sciences, and was also a member of the Institute of Medicine and National Research Council's Committee to Ensure Safe Food from Production to Consumption. More recently, he has been named to three additional National Academy of Sciences committees, including the Committee on Agricultural Biotechnology, Health and the Environment of the National Research Council, the Roundtable on Environmental Health Sciences, Research, and Medicine, and chairs the Dietary Reference Intakes Panel on Macronutrients of the IOM. In June 2000, he became the first recipient of the FDA's Distinguished Alumni Award. He is author or co-author of more than 200 original scientific publications. Dr. Miller received a B.S. in chemistry from the City College of New York, and a M.S. and Ph.D. from Rutgers University in physiology and biochemistry.

John Milner, Ph.D., is chief of the Nutritional Science Research Group, Division of Cancer Prevention, National Cancer Institute. In this position he promotes research that deals with the physiological importance of dietary bioactive compounds as modifiers of cancer risk and tumor behavior. Previously, Dr. Milner was Professor and Head in the Department of Nutrition at The Pennsylvania State University, where he also served as Director of the Graduate Program in Nutrition. Dr. Milner received his Doctorate in nutrition, with a minor in biochemistry and physiology, from Cornell University in 1974. He is a member of the American Society for Nutritional Sciences, American Association of Cancer Research, American Society for Clinical Nutrition, American Chemical Society's Food and Chemistry Division and the Institute of Food Technology. Dr. Milner is a fellow in the American Association for the Advancement of Science and serves on the editorial boards of the *Journal of Medical Food, Journal of Nutritional Biochemistry, Nutrition and Cancer, Comprehensive Reviews of Food Science/Food Safety and Nutrition, Nutrition and Foods, and the Journal of Nutrition*.

Suzanne P. Murphy, Ph.D., R.D., is a researcher (professor) at the Cancer Research Center of Hawaii at the University of Hawaii (Honolulu, HI) and director of the Nutrition Support Shared Resource at the center. Previously, Dr. Murphy was state director of the California Expanded Food and Nutrition Program at the University of California—Davis. Dr. Murphy's research interests include dietary assessment methodology, development of food and supplement composition databases, and nutritional epidemiology of chronic diseases (with emphasis on cancer and obesity). Dr. Murphy has served as a member of the National Nutrition Monitoring Advisory Council and the year 2000 Dietary Guidelines Advisory Committee. Currently, she serves on editorial boards for the *Journal of Food Composition and Analysis* and *Nutrition Today* and serves as contributing editor for *Nutrition Reviews*. She is a member of various professional organizations including the American Dietetic Association, the American Society for Nutritional Sciences, the American Public Health Association, the American Society for Clinical Nutrition, the Society for Nutrition Education, the Society for Epidemiological Research, and the Society for International Nutrition Research. Dr. Murphy has served on several IOM panels including the Subcommittee on Interpretation and Uses of Dietary Reference Intakes (as chair then member), the Subcommittee on Upper Safe Reference Levels of Nutrients (as member, and the Panel on Calcium and Related Nutrients (as member). She is currently completing service as chair of the Committee to Review the WIC Food Packages. Dr. Murphy earned a B.S. degree in mathematics from Temple University, Philadelphia, an M.S. degree in molecular biology from San Francisco State University, and a Ph.D. degree in nutrition from the University of California-Berkeley. She is a registered dietitian.

Greg Paoli, M.A., leads a consulting firm (Decisionalysis Risk Consultants) specializing in risk assessment and risk management in the field of public health and safety. He has experience in diverse risk domains including microbiological and toxicological hazards, climate change impact assessment, air and water quality, medical and engineering devices as well as risk-based priority-setting across multiple hazards. Mr. Paoli is currently serving as a Councilor of the Society for Risk Analysis (SRA). He has served as Chair of SRA's Biological Stressors Specialty Group and serves on SRA's Internationalization Task Force. Within Canada, Greg has served on Expert Committees of the National Roundtable on the Environment and the Economy and is a member of Health Canada's

Expert Advisory Committee on Antimicrobial Resistance Risk Assessment. Mr. Paoli has provided guest lectures at the Queen's University's Public Sector Executive Programme and School of Public Policy, University of Calgary's Faculty of Management and the University of Ottawa's Institute of Population Health. In the United States, he has served on an Institute of Medicine Committee tasked to Review the USDA *E. coli* 0157:H7 Farm-to-Table Process Risk Assessment. He was recently appointed to a NRC Committee entitled, *Improving Risk Analysis Approaches Used by the US Environmental Protection Agency*. He served for several years on an Expert Panel to develop a Risk Ranking Framework for the FDA and was on the Peer Review Panel for the Harvard BSE Risk Assessment. Mr. Paoli has served on several international expert panels including Expert Consultations as part of the Joint Food and Agriculture Organization and World Health Organization (FAO/WHO) Activities on Microbial Risk Assessment. He has provided training in risk assessment approaches across North America, Japan and South America. Mr. Paoli also provides lectures as part of the Harvard School of Public Health continuing education course in Probabilistic Risk Assessment. Mr. Paoli earned a Master of Applied Science degree in Systems Design Engineering and a Bachelor's Degree in Electrical and Computer Engineering from the University of Waterloo.

Barbara Petersen, M.P.H., Ph.D., is a Principal and serves as Director of Exponent's Food & Chemicals practice. Dr. Petersen is internationally recognized for her expertise in exposure assessment methodology, food consumption profile modeling, and applications of Monte Carlo techniques to conduct risk assessments. Dr. Petersen has pioneered the technical methods for incorporating information about dietary practices, actual agricultural practices and commercial food processing technologies into regulatory science issues. Dr. Petersen has successfully applied these approaches to develop software that maximizes the utility of data and provides realistic risk assessments that allow the user to understand the sources of potential exposure. Applications include FQPA compliance, regulatory strategies for existing products, intake calculations to support new pesticides, GRAS self-affirmations and preparation of food additive petitions, nutrition labeling justifications, new food product designs and marketing strategies, and product stewardship program designs. Dr. Petersen has directed the design and conduct of seven statistically based national market basket studies. These studies were designed for different purposes, including acute and chronic as-

sessments for pesticides, compliance assessments under Proposition 65, and market research.

Joseph V. Rodricks, Ph.D., was a Founding Principal of ENVIRON International Corporation in 1982. He is an internationally recognized expert in the field of toxicology and risk analysis and in their uses in regulation and in the evaluation of toxic tort and product liability cases. Since 1980, he has consulted for hundreds of manufacturers, for government agencies and the World Health Organization, and he has served on 20 Boards and Committees of the National Academy of Sciences and the Institute of Medicine. In 2003, he was elected a National Associate of the National Academies. He has more than 150 publications on toxicology and risk analysis, and has lectured nationally and internationally on these topics. Dr. Rodricks was formerly Deputy Associate Commissioner, Health Affairs, and Toxicologist, U.S. Food and Drug Administration (1965-1980); and is a Visiting Professor, The Johns Hopkins University School of Public Health. He has been certified as a Diplomate, American Board of Toxicology, since 1982. Dr. Rodricks' experience includes chemical products and contaminants in foods, food ingredients, air, water, hazardous wastes, the workplace, consumer products, and medical devices and pharmaceutical products. In 2005 Dr. Rodricks received the Outstanding Practioner Award from the Society for Risk Analysis. He is the author of *Calculated Risks* (Cambridge University Press), a nontechnical introduction to toxicology and risk analysis that is now in its sixth printing, and which won an award from the American Medical Writers Association. A second edition is now in press.

Robert M. Russell, M.D., is a professor of medicine and nutrition at Tufts University and director of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston. He has served on national and international advisory boards including the USDA Human Investigation Committee (Chairman), the FDA, U.S. Pharmacopoeia Convention, National Dairy Council Advisory Board, and the American Board of Internal Medicine. He has worked on international nutrition programs in several countries including Vietnam, Iran, Iraq, Guatemala, China, and the Philippines. Dr. Russell is a member of numerous professional societies, on the editorial boards of five professional journals, a councilor to the American Society for Clinical Nutrition, and a member of the Board of Directors of the American College of Nutrition. Dr. Russell co-authored the standards for parenteral and enteral nutrition to

be used in U.S. long-term care facilities. He is a staff gastroenterologist at the New England Medical Center Hospitals. Dr. Russell's primary work involves studying the effects of aging on gastrointestinal absorptive function. He is a noted expert in the area of human metabolism of retinoids and carotenoids. Dr. Russell served as a member of the FNB's Panel on Folate, Other B Vitamins, and Choline, and chair of the Panel on Micronutrients. Dr. Russell received his B.S. from Harvard University and M.D. from Columbia University. He is currently a member of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes.

Barbara O. Schneeman, Ph.D., is Director, Office of Nutritional Products, Labeling, and Dietary Supplements (ONPLDS), in the Center for Food Safety and Applied Nutrition (CFSAN), with the FDA. She oversees the development of policy and regulations for dietary supplements, nutrition labeling and food standards, infant formula, and medical foods. Prior to joining FDA, she served as a member of the faculty and administration at the University of California, Davis. She held appointments as professor in the Departments of Nutrition, Food Science and Technology, and Internal Medicine in the School of Medicine. Dr. Schneeman has served as Assistant Administrator for Nutrition in the Agricultural Research Service in the U.S. Department of Agriculture. She has many professional activities and honors to her credit. Dr. Schneeman received her B.S. from the University of California, Davis in food science and technology, and her Ph.D. in nutrition from the University of California, Berkeley.

Amy F. Subar, Ph.D., M.P.H., R.D., is a research nutritionist at the National Cancer Institute. She received her B.S. in Dietetics at the State University College at Buffalo; an M.P.H. at the University of Minnesota; and a Ph.D. at Syracuse University. Her research interests include developing, designing, and carrying out nutrition research related to dietary methods, development of dietary instruments, measurement error, dietary surveillance, and nutritional epidemiology. Dr. Subar recently directed the development and evaluation of a new food frequency questionnaire, the Diet History Questionnaire. This work encompassed all areas of questionnaire development: cognitive issues, methods to determine food and portion size lists, methods for creating nutrient databases for frequency questionnaires, testing of response rates, and comparative validation. This food frequency questionnaire has recently been modified to be

web-based for use in nutrition research. Dr. Subar's more recent research has focused on understanding measurement error in the biomarker-based, Observing Protein and Energy Nutrition, or OPEN Study. She has focused on analyses of underreporting, methods for surveillance of usual dietary intake, and development of short dietary screener instruments. Currently, Dr. Subar is leading a project to develop a web-based automated self-administered 24-hour dietary recall using multimedia computer technology. Dr. Subar serves as a member of the Editorial Board of the Journal of the American Dietetic Association.

Christine Lewis Taylor, Ph.D., is a scholar at the IOM where she is now working on issues related to Dietary Reference Intakes. She came to IOM in 2006 with a wealth of experience in nutrition science and policy, having served for more than 20 years in the US government, most recently as Director of FDA's Office of Nutritional Products, Labeling and Dietary Supplements. From 2004 through 2006 Dr. Taylor was assigned to the risk assessment group within the World Health Organization where she was the Project Director for their most recent nutrient risk assessment work.

Dr. Taylor holds numerous Public Health Service Awards including the Meritorious Service Award and the Outstanding Service Medal. She has been a member of various intragovernment working groups and liaison activities on science and policy, and she has represented FDA on a variety of panels ranging from the American Heart Association to the White House Commission on Alternative and Complementary Medicines FDA's in 2000-2002. She has served as Head of Delegation to the Codex Alimentarius Committee on Food Labeling and as Alternate Delegate to the Codex Committee on Nutrition and Foods for Special Dietary Uses.

Kathryn Wiemer, M.S., R.D., is director/Fellow, Regulatory and Issues Management General Mills Bell Institute of Health and Nutrition. She has been employed at General Mills for over 28 years. In her current position, she is responsible for ensuring that General Mills' products comply with existing government and corporate nutrition regulations and policies. She leads the development of Corporate positions and comments to government regulatory agencies on nutrition issues and serves as a liaison with these agencies, trade associations and health professional organizations in the area of nutrition.

Ms. Wiemer has extensive experience in providing direction to marketing and divisional research concerning nutrition issues and opportuni-

ties; coordinating product-related nutrition research studies and developing nutrition education materials and communication programs for health professionals and consumers.

She has been honored to receive two General Mills Champion's Award for her role in two major efforts: conducting clinical research and a communication campaign to consumers and health professionals related to the heart health benefits of Cheerios and securing the whole grain health claim and related communication programs.

After receiving her Bachelor of Science Degree in Nutrition and Dietetics from Iowa State University in 1976, she completed her Master's Degree in Human Nutrition at the University of Nebraska in 1978. Her area of research was iron bioavailability and interactions of dietary fiber, iron, and lead. Early in her career at General Mills, she co-edited the book entitled *Iron Fortification of Foods* and has coauthored several scientific papers.

Ms. Wiemer just completed serving as chair of the Grocery Manufacturers of America (GMA) Nutrition & Labeling Committee and serves as vice chair on the Board of Directors of the Wheat Foods Council. She serves on several committees of the International Life Sciences Institute (ILSI) and the International Food Information Council (IFIC), is a Registered Dietitian, a member of the American Dietetic Association (ADA), the Dietitians in Business and Communications practice group of the ADA and the Minnesota Dietetic Association.

Catherine E. Woteki, Ph.D., is global director of scientific affairs at Mars, Incorporated. Prior to coming to Mars she was dean of the College of Agriculture at Iowa State University. Dr. Woteki also held the appointments of senior research scientist with the College of Agriculture and Natural Resources at the University of Maryland and professor of nutrition and food safety at the University of Nebraska. Her extensive government experience includes service as USDA undersecretary for food safety and USDA deputy undersecretary for research, education, and economics, as well as leadership positions in the Office of Science and Technology Policy in the Executive Office of the President and the National Center for Health Statistics in the Centers for Disease Control and Prevention. She is a member of professional associations for nutrition, dietetics, public health, food technology, and nutrition education. Her awards include the Elijah White Award from the National Center for Health Statistics, the Special Recognition Award from the U.S. Public Health Service, and the Staff Achievement Award from the

Institute of Medicine. Dr. Woteki received a B.S. in biology and chemistry from Mary Washington College and M.S. and PhD in human nutrition from Virginia Polytechnic Institute and State University. She is an IOM member and a former director and chair of the Food and Nutrition Board. She is also a Fellow of the American Association for the Advancement of Science.

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Acronyms and Abbreviations

ADI	Acceptable Daily Intake
AHRQ	Agency for Healthcare Research and Quality
AI	Adequate Intake
AMD	age-related macular degeneration
ASA24	automated self-administered 24-hour recall
BMI	body mass index
BUI	Beneficial Utility Index
CVD	cardiovascular disease
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DRI	Dietary Reference Intakes
DV	Daily Value
EAR	Estimated Average Requirement
EPA	eicosapenataenoic acid
FDA	Food and Drug Administration
FFQ	food frequency questionnaire
IOM	Institute of Medicine
LOAEL	lowest-observed-adverse-effect level

NCI	National Cancer Institute
NFNAP	National Food and Nutrient Analysis Program
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
PICO	a mnemonic for the terms Population, Intervention, Comparator, Outcome
RAE	retinol activity equivalent
RDA	Recommended Dietary Allowances
SNP	single-nucleotide polymorphism
SR	National Nutrient Database for Standard Reference
UL	Tolerable Upper Intake Level
USDA	U.S. Department of Agriculture
U.S. RDA	U.S. Recommended Daily Allowances
WIC	Supplemental Nutrition Program for Women, Infants, and Children