

Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients

Food and Nutrition Board, Institute of Medicine

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Food and Nutrition Board
Institute of Medicine

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients¹

INTRODUCTION

The model for risk assessment of nutrients used to develop tolerable upper intake levels (ULs) is one of the key elements of the developing framework for Dietary Reference Intakes (DRIs). DRIs are dietary reference values for the intake of nutrients and food components by Americans and Canadians. The U.S. National Academy of Sciences recently released two reports in the series (IOM, 1997, 1998). The overall project is a comprehensive effort undertaken by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee) of the Food and Nutrition Board (FNB), Institute of Medicine, National Academy of Sciences in the United States, with active involvement of Health Canada. The DRI project is the result of significant discussion from 1991 to 1996 by the FNB regarding how to approach the growing concern that one set of quantitative estimates of recommended intakes, the Recommended Dietary Allowances (RDAs), was scientifically inappropriate to be used as the basis for many of the uses to which it had come to be applied. The lack of specific determinations of maximum or tolerable upper levels of intake was noted (IOM, 1994).

The two DRI reports issued to date provide recommended intakes (see [Appendix A](#)) and upper levels of intake for two groups of nutrients and food components: calcium and related nutrients, and folate, B vitamins, and choline. Currently, the DRI Committee and panels of experts are reviewing dietary antioxidants and related compounds, with similar reviews planned for other micronutrients including electrolytes and fluid, macronutrients, and other food

¹ Adapted from the two DRI reports published to date: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride* (IOM, 1997), and *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline* (IOM, 1998).

BOX 1 Uses of Dietary Reference Intakes for Healthy Individuals and Groups

<i>Type of Use</i>	<i>For the Individual</i>	<i>For a Group</i>
Planning	<p>RDA: aim for this intake.</p> <p>AI: aim for this intake.</p> <p>UL: Use as a guide to limit intake; chronic intake of higher amounts may increase risk of adverse effects.</p>	<p>EAR: use in conjunction with a measure of variability of the group's intake to set goals for the mean intake of a specific population.</p>
Assessment ^a	<p>EAR: use to examine the possibility of inadequacy; evaluation of true status requires clinical, biochemical, and/or anthropometric data.</p> <p>UL: use to examine the possibility of overconsumption; evaluation of true status requires clinical, biochemical, and/or anthropometric data.</p>	<p>EAR: use in the assessment of the prevalence of inadequate intakes within a group.</p>

RDA = Recommended Dietary Allowance
 EAR = Estimated Average Requirement
 AI = Adequate Intake
 UL = Tolerable Upper Intake Level

^a Requires statistically valid approximation of usual intake.

components not traditionally classified as "nutrients," but purported to play a beneficial role in human diets. It is expected that when evaluation of all groups of nutrients and food components are completed as part of this ongoing process, the model for risk assessment of nutrients will have been fully developed and validated.

WHAT ARE DIETARY REFERENCE INTAKES?

Dietary Reference Intakes (DRIs) are reference values that are quantitative estimates of nutrient intakes to be used for planning and assessing diets for healthy people. They include both recommended intakes and ULs as reference values (see **Box 1**). Although the reference values are based on data, the data are often scanty or drawn from studies that had limitations in addressing the question. Thus, scientific judgment is required in setting the reference values:

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- *Recommended Dietary Allowance (RDA)*: the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a group.
- *Adequate Intake (AI)*: a value based on observed or experimentally determined approximations of nutrient intake by a group (or groups) of healthy people—used when an RDA cannot be determined.
- *Tolerable Upper Intake Level (UL)*: 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. As intake increases above the UL, the risk of adverse effects increases.
- *Estimated Average Requirement (EAR)*: a nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a group.

The development of DRIs expands on the periodic reports called *Recommended Dietary Allowances*, which have been published since 1941 by the National Academy of Sciences. It is expected that as additional groups of nutrients and food components are reviewed over the next few years, the process and initial models developed will evolve and be further refined. As new information or processes develop, reference intakes will be periodically reassessed in keeping with this evolving process.

Recommended Dietary Allowance

The *Recommended Dietary Allowance (RDA)* is the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular gender and life stage group (life stage considers age and, when applicable, pregnancy or lactation).

Process for Setting the RDA

The process for setting the RDA depends on being able to set an *Estimated Average Requirement (EAR)*. That is, the RDA is derived from the nutrient requirement so if an EAR cannot be set, no RDA will be set. The EAR is the daily intake value of a nutrient that is estimated to meet the nutrient requirement of half the healthy individuals in a life stage and gender group. Before setting the EAR, a specific criterion of adequacy is selected, based on a careful review of the literature. When selecting the criterion, reduction of disease risk is considered along with many other health parameters. The RDA is set at the EAR plus twice the standard deviation (SD) if known ($RDA = EAR + 2 SD$); if data about variability in requirements are insufficient to calculate an SD, a coefficient of variation for the EAR of 10 percent is ordinarily assumed ($RDA = 1.2 \times EAR$).

The RDA for a nutrient is a value to be used as a goal for dietary intake by healthy individuals. The RDA is not intended to be used to assess the diets of either individuals or groups or to plan diets for groups.

Adequate Intake

The *Adequate Intake* (AI) is set instead of an RDA if sufficient scientific evidence is not available to calculate an EAR. The AI is based on observed or experimentally determined estimates of nutrient intake by a group (or groups) of healthy people. For example, the AI for young infants, for whom human milk is the recommended sole source of food for the first 4 to 6 months, is based on the daily mean nutrient intake supplied by human milk for healthy, full-term infants who are exclusively breastfed. The main intended use of the AI is as a goal for the nutrient intake of individuals. Other uses of AIs will be considered by another expert group.

Tolerable Upper Intake Level

The *Tolerable Upper Intake Level* (UL) is 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. As intake increases above the UL, the risk of adverse effects increases. The term *tolerable intake* was chosen to avoid implying a possible beneficial effect. Instead, the term is intended to connote a level of intake that can, with high probability, be tolerated biologically. The UL is not intended to be a recommended level of intake. There is no established benefit for healthy individuals if they consume nutrient intakes above the RDA or AI.

ULs are useful because of the increased interest in and availability of fortified foods and the increased use of dietary supplements. ULs are based on total intake of a nutrient from food, water, and supplements if adverse effects have been associated with total intake. However, if adverse effects have been associated with intake from supplements or food fortificants only, the UL is based on nutrient intake from those sources only, not on total intake. The UL applies to chronic daily use.

For many nutrients, there are insufficient data on which to develop a UL. This does not mean that there is no potential for adverse effects resulting from high intake. When data about adverse effects are extremely limited, extra caution may be warranted.

APPROACH FOR SETTING DIETARY REFERENCE INTAKES, INCLUDING TOLERABLE UPPER INTAKE LEVELS

The scientific data used to develop recommended intakes and ULs have come from observational and experimental studies. Studies published in peer-reviewed journals were the principal source of data. Life stage and gender were considered to the extent possible, but for some nutrients, the data did not provide a basis for proposing different requirements or upper levels for men and women or for adults in different age groups.

Three of the categories of reference values (EAR, RDA, and AI) are defined by specific criteria of nutrient adequacy; the fourth (UL) is defined by a specific endpoint of adverse effect if one is available. In all cases, data were examined closely to determine whether reduction of risk of a chronic degenerative disease or developmental abnormality could be used as a criterion of adequacy. The quality of studies was examined, considering study design, methods used for measuring intake and indicators of adequacy, and biases, interactions, and confounding factors. After careful review and analysis of the evidence, including examination of the extent of congruence of findings, scientific judgment was used to determine the basis for establishing the values.

Terminology

The term "tolerable" was chosen because it connotes a level of intake that can, with high probability, be tolerated biologically by individuals; it does not imply acceptability of that level in any other sense. The setting of a UL does not indicate that nutrient intakes greater than the RDA or AI are recommended as being beneficial to an individual. Many individuals are self-medicating with nutrients for curative or treatment purposes. It is beyond the scope of the model at this time to address the possible therapeutic benefits of higher nutrient intakes that may offset the risk of adverse effects. The UL is not meant to apply to individuals who are being treated with the nutrient or food component under medical supervision.

The term "adverse effect" is defined as any significant alteration in the structure or function of the human organism (Klaassen et al., 1986), or any impairment of a physiologically important function, in accordance with the definition set by the joint World Health Organization, Food and Agriculture Organization of the United Nations, and International Atomic Energy Agency (WHO/FAO/IAEA) Expert Consultation in *Trace Elements in Human Nutrition and Health* (WHO, 1996). In the case of nutrients, it is exceedingly important to consider the possibility that the intake of one nutrient may alter in detrimental ways the health benefits conferred by another nutrient. Any such alteration (referred to as an adverse nutrient-nutrient interaction) is considered an adverse

health effect. When evidence for such adverse interactions is available, it is considered in establishing a nutrient's UL.

Concept

Like all chemical agents, nutrients can produce adverse health effects if intakes from any combination of food, water, nutrient supplements, and pharmacologic agents are excessive. Some lower level of nutrient intake will ordinarily pose no likelihood (or risk) of adverse health effects in normal individuals even if the level is above that associated with any benefit. It is not possible to identify a single "risk-free" intake level for a nutrient that can be applied with certainty to all members of a population. However, it is possible to develop intake levels that are unlikely to pose risk of adverse health effects to most members of the general population, including sensitive individuals. For some nutrients or food components these intake levels may, however, pose a risk to subpopulations with extreme or distinct vulnerabilities.

MODEL FOR THE DERIVATION OF TOLERABLE UPPER INTAKE LEVELS

The possibility that the methodology used to derive ULs might be reduced to a mathematical model that could be generically applied to all nutrients was considered. Such a model might have several potential advantages, including ease of application and assurance of consistent treatment of all nutrients. It was concluded, however, that the current state of scientific understanding of toxic phenomena in general, and nutrient toxicity in particular, is insufficient to support the development of such a model. Scientific information regarding various adverse effects and their relationships to intake levels varies greatly among nutrients and depends on the nature, comprehensiveness, and quality of available data. The uncertainties associated with the unavoidable problem of extrapolating from the circumstances under which data are developed (for example, in the laboratory or clinic) to other circumstances (for example, to the healthy population) adds to the complexity.

Given the current state of knowledge, any attempt to capture in a mathematical model all the information and scientific judgments that must be made to reach conclusions regarding ULs would not be consistent with contemporary risk assessment practices. Instead, the model for the derivation of ULs consists of a set of scientific factors that always should be considered explicitly. The framework under which these factors are organized is called *risk assessment*. Risk assessment (NRC, 1983, 1994) is a systematic means of evaluating the probability of occurrence of adverse health effects in humans from excess exposure to an environmental agent (in this case, a nutrient or food component) (FAO/WHO, 1995; Health Canada, 1993). The hallmark of risk

assessment is the requirement to be explicit in all the evaluations and judgments that must be made to document conclusions.

RISK ASSESSMENT AND FOOD SAFETY

Basic Concepts

Risk assessment is a scientific undertaking having as its objective a characterization of the nature and likelihood of harm resulting from human exposure to agents in the environment. The characterization of risk typically contains both qualitative and quantitative information and includes a discussion of the scientific uncertainties in that information. In the present context, the agents of interest are nutrients, and the environmental media are food, water, and nonfood sources such as nutrient supplements and pharmacologic preparations.

Performing a risk assessment results in a characterization of the relationships between exposure(s) to an agent and the likelihood that adverse health effects will occur in members of exposed populations. Scientific uncertainties are an inherent part of the risk assessment process and are discussed below. Deciding whether the magnitude of exposure is "acceptable" in specific circumstances is not a component of risk assessment; this activity falls within the domain of *risk management*. Risk management decisions depend on the results of risk assessments but may also involve the public health significance of the risk, the technical feasibility of achieving various degrees of risk control, and the economic and social costs of this control. Because there is no single, scientifically definable distinction between "safe" and "unsafe" exposures, risk management necessarily incorporates components of sound, practical decision making that are not addressed by the risk assessment process (NRC, 1983, 1994).

A risk assessment requires that information be organized in rather specific ways but does not require any specific scientific evaluation methods. Rather, risk assessors must evaluate scientific information using what they judge to be appropriate methods; and they must make explicit the basis for their judgments, the uncertainties in risk estimates, and when appropriate, alternative interpretations of the available data that may be scientifically plausible (NRC, 1994; OTA, 1993).

Risk assessment is subject to two types of scientific uncertainties: (1) those related to data and (2) those associated with inferences that are required when directly applicable data are not available (NRC, 1994). Data uncertainties arise when evaluating information obtained from the epidemiologic and toxicologic studies of nutrient intake levels that are the basis for risk assessments. Examples of inferences include the use of data from experimental animals to estimate responses in humans and the selection of uncertainty factors to estimate inter and intraspecies variabilities in response to toxic substances. Uncertainties arise

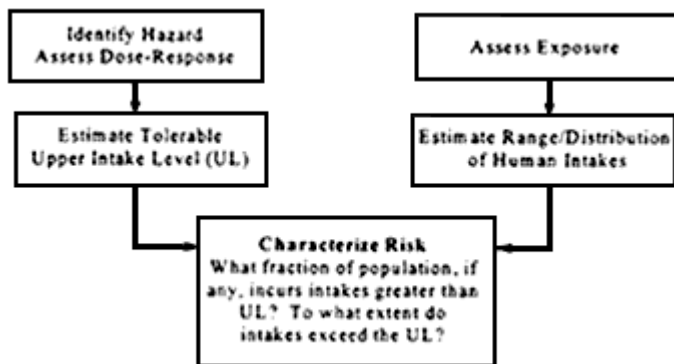


FIGURE 1.
Risk assessment model for nutrient toxicity.

whenever estimates of adverse health effects in humans are based on extrapolations of data obtained under dissimilar conditions (for example, from experimental animal studies). Options for dealing with uncertainties are discussed below and in detail in [Appendix B](#).

Steps in the Risk Assessment Process

The organization of risk assessment is based on a model proposed by the NRC (1983, 1994); that model is widely used in public health and regulatory decision making. The steps of risk assessment as applied to nutrients are as follows (see also [Figure 1](#)):

- Step 1. *Hazard identification* involves the collection, organization, and evaluation of all information pertaining to the adverse effects of a given nutrient. It concludes with a summary of the evidence concerning the capacity of the nutrient to cause one or more types of toxicity in humans.
- Step 2. *Dose-response assessment* determines the relationship between nutrient intake (dose) and adverse effect (in terms of incidence and severity). This step concludes with an estimate of the UL—it identifies 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. Different ULs may be developed for various life stage groups.
- Step 3. *Intake assessment* evaluates the distribution of usual total daily nutrient intakes among members of the general population.
- Step 4. *Risk characterization* summarizes the conclusions from Steps 1 through 3 and evaluates the risk. Generally, the risk is expressed as the fraction

of the exposed population, if any, having nutrient intakes (Step 3) in excess of the estimated UL (Steps 1 and 2). If possible, scientific characterization also covers the magnitude of any such excesses. Scientific uncertainties associated with both the UL and the intake estimates are described so that risk managers understand the degree of scientific confidence they can place in the risk assessment.

The risk assessment contains no discussion of recommendations for reducing risk; these are the focus of risk management.

Thresholds

A principal feature of the risk assessment process for noncarcinogens is the long-standing acceptance that no risk of adverse effects is expected unless a threshold dose (or intake) is exceeded. The adverse effects that may be caused by a nutrient or food component almost certainly occur only when the threshold dose is exceeded (NRC, 1994; WHO, 1996). The critical issues concern the methods used to identify the approximate threshold of toxicity for a large and diverse human population. Because most nutrients are not considered to be carcinogenic in humans, the approach to carcinogenic risk assessment (EPA, 1996) is not discussed here.

Thresholds vary among members of the general population (NRC, 1994). For any given adverse effect, if the distribution of thresholds in the population could be quantitatively identified, it would be possible to establish ULs by defining some point in the lower tail of the distribution of thresholds that would be protective for some specified fraction of the population. However, data are not sufficient to allow identification of the distribution of thresholds for all but a few, well-studied nutrients and compounds found in food (for example, acute toxic effects or for chemicals such as lead, where the human database is very large). The method described here for identifying thresholds for a general population is designed to ensure that almost all members of the population will be protected, but it is not based on an analysis of the theoretical (but practically unattainable) distribution of thresholds. By using the model to derive the threshold, however, there is considerable confidence that the threshold, which becomes the UL for nutrients or food components, lies very near the low end of the theoretical distribution, and is the end representing the most sensitive members of the population. For some nutrients, there may be subpopulations that are not included in the general distribution because of extreme or distinct vulnerabilities to toxicity. Such distinct groups, whose conditions warrant medical supervision, may not be protected by the UL.

The Joint FAO/WHO Expert Commission on Food Additives and various national regulatory bodies have identified factors (called *uncertainty factors* [UFs]) that account for interspecies and intraspecies differences in response to

the hazardous effects of substances and to account for other uncertainties (WHO, 1987). Uncertainty factors are used to make inferences about the threshold dose of substances for members of a large and diverse human population from data on adverse effects obtained in epidemiological or experimental studies. These factors are applied consistently when data of specific types and quality are available. They are typically used to derive acceptable daily intakes for food additives and other substances for which data on adverse effects are considered sufficient to meet minimum standards of quality and completeness (FAO/WHO, 1982). These adopted or recognized uncertainty factors have sometimes been coupled with other factors to compensate for deficiencies in the available data and other uncertainties regarding data.

When possible, the UL is based on a no-observed-adverse-effect level (NOAEL), which is the highest intake (or experimental oral dose) of a nutrient at which no adverse effects have been observed in the individuals studied. This is identified for a specific circumstance in the hazard identification and dose-response assessment steps of the risk assessment. If there are no adequate data demonstrating a NOAEL, then a lowest-observed-adverse-effect level (LOAEL) may be used. A LOAEL is the lowest intake (or experimental oral dose) at which an adverse effect has been identified. The derivation of a UL from a NOAEL (or LOAEL) involves a series of choices about what factors should be used to deal with uncertainties. Uncertainty factors (UFs) are applied in an attempt to deal both with gaps in data and incomplete knowledge regarding the inferences required (for example, the expected variability in response within the human population). The problems of both data and inference uncertainties arise in all steps of the risk assessment. A discussion of options available for dealing with these uncertainties is presented below and in greater detail in [Appendix B](#).

A UL is not, in itself, a description of human risk. It is derived by application of the hazard identification and dose-response evaluation steps (Steps 1 and 2) of the risk assessment model. To determine whether populations are at risk requires an intake or exposure assessment (Step 3, evaluation of intakes of the nutrient by the population) and a determination of the fractions of those populations, if any, whose intakes exceed the UL. In the intake assessment and risk characterization steps (Steps 3 and 4), the distribution of actual intakes for the population is used as a basis in determining whether and to what extent the population is at risk.

APPLICATION OF THE RISK ASSESSMENT MODEL TO NUTRIENTS

This section provides guidance for applying the risk assessment framework (the model) to the derivation of ULs for nutrients.

Special Problems Associated with Substances Required for Human Nutrition

Although the risk assessment model outlined above can be applied to nutrients to derive ULs, it must be recognized that nutrients possess some properties that distinguish them from the types of agents for which the risk assessment model was originally developed (NRC, 1983). In the application of accepted standards for assessing risks of environmental chemicals to the risk assessment of nutrients and food components, a fundamental difference between the two categories must be recognized: within a certain range of intakes, many nutrients are essential for human well-being and usually for life itself. Nonetheless, they may share with other chemicals the production of adverse effects at excessive exposures. Because the consumption of balanced diets is consistent with the development and survival of humankind over many millennia, there is less need for the large uncertainty factors that have been used in the typical risk assessment of nonessential chemicals. In addition, if data on the adverse effects of nutrients are available primarily from studies in human populations, there will be less uncertainty than is associated with the types of data available on nonessential chemicals.

There is no evidence to suggest that nutrients consumed at the recommended intake (the RDA or AI) present a risk of adverse effects to the general population. It is clear, however, that the addition of nutrients to a diet, either through the ingestion of large amounts of highly fortified food or nonfood sources such as supplements, or both, may (at some level) pose a risk of adverse health effects.² The UL is 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. As intake increases above the UL, the risk of adverse effects increases.

If adverse effects have been associated with total intake, ULs are based on total intake of a nutrient from food, water, and supplements. For cases in which adverse effects have been associated with intake only from supplements and/or food fortificants, the UL is based on intake from those sources only, rather than on total intake. The effects of nutrients from fortified foods or supplements may differ from those of naturally occurring constituents of foods because of several factors: the chemical form of the nutrient, the timing of the intake and amount consumed in a single bolus dose, the matrix supplied by the food, and the relation of the nutrient to the other constituents of the diet. Nutrient requirements and food intake are related to the metabolizing body mass, which is also at least an indirect measure of the space in which the nutrients are

² It is recognized that possible exceptions to this generalization relate to specific geochemical areas with excessive environmental exposures to certain trace elements (for example, selenium) and to rare case reports of adverse effects associated with highly eccentric consumption of specific foods. Data from such findings are not useful for setting ULs for the general North American population.

distributed. This relation between food intake and space of distribution supports homeostasis, which maintains nutrient concentrations in that space within a range compatible with health. However, excessive intake of a single nutrient from supplements or fortificants may compromise this homeostatic mechanism. Such elevations alone may pose risks of adverse effects; imbalances among the concentrations of mineral elements (for example, calcium, iron, zinc, and copper) can result in additional risks (Mertz et al., 1994). These reasons and those discussed previously support the need to include the form and pattern of consumption in the assessment of risk from high nutrient intake.

Consideration of Variability in Sensitivity

The risk assessment model outlined in this paper is consistent with classical risk assessment approaches in that it must consider variability in the sensitivity of individuals to adverse effects of nutrients. A discussion of how variability is dealt with in the context of nutritional risk assessment follows.

Physiological changes and common conditions associated with growth and maturation that occur during an individual's lifespan may influence sensitivity to nutrient toxicity. For example, (1) sensitivity increases with declines in lean body mass and with declines in renal and liver function that occur with aging; (2) sensitivity changes in direct relation to intestinal absorption or intestinal synthesis of nutrients (for example, vitamin K, biotin); (3) in the newborn infant, sensitivity is also increased because of rapid brain growth and limited ability to secrete or biotransform toxicants; and (4) sensitivity increases with decreases in the rate of metabolism of nutrients. During pregnancy, the increase in total body water and glomerular filtration results in lower blood levels of water soluble vitamins dose-for-dose, and therefore, reduced susceptibility to potential adverse effects. However, in the unborn fetus this may be offset by active placental transfer, accumulation of certain nutrients in the amniotic fluid, and rapid development of the brain. Examples of life stage groups that may differ in terms of nutritional needs and toxicological sensitivity include infants and children, the elderly, and women during pregnancy and lactation.

Even within relatively homogeneous life stage groups, there is a range of sensitivities to toxic effects. The model described below accounts for normally expected variability in sensitivity, but it excludes subpopulations with extreme and distinct vulnerabilities. Such subpopulations consist of individuals needing medical supervision; they are better served through the use of public health screening, product labeling, or other individualized health care strategies. (Such populations may not be at "negligible risk" when their intakes reach the UL developed for the healthy population.) The decision to treat identifiable vulnerable subgroups as distinct (not protected by the UL) is a matter of judgment and is made evident in the rationale provided for characterizing the UL.

Bioavailability

In the context of toxicity, the bioavailability of an ingested nutrient can be defined as its accessibility to normal metabolic and physiological processes. Bioavailability influences a nutrient's beneficial effects at physiological levels of intake and also may affect the nature and severity of toxicity due to excessive intakes. Factors that affect bioavailability include the concentration and chemical form of the nutrient, the nutrition and health of the individual, and excretory losses. Bioavailability data for specific nutrients must be considered and incorporated by the risk assessment process.

Some nutrients, for example, folate, may be less readily absorbed when they are part of a meal than when taken separately. Supplemental forms of some nutrients, such as some of the B vitamins, phosphorus, or magnesium, may require special consideration if they have higher bioavailability and therefore may present a higher risk of producing adverse effects than equivalent amounts from the natural form found in food.

Nutrient-Nutrient Interactions

A diverse array of adverse health effects can occur as a result of the interaction of nutrients. The potential risks of adverse nutrient-nutrient interactions increase when there is an imbalance in the intake of two or more nutrients. Excessive intake of one nutrient may interfere with absorption, excretion, transport, storage, function, or metabolism of a second nutrient. For example, dietary interactions can affect the chemical forms of elements at the site of absorption through ligand binding or changes in the valence state of an element (Mertz et al., 1994). Phytates, phosphates, and tannins are among the most powerful depressants of bioavailability, and organic acids, such as citric and ascorbic acid, are strong enhancers for some minerals and trace elements. Thus dietary interactions strongly influence the bioavailability of elements by affecting their partition between the absorbed and the nonabsorbed portion of the diet. The large differences of bioavailability ensuing from these interactions support the need to specify the chemical form of the nutrient when setting ULs. Dietary interactions can also alter nutrient bioavailability through their effect on excretion. For example, dietary intake of protein, phosphorus, sodium, and chloride all affect urinary calcium excretion and hence calcium bioavailability. Interactions that significantly elevate or reduce bioavailability may represent adverse health effects.

Although it is critical to include knowledge of any such interactions in the risk assessment, it is difficult to evaluate the possibility of interactions without reference to a particular level of intake. This difficulty can be overcome if a UL for a nutrient or food component is first derived based on other measures of

toxicity. Then an evaluation can be made of whether intake at the UL has the potential to affect the bioavailability of other nutrients.

Possible adverse nutrient-nutrient interactions, then, are considered as a part of setting a UL. Nutrient-nutrient interactions may be considered either as a critical endpoint on which to base a UL for that nutrient or as supportive evidence for a UL based on another endpoint.

Other Relevant Factors Affecting Bioavailability of Nutrients

In addition to nutrient interactions, other considerations have the potential to influence nutrient bioavailability, such as the nutritional status of an individual and the form of intake. These issues should be considered in the risk assessment. The absorption and utilization of most minerals, trace elements, and some vitamins are a function of the individual's nutritional status, particularly regarding the intake of other specific nutrients such as iron (Barger-Lux et al., 1995; Mertz et al., 1994).

With regard to the form of intake, minerals and trace elements often are less readily absorbed when they are part of a meal than when taken separately or when present in drinking water (NRC, 1989). The opposite is true for fat-soluble vitamins whose absorption depends on fat in the diet. ULs must therefore be based on nutrients as part of the total diet, including the contribution from water. Nutrient supplements that are taken separately from food require special consideration, since they are likely to have different availabilities and therefore may represent a greater risk of producing toxic effects.

STEPS IN THE DEVELOPMENT OF THE TOLERABLE UPPER INTAKE LEVEL

Step 1. Hazard Identification

Based on a thorough review of the scientific literature, the hazard identification step outlines the adverse health effects that have been demonstrated to be caused by the nutrient (see [Box 2](#)). The primary types of data used as background for identifying nutrient hazards in humans are as follows:

- *Human studies.* Human data provide the most relevant kind of information for hazard identification, and, when they are of sufficient quality and extent, are given greatest weight. However, the number of controlled human toxicity studies conducted in a clinical setting is very limited for ethical reasons. Such studies are generally most useful for identifying very mild (and ordinarily reversible) adverse effects. Observational studies that focus on well-defined populations with clear exposures to a range of nutrient intake levels are useful for establishing a relationship between exposure and effect. Observational data

in the form of case reports or anecdotal evidence are used for developing hypotheses that can lead to knowledge of causal associations. Sometimes a series of case reports, if it shows a clear and distinct pattern of effects, may be reasonably convincing on the question of causality.

BOX 2 DEVELOPMENT OF TOLERABLE UPPER INTAKE LEVELS (ULS)

- *Components of Hazard Identification*

- Evidence of adverse effects in humans
- Causality
- Relevance of experimental data
- Mechanisms of toxic action
- Quality and completeness of the database
- Identification of distinct and highly sensitive subpopulations

Components of Dose-Response Assessment

- Data selection
- Identification of no-observed-adverse-effect level (NOAEL) (or lowest-observed-adverse-effect level [LOAEL] and critical endpoint
- Uncertainty assessment
- Derivation of a UL
- Characterization of the estimate and special considerations

- *Animal studies.* The majority of the available data used in regulatory risk assessments comes from controlled laboratory experiments in animals, usually mammalian species other than humans (for example, rodents). Such data are used in part because human data on food-derived substances, particularly nonessential chemicals, are generally very limited. Because well-conducted animal studies can be controlled, establishing causal relationships is generally not difficult. However, cross species differences make the usefulness of animal data for establishing ULs problematic (see below).

Key issues that are addressed in the data evaluation of human and animal studies are the following:

- *Evidence of adverse effects in humans.* The hazard identification step involves the examination of human, animal, and in vitro published evidence addressing the likelihood of a nutrient or food component eliciting an adverse effect in humans. Decisions regarding which observed effects are adverse are based on scientific judgments. Although toxicologists generally regard any demonstrable structural or functional alteration to represent an adverse effect, some alterations may be considered of little or self-limiting biological importance.

As noted earlier, adverse nutrient-nutrient interactions are considered in the definition of an adverse effect.

- *Causality.* Is a causal relationship established by the published human data? The criteria of Hill (1971) are considered in judging the causal significance of an exposure-effect association indicated by epidemiologic studies. These criteria include: demonstration of a temporal relationship, consistency, narrow confidence intervals for risk estimates, a biological gradient or dose response, specificity of effect, biological plausibility, and coherence.
- *Relevance of experimental data.* Consideration of the following issues can be useful in assessing the relevance of experimental data.
- *Animal data.* Animal data may be of limited utility in judging the toxicity of nutrients because of highly variable interspecies differences in nutrient requirements. Nevertheless, relevant animal data are considered in the hazard identification and dose-response assessment steps where applicable.
- *Route of exposure.*³ Data derived from studies involving oral exposure (rather than parenteral, inhalation, or dermal exposure) are most useful for the evaluation of nutrients and food components. Data derived from studies involving parenteral, inhalation, or dermal routes of exposure may be considered relevant if the adverse effects are systemic and data are available to permit interroute extrapolation.
- *Duration of exposure.* Because the magnitude, duration, and frequency of exposure can vary considerably in different situations, consideration needs to be given to the relevance of the exposure scenario (for example, chronic daily dietary exposure versus short-term bolus doses) to dietary intakes by human populations.
- *Mechanisms of toxic action.* Knowledge of molecular and cellular events underlying the production of toxicity can assist in dealing with the problems of extrapolation between species and from high to low doses. It may also aid in understanding whether the mechanisms associated with toxicity are those associated with deficiency. In most cases, however, because knowledge of the biochemical sequence of events resulting from toxicity and deficiency is still incomplete, it is not yet possible to state with certainty whether or not these sequences share a common pathway. Iron, the most thoroughly studied trace element, may represent the only exception to this statement. Deficient to near-toxic exposures share the same pathway, which maintains controlled oxygen transport and catalysis. Toxicity sets in when the exposure exceeds the specific iron-complexing capacity of the organism, resulting in free iron species initiating peroxidation.

³ The terms *route of exposure* and *route of intake* refer to how a substance enters the body, for example, by ingestion, injection, or dermal absorption. These terms should not be confused with *form of intake*, which refers to the medium or vehicle used, for example, supplements, food, or drinking water.

- *Quality and completeness of the database.* The scientific quality and quantity of the database are evaluated. Human or animal data are reviewed for suggestions that the substances have the potential to produce additional adverse health effects. If suggestions are found, additional studies may be recommended.
- *Identification of distinct and highly sensitive subpopulations.* The ULs are based on protecting the most sensitive members of the general population from adverse effects of high nutrient intake. Some highly sensitive subpopulations have responses (in terms of incidence, severity, or both) to the agent of interest that are clearly distinct from the responses expected for the healthy population. The risk assessment process recognizes that there may be individuals within any life stage group that are more biologically sensitive than others, and thus their extreme sensitivities do not fall within the range of sensitivities expected for the general population. The UL for the general population may not be protective for these subgroups. As indicated earlier, the extent to which a distinct subpopulation will be included in the derivation of a UL for the general population is an area of judgment to be addressed on a case-by-case basis.

Step 2. Dose-Response Assessment

The process for deriving the UL is described in this section and outlined in [Box 2](#). It includes selection of the critical data set, identification of a critical endpoint with its NOAEL (or LOAEL), and assessment of uncertainty.

Data Selection

The data evaluation process results in the selection of the most appropriate or critical data set(s) for deriving the UL. Selecting the critical data set includes the following considerations:

- Human data are preferable to animal data.
- In the absence of appropriate human data, information from an animal species whose biological responses are most like those of humans is most valuable.
- If it is not possible to identify such a species or to select such data, data from the most sensitive animal species, strain, or gender combination are given the greatest emphasis.
- The route of exposure that most resembles the route of expected human intake is preferable. This includes considering the digestive state (for example, fed or fasted) of the subjects or experimental animals. Where this is not possible, the differences in route of exposure are noted as a source of uncertainty.

- The critical data set defines a dose-response relationship between intake and the extent of the toxic response known to be most relevant to humans. Data on bioavailability are considered and adjustments in expressions of dose response are made to determine whether any apparent differences in response can be explained. For example, it is known that different metal salts can display different degrees of bioavailability. If the database involves studies of several different salts (for example, iron or chromium valence states), and the effect of the nutrient is systemic, then apparent differences in the degree and/or form of the toxic response among different salts may simply reflect differences in bioavailability. Data on bioavailability are considered and adjustments in expressions of dose response are made to determine whether any apparent differences in response can be explained.
- The critical data set documents the route of exposure and the magnitude and duration of the intake. Furthermore, the critical data set documents the intake that does not produce adverse effects (the NOAEL), as well as the intake producing toxicity.

Identification of NOAEL (or LOAEL) and Critical Endpoint

A nutrient can produce more than one toxic effect (or endpoint), even within the same species or in studies using the same or different exposure durations. The NOAELs and LOAELs for these effects will differ. The critical endpoint used to establish a UL is the adverse biological effect exhibiting the lowest NOAEL (for example, the most sensitive indicator of a nutrient or food toxicity). The derivation of a UL based on the most sensitive endpoint will ensure protection against all other adverse effects.

For some nutrients, there may be inadequate data on which to develop a UL. The lack of reports of adverse effects following excess intake of a nutrient does not mean that adverse effects do not occur. As the intake of any nutrient increases, a point (A, see [Figure 2](#)) is reached at which intake begins to pose a risk. Above this point, increased intake increases the risk of adverse effects. For some nutrients, and for various reasons, there are inadequate data to identify point A, or even to make an estimate of its location.

Because adverse effects are almost certain to occur for any nutrient at some level of intake, it should be assumed that such effects may occur for nutrients for which a scientifically documentable UL cannot now be derived. Until a UL is set or an alternative approach to identifying protective limits is developed, intakes greater than the RDA or AI should be viewed with caution.

Uncertainty Assessment

Several judgments must be made regarding the uncertainties and thus the uncertainty factor (UF) associated with extrapolating from the observed data to

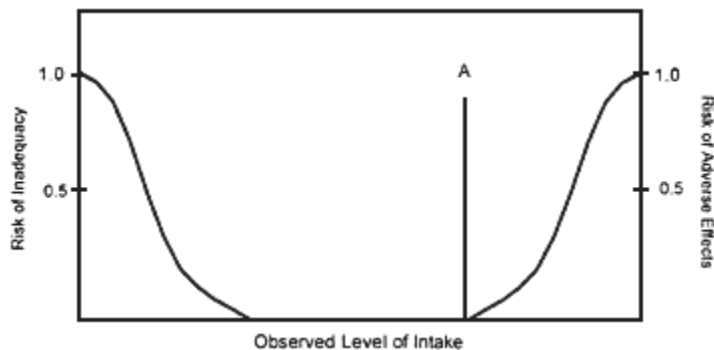


FIGURE 2.

Theoretical description of health effects of a nutrient as a function of level of intake. The Tolerable Upper Intake Level (UL) at point A is 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. At intakes above the UL, the risk of adverse effects increases.

the general population (see [Appendix B](#)). Applying a UF to a NOAEL (or LOAEL) results in a value for the derived UL that is less than the experimentally derived NOAEL, unless the UF is 1.0. The larger the uncertainty, the larger the UF and the smaller the UL. This is consistent with the ultimate goal of the risk assessment: to provide an estimate of a level of intake that will protect the health of the healthy population (Mertz et al., 1994).

Although several reports describe the underlying basis for UFs (Dourson and Stara, 1983; Zielhuis and van der Kreek, 1979), the strength of the evidence supporting the use of a specific UF will vary. Because the imprecision of the UFs is a major limitation of risk assessment approaches, considerable leeway must be allowed for the application of scientific judgment in making the final determination. Since data are generally available regarding intakes of nutrients and food components in human populations, the data on nutrient toxicity may not be subject to the same uncertainties as with nonessential chemical agents, resulting in UFs for nutrients and food components typically less than 10. They are lower with higher quality data and when the adverse effects are extremely mild and reversible.

In general, when determining a UF, the following potential sources of uncertainty are considered and combined into the final UF:

- *Interindividual variation in sensitivity.* Small UFs (close to 1) are used to represent this source of uncertainty if it is judged that little population variability is expected for the adverse effect, and larger factors (close to 10) are used if variability is expected to be great (NRC, 1994).

- *Experimental animal to human.* A UF to account for the uncertainty in extrapolating animal data to humans is generally applied to the NOAEL when animal data are the primary data set available. Larger UFs (close to 10) may be used if it is believed that the animal responses will underpredict average human responses (NRC, 1994).
- *LOAEL to NOAEL.* If a NOAEL is not available, a UF may be applied to account for the uncertainty in deriving a UL from the LOAEL. The size of the UF applied involves scientific judgment based on the severity and incidence of the observed effect at the LOAEL and the steepness (slope) of the dose response.
- *Subchronic NOAEL to predict chronic NOAEL.* When data are lacking on chronic exposures, scientific judgment is necessary to determine whether chronic exposure is likely to lead to adverse effects at lower intakes than those producing effects after subchronic exposures (exposures of shorter duration).

Characterization of the Estimate and Special Considerations

ULs are derived for various life stage groups using relevant databases, NOAELs and LOAELs, and UFs. In cases where no data exist with regard to NOAELs or LOAELs for the group under consideration, extrapolations from data in other age groups and/or animal data are made on the basis of known differences in body size, physiology, metabolism, absorption, and excretion of the nutrient.

If the data review reveals the existence of subpopulations having distinct and exceptional sensitivities to a nutrient's toxicity, these subpopulations should be explicitly discussed and concerns related to adverse effects noted; however the use of the data is not included in the identification of the NOAEL or LOAEL upon which the UL for the general population is based.

DERIVATION OF ULs: SUMMARY OF PROGRESS TO DATE

Derivation of UFs

The model described in this document has been applied to two groups of nutrients and food components as part of the continuing DRI process. The selection of a UF of approximately 1.0 for fluoride and magnesium is primarily based on the very mild (and in the case of magnesium, reversible) nature of the adverse effects observed. A slightly larger UF (1.2) was selected for vitamin D intake in adults and in other life stage groups except infants as the short duration of the study used (Narang et al., 1984) and the small sample size supports the selection of a slightly larger UF. For vitamin D in infants, a larger UF (1.8) was selected due to the insensitivity of the critical endpoint, the small sample sizes of the studies, and the limited data about the sensitivity at the tails of the

distribution. A UF of 2 was selected for calcium to account for the potential increased susceptibility to high calcium intake by individuals who form renal stones and the potential to increase the risk of mineral depletion due to the interference of calcium on mineral bioavailability, especially iron and zinc. The UF for phosphorus is based on the lack of information concerning potential adverse effects of serum inorganic phosphate values in the range between normal serum phosphate levels and levels associated with ectopic mineralization. The selection of a UF of 2.5 for phosphorus was due to the relative lack of human data describing adverse effects of excess phosphorus intakes.

With regard to the B vitamins and choline, because of lack of suitable data that met the requirements of the model, NOAELs (and LOAELs) could not be determined for thiamin, riboflavin, vitamin B₁₂, pantothenic acid, or biotin. The UF for folate added to food or as a supplement was 5, based primarily on the severity of the neurological complications observed but also on the use of a LOAEL rather than a NOAEL to derive the UL. For niacin as a supplement or food fortificant, the UF selected was 1.5, based on the transient nature of the adverse effect of flushing, and the consideration that it was applied to a LOAEL and not a NOAEL. The UF for both vitamin B₆ and choline was 2. In the case of vitamin B₆, there were less data available involving responses to pyridoxine doses under 500 mg/day, and thus more limited information upon which to base a UL. The UF of 2 for choline was selected because of the limited data regarding hypotension and the magnitude of the interindividual variation in response to cholinergic effects.

Derivation of a UL

UL values have been established for broad age groups for nutrients for which adequate data are available (see [Table 1](#)). Values are set at levels that are unlikely to pose risk to the most sensitive members of the general population. They cannot be used to assess the prevalence of the population at risk for adverse effects as a result of excess intakes. The UL for magnesium is from supplement intake only, and for niacin and folate from fortified food and supplement intake only. In all three cases, the nutrient naturally found in foods is excluded from concern. The adverse effect or critical endpoint used for each nutrient is given in [Table 2](#). Three case studies (calcium, folate, and riboflavin) are described in [Appendix D](#).

Derivation of a UL for Other Groups

The UL is derived by dividing the NOAEL (or LOAEL) by a single UF that incorporates all relevant uncertainties for the life stage category for which the data are available (see [Table 1](#)). The derivation of a UL involves the use of

TABLE 1. Dietary Reference Intakes: Tolerable Upper Intake Levels (ULs) for Certain Nutrients and Food Components

Life Stage	Calcium (g/day)	Phosphorus (g/day)	Magnesium (mg/day) ^b	Vitamin D (µg/day)	Fluoride (mg/day)	Niacin (mg/day) ^c	Vitamin B ₆ (mg/day)	Folate (µg/day) ^c	Choline (g/day)
0–6 months	ND ^d	ND	ND	25	0.7	ND	ND	ND	ND
7–12 months	ND	ND	ND	25	0.9	ND	ND	ND	ND
1–3 years	2.5	3	65	50	1.3	10	30	300	1.0
4–8 years	2.5	3	110	50	2.2	15	40	400	1.0
9–13 years	2.5	4	350	50	10	20	60	600	2.0
14–18 years	2.5	4	350	50	10	30	80	800	3.0
19–70 years	2.5	4	350	50	10	35	100	1,000	3.5
> 70 years	2.5	3	350	50	10	35	100	1,000	3.5
<i>Pregnancy</i>									
18 years	2.5	3.5	350	50	10	30	80	800	3.0
19–50 years	2.5	3.5	350	50	10	35	100	1,000	3.5
<i>Lactation</i>									
18 years	2.5	4	350	50	10	30	80	800	3.0
19–50 years	2.5	4	350	50	10	35	100	1,000	3.5

^a UL = the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for thiamin, riboflavin, vitamin B₁₂, pantothenic acid, or biotin. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

^b The UL for magnesium represents intake from a pharmacological agent only and does not include intake from food and water.

^c The ULs for niacin and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of the two.

^d ND = not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts.

Source of intake should be from food only to prevent high levels of intake.

TABLE 2. UL Critical Adverse Effects

Nutrient	Adverse Effect
Calcium	Milk-alkali syndrome
Phosphorus	Elevated serum P _i
Magnesium	Osmotic diarrhea
Vitamin D	Serum calcium > 11 mg/dl
Fluoride	Children: moderate dental fluorosis Adults: moderate skeletal fluorosis
Niacin	Flushing
Vitamin B ₆	Sensory neuropathy
Folate	Neuropathy in B ₁₂ -deficient individuals
Choline	Hypotension, fishy body odor

scientific judgment to select the appropriate NOAEL (or LOAEL) and UF. The risk assessment requires explicit consideration and discussion of all choices made, both regarding the data used and the uncertainties accounted for.

For infants, ULs were not determined for any of the B vitamins, choline, magnesium, phosphorus, or calcium because of the lack of data on adverse effects in this age group and concern regarding infants' possible lack of ability to handle excess amounts. Thus, caution is warranted; food should be the source of intake of these nutrients by infants. For vitamin D and fluoride, due to the significant information on effects from various levels of intake by infants for these nutrients, ULs were developed.

When data were not available on children or adolescents, ULs were determined by extrapolating from the UL for adults based on body weight differences using the formula:⁴

$$UL_{\text{child}} = (UL_{\text{adult}})(\text{Weight}_{\text{child}}/\text{Weight}_{\text{adult}}).$$

The reference weight for males aged 19 through 30 years (see [Appendix C](#)) was used for adults and the reference weights for female children and adolescents were used in the formula above to obtain the UL for each age group. The use of these reference weights yields a conservative UL to protect the sensitive individuals in each age group.

⁴ In the case of niacin, vitamin B₆, folate, and choline, the formula was based on metabolic size:

$$UL_{\text{child}} = (UL_{\text{adult}})(\text{Weight}_{\text{child}}/\text{Weight}_{\text{adult}})^{0.75}$$

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Appendix A

Recommended Dietary Intakes for Individuals

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TABLE A. Recommended Intakes For Individuals

Life Stage Group	Calcium (mg/d)	Phosphorus (mg/d)	Magnesium (mg/d)	Vitamin D (μ g/d) ^{a,b}	Fluoride (mg/d)	Thiamin (mg/d)
Infants						
0–6 mo	210*	100*	30*	5*	0.01*	0.2*
7–12 mo	270*	275*	75*	5*	0.5*	0.3*
Children						
1–3 y	500*	460	80	5*	0.7*	0.5
4–8 y	800*	500	130	5*	1*	0.6
Males						
9–13 y	1,300*	1,250	240	5*	2*	0.9
14–18 y	1,300*	1,250	410	5*	3*	1.2
19–30 y	1,000*	700	400	5*	4*	1.2
31–50 y	1,000*	700	420	5*	4*	1.2
51–70 y	1,200*	700	420	10*	4*	1.2
> 70 y	1,200*	700	420	15*	4*	1.2
Females						
9–13 y	1,300*	1,250	240	5*	2*	0.9
14–18 y	1,300*	1,250	360	5*	3*	1.0
19–30 y	1,000*	700	310	5*	3*	1.1
31–50 y	1,000*	700	320	5*	3*	1.1
51–70 y	1,200*	700	320	10*	3*	1.1
> 70 y	1,200*	700	320	15*	3*	1.1
Pregnancy						
≤ 18 y	1,300*	1,250	400	5*	3*	1.4
19–30 y	1,000*	700	350	5*	3*	1.4
31–50 y	1,000*	700	360	5*	3*	1.4
Lactation						
≤ 18 y	1,300*	1,250	360	5*	3*	1.5
19–30 y	1,000*	700	310	5*	3*	1.5
31–50 y	1,000*	700	320	5*	3*	1.5

NOTE: This table presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

^a As cholecalciferol. 1 (μ)g cholecalciferol = 40 IU vitamin D.

^b In the absence of adequate exposure to sunlight.

^c As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0–6 months = preformed niacin (not NE).

^d As dietary folate equivalents (DFE). 1 DFE = 1 (μ)g food folate = 0.6 (μ)g of folic acid from fortified food or as a supplement consumed with food = 0.5 (μ)g of a supplement taken on an empty stomach.

^e Although AIs have been set for choline, there are too few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

Riboflavin (mg/d)	Niacin (mg/d) ^c	Vitamin B ₆ (mg/d)	Folate (μg/d) ^d	Vitamin B ₁₂ (μg/d)	Pantothenic Acid (mg/d)	Biotin (μg/d)	Choline (mg/d) ^e
0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*
0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*
0.5	6	0.5	150	0.9	2*	8*	200*
0.6	8	0.6	200	1.2	3*	12*	250*
0.9	12	1.0	300	1.8	4*	20*	375*
1.3	16	1.3	400	2.4	5*	25*	550*
1.3	16	1.3	400	2.4	5*	30*	550*
1.3	16	1.3	400	2.4	5*	30*	550*
1.3	16	1.7	400	2.4^f	5*	30*	550*
1.3	16	1.7	400	2.4^f	5*	30*	550*
0.9	12	1.0	300	1.8	4*	20*	375*
1.0	14	1.2	400^g	2.4	5*	25*	400*
1.1	14	1.3	400^g	2.4	5*	30*	425*
1.1	14	1.3	400^g	2.4	5*	30*	425*
1.1	14	1.5	400	2.4^f	5*	30*	425*
1.1	14	1.5	400	2.4^f	5*	30*	425*
1.4	18	1.9	600^h	2.6	6*	30*	450*
1.4	18	1.9	600^h	2.6	6*	30*	450*
1.4	18	1.9	600^h	2.6	6*	30*	450*
1.6	17	2.0	500	2.8	7*	35*	550*
1.6	17	2.0	500	2.8	7*	35*	550*
1.6	17	2.0	500	2.8	7*	35*	550*

^f Because 10 to 30 percent of older people may malabsorb food-bound B₁₂, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with B₁₂ or a supplement containing B₁₂.

^g In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet.

^h It is assumed that women will continue consuming 400 μg from supplements or fortified foods until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptual period—the critical time for formation of the neural tube.

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Appendix B

Options for Dealing with Uncertainties

Methods for dealing with uncertainties in scientific data are generally understood by working scientists and require no special discussion here, except to point out that such uncertainties should be explicitly acknowledged and taken into account whenever a risk assessment is undertaken. More subtle and difficult problems are created by uncertainties associated with some of the inferences that need to be made in the absence of directly applicable data; much confusion and inconsistency can result if they are not recognized and dealt with in advance of undertaking a risk assessment.

The most significant inference uncertainties arise in risk assessments whenever attempts are made to answer the following questions (NRC, 1994):

- What set(s) of hazard and dose-response data (for a given substance) should be used to characterize risk in the population of interest?
- If animal data are to be used for risk characterization, which endpoints for adverse effects should be considered?
- If animal data are to be used for risk characterization, what measure of dose (e.g., dose per unit body weight, body surface, dietary intake) should be used for scaling between animals and humans?
- What is the expected variability in dose response between animals and humans?
- If human data are to be used for risk characterization, which adverse effects should be used?
- What is the expected variability in dose response among members of the human population?
- How should data from subchronic exposure studies be used to estimate chronic effects?
- How should problems of differences in route of exposure within and between species be dealt with?
- How should the threshold dose be estimated for the human population?

- If a threshold in the dose-response relationship seems unlikely, how should a low-dose risk be modeled?
- What model should be chosen to represent the distribution of exposures in the population of interest, when data relating to exposures are limited?
- When interspecies extrapolations are required, what should be assumed about relative rates of absorption from the gastrointestinal tract of animals and of humans?
- For which percentiles on the distribution of population exposures should risks be characterized?

Depending on the nutrient under review, at least partial, empirically based answers to some of these questions may be available, but in no case is scientific information likely to be sufficient to provide a highly certain answer; in many cases there will be no relevant data for the nutrient in question.

It should be recognized that, for several of these questions, certain inferences have been widespread for long periods of time, and thus it may seem unnecessary to raise these uncertainties anew. When several sets of animal toxicology data are available, for example, and data are insufficient to identify the set (i.e., species, strain, adverse effects endpoint) that "best" predicts human response, it has become traditional to select that set in which toxic responses occur at lowest dose ("most sensitive"). In the absence of definitive empirical data applicable to a specific case, it is generally assumed that there will not be more than a 10-fold variation in response among members of the human population. In the absence of absorption data, it is generally assumed that humans will absorb the chemical at the same rate as the animal species used to model human risk. In the absence of complete understanding of biological mechanisms, it is generally assumed that, except possibly for certain carcinogens, a threshold dose must be exceeded before toxicity is expressed. These types of long-standing assumptions, which are necessary to complete a risk assessment, are recognized by risk assessors as attempts to deal with uncertainties in knowledge (NRC, 1994).

A past National Research Council (NRC) report (1983) recommended the adoption of the concepts and definitions that have been discussed in this report. The NRC committee recognized that throughout a risk assessment, data and basic knowledge will be lacking and that risk assessors will be faced with several scientifically plausible options (called "inference options" by the NRC committee) for dealing with questions such as those presented above. For example, there are several scientifically supportable options for dose scaling across species and for high-to-low dose extrapolation, but no ready means to identify those that are clearly best supported. The NRC committee recommended that regulatory agencies in the United States identify the needed inference options in risk assessment and specify, through written risk assessment guidelines, the specific options that will be used for all assessments. Agencies in

the United States have identified the specific models to be used to fill gaps in data and knowledge; these have come to be called *default options* (EPA, 1986).

The use of defaults to fill knowledge and data gaps in risk assessment has the advantage of ensuring *consistency* in approach (the same defaults are used for each assessment) and for minimizing or eliminating case-by-case manipulations of the conduct of risk assessment to meet predetermined risk management objectives. The major disadvantage of the use of defaults is the potential for displacement of scientific judgment by excessively rigid guidelines. A remedy for this disadvantage was also suggested by the NRC committee: risk assessors should be allowed to replace defaults with alternative factors in specific cases of chemicals for which relevant scientific data are available to support alternatives. The risk assessors' obligation in such cases is to provide explicit justification for any such departure. Guidelines for risk assessment issued by the U.S. Environmental Protection Agency, for example, specifically allow for such departures (EPA, 1986).

The use of preselected defaults is not the only way to deal with model uncertainties. Another option is to allow risk assessors complete freedom to pursue whatever approaches they judge applicable in specific cases. Because many of the uncertainties cannot be resolved scientifically, case-by-case judgments without some guidance on how to deal with them will lead to difficulties in achieving scientific consensus, and the results of the assessment may not be credible.

Another option for dealing with uncertainties is to allow risk assessors to develop a range of estimates, based on application of both defaults and alternative inferences that, in specific cases, have some degree of scientific support. Indeed, appropriate analysis of uncertainties would seem to require such a presentation of risk results. Although presenting a number of plausible risk estimates has clear advantages in that it would seem to reflect more faithfully the true state of scientific understanding, there are no well-established criteria for using such complex results in risk management.

The various approaches to dealing with uncertainties inherent to risk assessment, and discussed in the foregoing sections, are summarized in [Table B](#).

Specific default assumptions for assessing nutrient risks have not been recommended. Rather, the approach calls for case-by-case judgments, with the recommendation that the basis for the choices made be explicitly stated. Some general guidelines for making these choices will, however, be offered.

TABLE B. Approaches for Dealing with Uncertainties in a Risk-Assessment Program

Program Model	Advantages	Disadvantages
Case-by-case judgments by experts	Flexibility High potential to maximize use of most relevant scientific information bearing on specific issues	Potential for inconsistent treatment of different issues Difficulty in achieving consensus Need to agree on defaults
Written guidelines specifying defaults for data and model uncertainties (with allowance for departures in specific cases)	Consistent treatment of different issues Maximizes transparency of process Allows resolution of scientific disagreements by resorting to defaults	May be difficult <ul style="list-style-type: none"> • to justify departure • to achieve consensus among scientists that departures are justified in specific cases Danger that uncertainties will be overlooked
Assessors asked to present full array of estimates, using all scientifically plausible models	Maximizes use of scientific information Reasonably reliable portrayal of true state of scientific understanding	Highly complex characterization of risk, with no easy way to discriminate among estimates Size of required effort may not be commensurate with utility of the outcome

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Appendix C

Reference Heights and Weights for Children and Adults

Gender	Age	Median Body Mass Index ^a	Reference Height (cm [in])	Reference Weight, ^b (kg [lb])
Male, female	2–6 mo	-	64 (25)	7 (16)
	7–11 mo	-	72 (28)	9(20)
	1–3 y	-	91 (36)	13 (29)
	4–8 y	15.8	118 (46)	22 (48)
Male	9–13 y	18.5	147 (58)	40 (88)
	14–18 y	21.3	174 (68)	64 (142)
	19–30 y	24.4	176 (69)	76 (166)
Female	9–13 y	18.3	148 (58)	40 (88)
	14–18 y	21.3	163 (64)	57 (125)
	19–30 y	22.8	163 (64)	61 (133)

Adapted from: Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994.

^a In kg/m².

^b Calculated from median body mass index and median heights for ages 4–8 years and older.

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Appendix D

Case Studies of Application of Risk Assessment Model for Nutrients¹

A. Calcium

Hazard Identification

Calcium is among the most ubiquitous of elements found in the human system. Calcium plays a major role in the metabolism of virtually every cell in the body and interacts with a large number of other nutrients. As a result, disturbances of calcium metabolism give rise to a wide variety of adverse reactions. Disturbances of calcium metabolism, particularly those that are characterized by changes in extracellular ionized calcium concentration, can cause damage in the function and structure of many organs and systems.

Currently, the available data on the adverse effects of excess calcium intake in humans primarily concerns calcium intake from nutrient supplements and antacids. Of the many possible adverse effects of excessive calcium intake, the three most widely studied and biologically important are: kidney stone formation (nephrolithiasis), the syndrome of hypercalcemia and renal insufficiency with and without alkalosis (referred to historically as milk-alkali syndrome when associated with a constellation of peptic ulcer treatments), and the interaction of calcium with the absorption of other essential minerals. These are not the only adverse effects associated with excess calcium intake. However, the vast majority of reported effects are related to or result from one of these three conditions.

¹ Taken from the two DRI reports published to date: *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride* (IOM, 1997), and *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline* (IOM, 1998).

Nephrolithiasis

Twelve percent of the U.S. population will form a renal stone over their lifetime (Johnson et al., 1979), and it has generally been assumed that nephrolithiasis is, to a large extent, a nutritional disease. Research over the last 40 years has shown that there is a direct relationship between periods of affluence and increased nephrolithiasis (Robertson, 1985). A number of dietary factors seem to play a role in determining the incidence of this disease. In addition to being associated with increased calcium intakes, nephrolithiasis appears to be associated with higher intakes of oxalate, protein, and vegetable fiber (Massey et al., 1993). Goldfarb (1994) argued that dietary calcium plays a minor role in nephrolithiasis because only 6 percent of the overall calcium load appears in the urine of normal individuals. Also, the efficiency of calcium absorption is substantially lower when calcium supplements are consumed (Sakhaee et al., 1994).

The issue is made more complex by the association between high sodium intakes and hypercalciuria, since sodium and calcium compete for reabsorption at the same sites in the renal tubules (Goldfarb, 1994). Other minerals, such as phosphorus and magnesium, also are risk factors in stone formation (Pak, 1988). These findings suggest that excess calcium intake may play only a contributing role in the development of nephrolithiasis.

Two recent companion prospective epidemiologic studies in men (Curhan et al., 1993) and women (Curhan et al., 1997) with no history of kidney stones found that intakes of dietary calcium greater than 1,050 mg (26.3 mmol)/day in men and greater than 1,098 mg (27.5 mmol)/day in women were associated with a reduced risk of symptomatic kidney stones. This association for dietary calcium was attenuated when the intake of magnesium and phosphorus were included in the model for women (Curhan et al., 1997). This apparent protective effect of dietary calcium is attributed to the binding by calcium in the intestinal lumen of oxalate, which is a critical component of most kidney stones. In contrast, Curhan et al. (1997) found that after adjustment for age, intake of supplemental calcium was associated with an increased risk for kidney stones. After adjustment for potential confounders, the relative risk among women who took supplemental calcium, compared with women who did not, was 1.2. Calcium supplements may be taken without food, which limits opportunity for the beneficial effect of binding oxalate in the intestine. A similar effect of supplemental calcium was observed in men (Curhan et al., 1993), but failed to reach statistical significance. Neither study controlled for the time that calcium supplements were taken (for example, with or without meals); thus, it is possible that the observed significance of the results in women may be due to different usage of calcium supplements by men and women. Clearly, more carefully controlled studies are needed to determine the strength of the causal association between calcium intake vis-à-vis the intake of other nutrients and kidney stones in healthy individuals.

The association between calcium intake and urinary calcium excretion is weaker in children than in adults. However, as observed in adults, increased levels of dietary sodium are significantly associated with increased urinary calcium excretion in children (Matkovic et al., 1995, O'Brien et al., 1996).

Hypercalcemia and Renal Insufficiency (Milk-Alkali Syndrome)

The syndrome of hypercalcemia and, consequently, renal insufficiency with or without metabolic alkalosis is associated with severe clinical and metabolic derangements affecting virtually every organ system (Orwoll, 1982). Renal failure may be reversible but may also be progressive if the syndrome is unrelieved. Progressive renal failure may result in the deposition of calcium in soft tissues including the kidney (for example, nephrocalcinosis) with a potentially fatal outcome (Junor and Catto, 1976). This syndrome was first termed milk-alkali syndrome (MAS) in the context of the high milk and absorbable antacid intake which derived from the "Sippy diet" regimen for the treatment of peptic ulcer disease. MAS needs to be distinguished from primary hyperparathyroidism, in which primary abnormality of the parathyroid gland results in hypercalcemia, metabolic derangement, and impaired renal calcium resorption. As the treatment of peptic ulcers has changed (for example, systemically absorbed antacids and large quantities of milk are now rarely prescribed), the incidence of this syndrome has decreased (Whiting and Wood, 1997).

A review of the literature revealed 26 reported cases of MAS linked to high calcium intake from supplements and food since 1980 without other causes of underlying renal disease (Table D-1). These reports described what appears to be the same syndrome at supplemental calcium intakes of 1.5 to 16.5 g (37.5 to 412.5 mmol)/day for 2 days to 30 years. Estimates of the occurrence of MAS in the North American population may be low since mild cases are often overlooked and the disorder may be confused with a number of other syndromes presenting with hypercalcemia.

No reported cases of MAS in children were found in the literature. This was not unexpected since children have very high rates of bone turnover and calcium utilization relative to adults (Abrams et al., 1992). A single case of severe constipation directly linked to daily calcium supplementation of 1,000 mg (25 mmol) or more has been reported in an 8-year-old boy, but this may represent an idiosyncratic reaction of calcium ions exerted locally in the intestine or colon (Frithz et al., 1991).

Calcium/Mineral Interactions

Calcium interacts with iron, zinc, magnesium, and phosphorus (Clarkson et al., 1967; Hallberg et al., 1992; Schiller et al., 1989; Spencer et al., 1965).

TABLE D-1. Case Reports of Patients with Milk Alkali Syndrome (single dose reported)^a

Studies	Ca Intake (g/day) ^b	Duration	Mitigating Factors
Hart et al., 1982	10.6 ^c	Not stated	NaHCO ₃ , 2 g/d
Carroll et al., 1983	4.2 ^c	30 years	none reported
	2 ^d	5 years	none reported
	3.8 ^c	2 months	vitamins A and E
	2.8 ^c	10 years	NaHCO ₃ , 5 g/d
Kallmeyer and Funston, 1983	8 ^c	10 years	alkali in antacid
Schuman and Jones, 1985	9.8 ^c	20 years	none reported
	4.8 ^c	6 weeks	10 year history of antacid intake
French et al., 1986	8 ^d	2 years	none reported
	4.2 ^d	> 2 years	thiazide
Kapsner et al., 1986	10 ^c	10 months	none reported
	6.8 ^c	7 months	none reported
	4.8 ^d	2 days	10 year history of antacid use
Bullimore and Miloszewski, 1987	6.5 ^c	23 years	alkali in antacid
Gora et al., 1989	4 ^d	2 years	thiazide
Kleinman et al., 1991	16.5 ^c	2 weeks	10 year history of antacid use
Abreo et al., 1993	9.6 ^d	> 3 months	none reported
	3.6 ^d	> 2 years	none reported
	10.8 ^c	Not stated	none reported
Brandwein and Sigman, 1994	2.7 ^d	2 years, 8 months	none reported
Campbell et al., 1994	5 ^c	3 months	none reported
Lin et al., 1996	1.5 ^d	4 weeks	none reported
Muldowney and Mazbar, 1996	1.7 ^d	13 months (52 weeks)	none reported
Whiting and Wood, 1997	2.4 ^d	> 1 year	none reported
Whiting and Wood, 1997	2.3–4.6 ^d	> 1 year	none reported
<i>Number of Subjects</i>	26	–	–
Mean	5.9	3 years, 8 months	–
Median	4.8	13 months	–
Range	1.5–>16.5	2 days–23 years	–

^a Case reports of patients with renal failure are not included in this table.

^b Intake estimates provided by Whiting and Wood (1997).

^c Calcium intake from supplements and diet reported (for example, milk and yogurt consumption). Other dietary sources of calcium not reported are not included.

^d Calcium intake from supplements reported only.

Calcium-mineral interactions are more difficult to quantify than nephrolithiasis and MAS, since in many cases the interaction of calcium with several other

minerals results in changes in the absorption and utilization of each. Thus, it is virtually impossible to determine a dietary level at which calcium intake alone disturbs the absorption or metabolism of other minerals. Nevertheless, calcium clearly inhibits iron absorption in a dose-dependent and dose-saturable fashion (Hallberg et al., 1992). However, the available human data fail to show cases of iron deficiency or even reduced iron stores as a result of calcium intake (Snedeker et al., 1982; Sokoll and Dawson-Hughes, 1992). Similarly, except for a single report of negative zinc balance in the presence of calcium supplementation (Wood and Zheng, 1990), the effects of calcium on zinc absorption have not been shown to be associated with zinc depletion or undernutrition. Neither have interactions of high levels of calcium with magnesium or phosphorus shown evidence of depletion of the affected nutrient (Shils, 1994).

Thus, in the absence of clinically or functionally significant depletion of the affected nutrient, calcium interaction with other minerals represents a potential risk rather than an adverse effect, in the sense that nephrolithiasis or hypercalcemia are adverse effects. Still, the potential for increased risk of mineral depletion in vulnerable populations such as those on very low mineral intakes or the elderly needs to be incorporated into the uncertainty factor in deriving a Tolerable Upper Intake Level (UL) for calcium. Furthermore, because of their potential to increase the risk of mineral depletion in vulnerable populations, calcium-mineral interactions should be the subject of additional studies.

Dose-Response Assessment

Adults: Ages 19 through 70 Years

Data Selection. Based on the discussion of adverse effects of excess calcium intake above, the most appropriate data available for identifying a critical endpoint and a no-observed-adverse-effect level (NOAEL) (or lowest-observed-adverse-effect level [LOAEL]) concern the risks of MAS and nephrolithiasis. There are few well-controlled, chronic studies of calcium that show a dose-response relationship. While there are inadequate data on nephrolithiasis to establish a dose-response relationship and to identify a NOAEL (or LOAEL), there are adequate data on MAS that can be used.

Identification of a NOAEL (or LOAEL) and Critical Endpoint. Using MAS as the clinically defined critical endpoint, a LOAEL in the range of 4 to 5 grams (100 to 125 mmol)/day can be identified for adults (Table D-1). A review of these reports revealed calcium intakes from supplements (and in some cases from dietary sources as well) in the range of 1.5 to 16.5 g (37.5 to 412.5 mmol)/day. A median intake of 4.8 g (120 mmol)/day resulted in documented cases. Since many of these reports included dietary calcium intake as well as

intake from supplements, an intake in the range of 5 g (125 mmol)/day represents a LOAEL for total calcium intake (for example, from both supplements and food). A solid figure for a NOAEL is not available, but researchers have observed that daily calcium intakes of 1,500 to 2,400 mg (37.5 to 60 mmol) (including supplements), used to treat or prevent osteoporosis, did not result in hypercalcemic syndromes (Kochersberger et al., 1991; McCarron and Morris, 1985; Riggs et al., 1996; Saunders et al., 1988; Smith et al., 1989; Thys-Jacobs et al., 1989).

Consideration of hypercalciuria may have additional relevance to the derivation of a UL for adults. Hypercalciuria is observed in approximately 50 percent of patients with calcium oxalate/apatite nephrolithiasis and is an important risk factor for nephrolithiasis (Lemann et al., 1991; Whiting and Wood, 1997). Therefore, it is plausible that high calcium intakes associated with hypercalciuria could produce nephrolithiasis. Burtis et al. (1994) reported a significant positive association between both dietary calcium and sodium intake and hypercalciuria in 282 renal stone patients and derived a regression equation to predict the separate effects of dietary calcium and urinary sodium on urinary calcium excretion. Setting urinary sodium excretion at 150 mmol/day and defining hypercalciuria for men as greater than 300 mg (7.5 mmol) of calcium/day excreted (Burtis et al., 1994), the calcium intake that would be associated with hypercalciuria was 1,685 mg (42.1 mmol)/day. For women, for whom hypercalcemia was defined as greater than 250 mg (6.2 mmol)/day excreted, it would be 866 mg (21.6 mmol)/day. The results of these calculations from the Burtis et al. (1994) equation suggest that calcium intakes lower than the recommended intake levels derived for females ([Appendix A](#)) could result in hypercalciuria in susceptible individuals.

Although Burtis et al. (1994) identified what could be defined as LOAELs for hypercalciuria, 1,685 mg (42.1 mmol)/day in men and 866 mg (21.6 mmol)/day in women, these values are not considered as appropriate for use as the LOAEL for healthy adults because they were based on patients with renal stones. However, they provide support for the need for conservative estimates of the UL.

Uncertainty Assessment. An uncertainty factor (UF) of 2 is recommended to take into account the potential for increased risk due to high calcium intakes based on the following concerns: (1) the 12 percent of the American population with renal stones, (2) the occurrence of hypercalciuria with intakes as low as 1,700 mg (42.5 mmol)/day in male and 870 mg (21.7 mmol)/day in female patients with renal stones (Burtis et al., 1994), and (3) the potential to increase the risk of mineral depletion in vulnerable populations due to the interference of calcium on mineral bioavailability, especially iron and zinc.

Derivation of the UL. A UL of 2.5 g (62.5 mmol) of calcium/day is calculated by dividing a LOAEL of 5 g (125 mmol)/day by the UF of 2. The

TABLE D-2. Case Reports of Milk Alkali Syndrome at Higher Dose (multi- and increasing doses reported)

	Ca Intake		Ca Intake	
	1st Dose (g/day)	Duration (months)	2nd Dose (g/day)	Duration
Malone and Horn, 1971	not reported	13	3 ^a	4.5 weeks
Hakim et al., 1979	1 ^a	13	2.5 ^a	3.5 weeks
Carroll et al., 1983	2.5	13	3	13 months
Schuman and Jones, 1985	not reported	13	4.6	6 weeks
Dorsch, 1986	not reported	13	2.1 ^a	6 months
Newmark and Nugent, 1993	not reported	13	8.4 ^a	< 1 year (recent)
Beall and Scofield, 1995	1 ^a	13	2.4 ^a	2 weeks
	1	13	4.2	2 weeks
	0.3	6	1.8 ^a	1 month
<i>Number of Subjects</i>	9		9	
Mean (SD)	1.2 (0.8)	12	3.6 (2.0)	16.7 (21)
Median	1	13	3	4.5
Range	0.3–2.5	6–13	1.8–8.4	2–53

^a Data do not include intake of calcium from dietary sources.

data summarized in [Table D-2](#) show that calcium intakes of 0.3 to 2.5 g (7.5 to 62.5 mmol)/day will not cause MAS and provide supportive evidence for a UL of 2,500 mg (62.5 mmol)/day for adults. The estimated UL for calcium in adults is judged to be conservative. For individuals who are particularly susceptible to high calcium intakes, such as those with hypercalcemia and hyperabsorptive hypercalciuria, this level or below should be protective.

UL for Adults Ages 19 through 70 years 2,500 mg (62.5 mmol) of calcium/day

Infants: Ages 0 through 12 Months

The safety of calcium intakes above the levels provided by infant formulas and weaning foods has recently been studied by Dalton et al. (1997). They did not find any effect on iron status of calcium intakes of approximately 1,700 mg (42.5 mmol)/day in infants, which was attained using calcium-fortified infant formula. However, further studies are needed before a UL specific to infants can be established.

UL for Infants	Ages 0 through 12 months	Not possible to establish; source of intake should be from formula and food only
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Toddlers, Children, and Adolescents: Ages 1 through 18 years

Although the safety of excess calcium intake in children ages 1 through 18 years has not been studied, a UL of 2,500 mg (62.5 mmol)/day is recommended for these life stage groups. Although calcium supplementation in children may appear to pose minimal risk of MAS or hyperabsorptive hypercalciuria, risk of depletion of other minerals associated with high calcium intakes may be greater. With high calcium intake, small children may be especially susceptible to deficiency of iron and zinc (Golden and Golden, 1981; Schlesinger et al., 1992; Simmer et al., 1988). However, no dose-response data exist regarding these interactions or the development of adaptation to chronic high calcium intakes in children. After age 9, rates of calcium absorption and bone formation begin to increase in preparation for pubertal development, but a conservative UL of 2,500 mg (62.5 mmol)/day (from diet and supplements) is recommended for children due to the lack of data.

UL for Children	Ages 1 through 18 years	2,500 mg (62.5 mmol) of calcium/day
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Older Adults: Ages > 70 Years

Several physiologic differences in older adults need to be considered in setting the UL for people over age 70. Because this population is more likely to have achlorhydria (Recker, 1985), absorption of calcium, except when associated with meals, is likely to be somewhat impaired, which would protect these individuals from the adverse effects of high calcium intakes. Furthermore, there is a decline in calcium absorption associated with age that results from changes in function of the intestine (Ebeling et al., 1994). However, the elderly population is also more likely to have marginal zinc status, which theoretically would make them more susceptible to the negative interactions of calcium and zinc (Wood and Zheng, 1990). This matter deserves more study. These effects serve to increase the UL on the one hand and decrease it on the other, with the final result being to use the same UL for older adults as for younger adults.

UL for Older Adults	Ages > 70 years	2,500 mg (62.5 mmol) of calcium/day
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Pregnancy and Lactation

The available data were judged to be inadequate for deriving a UL for pregnant and lactating women that is different from the UL for the nonpregnant and nonlactating female.

UL for Pregnancy	Ages 14 through 50 years	2,500 mg (62.5 mmol) of calcium/day
UL for Lactation	Ages 14 through 50 years	2,500 mg (62.5 mmol) of calcium/day

Special Considerations

Not surprisingly, the ubiquitous nature of calcium results in a population of individuals with a wide range of sensitivities to its toxic effects. Subpopulations known to be particularly susceptible to the toxic effects of calcium include individuals with renal failure, those using thiazide diuretics (Whiting and Wood, 1997), and those with low intakes of minerals that interact with calcium (for example, iron, magnesium, and zinc). For the majority of the general population, intakes of calcium *from food* substantially above the UL are probably safe.

Exposure Assessment

The highest median intake of calcium for any age group found in the 1994 CSFII data, adjusted for day-to-day variation (Nusser et al., 1996), was for boys 14 through 18 years of age with a median intake of 1,094 mg (27.4 mmol)/day and a ninety-fifth percentile intake of 2,039 mg (51 mmol)/day. Calcium supplements were used by less than 8 percent of young children, 14 percent of men, and 25 percent of women in the United States (Moss et al., 1989). Daily dosages from supplements at the ninety-fifth percentile were relatively small for children (160 mg [4 mmol]), larger for men (624 mg [15.6 mmol]), and largest for women (904 mg [22.6 mmol]) according to Moss et al. (1989).

Risk Characterization

Although the ninety-fifth percentile of daily intake did not exceed the UL for any age group (2,101 mg [52.5 mmol] in males 14 through 18 years of age) in the 1994 CSFII data, persons with a very high caloric intake, especially if intakes of dairy products are also high, may exceed the UL of 2,500 mg (62.5 mmol)/day.

Even if the ninety-fifth percentile of intake from foods and the most recently available estimate of the ninety-fifth percentile of supplement use

(Moss et al., 1989) are added together for teenage boys (1,920 + 928 mg/day) or for teenage girls (1,236 + 1,200 mg/day), total intakes are just at or slightly above the UL. Although users of dietary supplements (of any kind) tend to also have higher intakes of calcium from food than nonusers (Slesinski et al., 1996), it is unlikely that the same person would fall at the upper end of both ranges. Furthermore, the prevalence of usual intakes (from foods plus supplements) above the UL is well below 5 percent, even for age groups with relatively high intakes. Nevertheless, an informal survey of food products in supermarkets in the Washington, D.C. metropolitan area between 1994 and 1996 showed that the number of calcium-fortified products doubled in the 2-year period (Y. Park, Food and Drug Administration, February 1997, personal communication). Therefore, it is important to maintain surveillance of calcium-fortified products in the marketplace and monitor their impact on calcium intake.

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B. Folate

Hazard Identification

The potential hazards associated with high intake of folate were reviewed as the first step in developing a Tolerable Upper Intake Level (UL). Careful consideration was given to the metabolic interrelationships between folate and vitamin B₁₂, which include (1) shared participation of the two vitamins in an enzymatic reaction; (2) identical hematological complications resulting from deficiency of either nutrient; (3) amelioration, by folate administration, of the hematologic complications caused by either folate or B₁₂ deficiency; and (4) in B₁₂ deficiency, the occurrence of neurological complications that do not respond to folate administration.

Adverse Effects

No adverse effects have been associated with the consumption of the amounts of folate normally found in unfortified foods (Butterworth and Tamura, 1989). Therefore, this review is limited to evidence concerning intake of supplementary folate. The experimental data in animal studies and in vitro tissue and cell culture studies were considered briefly to determine whether they supported the limited human data.

Neurologic Effects. The risk of neurologic effects described in this section applies to individuals with vitamin B₁₂ deficiency. Vitamin B₁₂ deficiency is often undiagnosed but may affect a substantial percentage of the population, especially older adults. Three types of evidence suggest that excess supplementary folate intake may precipitate or exacerbate the neurologic damage of B₁₂ deficiency. First, numerous human case reports show onset or progression of neurologic complications in vitamin B₁₂-deficient individuals receiving supplemental folate (Table D-3). Second, studies in monkeys (Agamanolis et al., 1976) and fruit bats (van der Westhuyzen and Metz, 1983; van der Westhuyzen et al., 1982) show that vitamin B₁₂-deficient animals receiving supplemental folate develop signs of neuropathology earlier than do controls. The monkey studies used dietary methods to induce vitamin B₁₂ deficiency, whereas the fruit bat studies used a well-described method involving nitrous oxide (Metz and van der Westhuyzen, 1987). Third, a metabolic interaction between folate and vitamin B₁₂ is well documented (Chanarin et al., 1989). Although the association between folate treatment and neurological damage observed in human case reports does not provide proof of causality, the hazard associated with excess supplemental folate cannot be ruled out. The hazard remains plausible given the findings from animal studies and the demonstrated biochemical interaction of

TABLE D-3. Dose and Duration of Oral Folate Administration and the Occurrence of Neurological Manifestations in Patients with Pernicious Anemia

Study	Number of Subjects	Dose (mg/d)	Duration	Occurrence of Neurological Manifestations ^a
Crosby, 1960	1	0.35	2 y	1 of 1
Ellison, 1960	1	0.33–1	3 mo	1 of 1
Allen et al., 1990	3	0.4–1	3–18 mo	3 of 3
Baldwin and Dalessio, 1961	1	0.5	16 mo	1 of 1
Ross et al., 1948	4	1.25	9–23 mo	1 of 4
Chodos and Ross, 1951	4	1.25 ^b	3.5–26 mo	3 of 4
Victor and Lear, 1956	2	1.5–2.55	10–39 mo	2 of 2
Conley and Krevans, 1951	1	4.5	3 y	1 of 1
Schwartz et al., 1950	48	5	48 mo	32 of 48
Ross et al., 1948	2	5	20–23 mo	1 of 2
Conley and Krevans, 1951	2	5–8	2–2.5 y	2 of 2
Will et al., 1959	36	5–10	1–10 y	16 of 36
Bethell and Sturgis, 1948	15	5–20	12 mo	4 of 15
Chodos and Ross, 1951	11	5–30	3–25 mo	7 of 11
Israels and Wilkinson, 1949	20	5–40	35 mo	16 of 20
Wagley, 1948	10	5–600	12 mo	8 of 10
Ellison, 1960	1	5.4–6.4	2 y	1 of 1
Victor and Lear, 1956	1	6.68	2.5 y	1 of 1
Berk et al., 1948	12	10	>17 mo	3 of 12
Best, 1959	1	10	26 mo	1 of 1
Spies and Stone, 1947	1	10	22 d	1 of 1
Ross et al., 1948	6	10–15	≤ 12 mo	4 of 6
Hall and Watkins, 1947	14	10–15	2–5 mo	3 of 14
Heinle et al., 1947	16	10–40	≤ 12 mo	2 of 16
Jacobson et al., 1948	1	10–65	5 mo	1 of 1
Heinle and Welch, 1947	1	10–100	4 mo	1 of 1
Spies et al., 1948	38	≥10	24 mo	28 of 38
Ross et al., 1948	7	15	28–43 mo ^c	3 of 7
Chodos and Ross, 1951	1	15	10.5 mo ^c	1 of 1
Fowler and Hendricks, 1949	2	15–20	4–5 mo	2 of 2
Vilter et al., 1947	21	50–500	10–40 d	4 of 4

NOTE: All studies except Allen et al. (1990) were conducted before folate was added to any foods as a fortificant. In most of the case reports for which hematological status was reported, some degree of hematological improvement occurred. Studies are presented in increasing order by dose. When different doses were reported within a study, there is more than one entry for that study. Case reports that covered hematological rather than neurologic effects were excluded, namely, Alperin (1966), Heinle and Welch (1947), Herbert (1963), Reisner and Weiner (1952), Ritz et al. (1951), Sheehy et al. (1961), and Thirkette et al. (1964). The exception was the study by Allen et al. (1990), in which the subjects were vitamin B₁₂ deficient but did not have pernicious anemia.

^a Refers to neurological relapses or progression of preexisting neurological manifestations while on folate therapy.

^b In two patients, the neurological progression was characterized as minimal or slight. Neurological progression was also observed when the dose was increased to 15 mg/day in these patients.

^c The initial dosage of 1.25 mg/day was increased to 15 mg/day after variable durations of treatment. Neurological progression occurred only at 15 mg/day in these patients.

the two nutrients. The resulting neurological damage may be serious, irreversible, and crippling.

For many years, it has been recognized that excessive intake of folate supplements may obscure or mask and potentially delay the diagnosis of vitamin B₁₂ deficiency. Delayed diagnosis can result in an increased risk of progressive, unrecognized neurological damage.

Evidence from animal as well as in vitro tissue and cell culture (Baxter et al., 1973; Hommes and Obbens, 1972; Kehl et al., 1984; Loots et al., 1982; Olney et al., 1981; Spector, 1972; Weller et al., 1994) studies suggests that folate is neurotoxic and epileptogenic in animals; however, clear evidence of folate-induced neurotoxicity in humans is lacking. Concerns have been raised about the possibility of decreased effectiveness of treatment if individuals treated with anticonvulsant drugs take high doses of folate. However, the UL does not apply to drug-drug interactions or to high doses taken under medical supervision.

General Toxicity. In one nonblinded, uncontrolled trial, oral doses of 15 mg/day of folate for 1 month were associated with mental changes, sleep disturbances, and gastrointestinal effects (Hunter et al., 1970). However, studies using comparable or higher doses, longer durations, or both failed to confirm these findings (Gibberd et al., 1970; Hellstrom, 1971; Richens, 1971; Sheehy, 1973; Suarez et al., 1947).

Reproductive and Developmental Effects. Many studies have evaluated the periconceptual use of supplemental folate (in doses of approximately 0.4 to 5.0 mg) to prevent neural tube defects (see [Table D-4](#)). No adverse effects have been demonstrated, but the studies were not specifically designed to assess adverse effects. No reports were found of adverse effects attributable to folate in long-term folate supplement users or in infants born each year to mothers who take supplements, but this has not been investigated systematically. Because it is possible that subtle effects might have been missed, investigations designed to detect adverse effects are needed.

Carcinogenicity. In a large epidemiological study, positive associations were found between supplementary folate intake and the incidence of cancer of the oropharynx and hypopharynx, and total cancer (Selby et al., 1989). However, the authors of this study suggest that these associations might have been related to unmeasured confounding variables such as alcohol and smoking. Additionally, other studies suggest that folate might be anticarcinogenic (Campbell, 1996).

Hypersensitivity. Individual cases of hypersensitivity reactions to oral and parenteral folate administration have been reported (Gotz and Lauper, 1980;

TABLE D-4. Assessing Adverse Reproductive Effects from Studies Involving Supplemental Folate

Reference	Subjects	Duration of Study	Study Design
Laurence et al., 1981	95 women	≥ 9 wk	Clinical trial: randomized, controlled, double-blinded
Smithells et al., 1981	550 women	110 d (mean duration)	Clinical trial: controlled
Mukherjee et al., 1984	450 pregnant women	≥ 9 mo	Prospective cohort study
Vergel et al., 1990	81 women	≥ 3 mo	Clinical trial: controlled
Wald et al., 1991	910 women	A few months ^d	Clinical trial: randomized, double-blinded controlled
Czeizel and Dudas, 1992	4,753 women (<35 y)	3 mo	Clinical trial: randomized, controlled
Holmes-Siedle et al., 1992	100 women	Periconceptional period; 7–10 y follow-up	Observational study
Kirke et al., 1992	354 pregnant women	5 mo	Clinical trial: randomized, controlled
Czeizel et al., 1994	5,502 women	3 mo	Randomized, controlled trial

^a NR=not reported. Study was not designed to assess adverse effects.

^b Plasma folate was measured at different times in pregnancy, but compliance with prenatal vitamin use was not recorded.

^c There was no control of confounding variables making it difficult to interpret the results.

^d The average duration of exposure is not indicated in the publication, but was likely a few months.

Mathur, 1966; Mitchell et al., 1949; Sesin and Kirschenbaum, 1979; Sparling and Abela, 1985). Such hypersensitivity is rare, but reactions have occurred at supplemental folate doses as low as 1 mg/day (Sesin and Kirschenbaum, 1979).

Intestinal Zinc Absorption. Although there has been some controversy regarding whether supplemental folate intake adversely affects intestinal zinc absorption (Butterworth and Tamura, 1989), a comprehensive review of the literature reveals that folate supplementation has either no effect on zinc nutriture or an extremely subtle one (Arnaud et al., 1992; Butterworth et al., 1988; Hambidge et al., 1993; Keating et al., 1987; Milne et al., 1984; Tamura,

Folate Dose (mg/d)	Adverse Effects Observed	Method(s) for Assessing Association and Adverse Effects
4	None	NR ^a
1	None	NR
0.4–1 ^b	Pregnancy complications, fetal distress ^c	Statistical association between 12 indices of nutrient status and 7 poorly defined categories of complications
5	None	NR
4	None	Medical exams performed ^b
0.8	None	NR
1	Frequency of developmental anomalies not greater than expected ^e	NR
0.36	None	NR
0.8	13.4% fetal death rate in supplemented group compared with 11.5% fetal death rate on controls ^f	Documentation for all pregnancy outcomes was collected. Statistical evaluation based on two-tailed chi-square test.

^e The frequency of developmental anomalies was not greater than expected; but parental reports of worries, fearfulness, and fussiness in the children were greater than expected.

^f This may be a chance finding resulting from multiple comparisons. It has been reported that prenatal multivitamin supplementation (which includes folate) can reduce preterm deliveries, causing an apparent increase in recognized abortions as the duration of all pregnancies increases (Scholl et al., 1997).

Mukherjee et al. (1984) noted a significant association between the occurrence of fetomaternal complications and the combination of low maternal plasma zinc and high maternal plasma folate concentrations. However, this study may have failed to control for potential confounding factors. Furthermore, these findings are not supported by Tamura and colleagues (1992), who found high serum folate concentrations to be associated with favorable pregnancy outcomes including (1) higher birth weight and Apgar scores of newborns, (2) reduced prevalence of fetal growth retardation, and (3) lower incidence of maternal infection close to the time of delivery.

Summary

The weight of the limited, but suggestive evidence that excessive folate intake may precipitate or exacerbate neuropathy in vitamin B₁₂-deficient individuals justifies the selection of this endpoint as the critical endpoint for the development of a UL for folate.

Dose-Response Assessment

Adults

Data Selection. To evaluate a dose-response relationship and derive a UL for folate, case reports were used that involved oral administration of folate in patients with vitamin B₁₂ deficiency who showed development or progression of neurological complications. Because a number of apparently healthy individuals are vitamin B₁₂ deficient (IOM, 1998), these individuals are considered part of the general population in setting a UL.

Identification of a NOAEL or LOAEL. The literature was reviewed to find cases in which vitamin B₁₂-deficient patients who were receiving oral doses of folate experienced progression of neurologic disorders. Data were not available on which to set a no-observed-adverse-effect level (NOAEL). A lowest-observed-adverse-effect level (LOAEL) of 5 mg of folate is based on the data presented in [Table D-3](#) and summarized below:

- At doses of folate of 5 mg/day and above, there were more than 100 reported cases of neurological progression.
- At doses of less than 5 mg/day of folate (0.33 to 2.5 mg/day), there are only eight well-documented cases.
- In the majority of cases throughout the dose range, folate supplementation maintained the patients in hematologic remission over a considerable time span.
- The background intake of folate from food was not specified, but all except for three cases (those reported by Allen and coworkers [1990]) occurred before the fortification of breakfast cereal with added folate.

Uncertainty Assessment. An uncertainty factor (UF) of 5 was selected. Compared with the UFs used to date for other nutrients for which there was also a lack of controlled, dose-response data, a UF of 5 is large. The selection of a relatively large UF is based primarily on the severity of the neurological complications observed, but also on the use of a LOAEL rather than a NOAEL to derive the UL. The UF is not larger than 5 on the basis of the uncontrolled observation that millions of people have been exposed to self treatment with about one-tenth of the LOAEL (i.e., 400 µg in vitamin pills) without reported harm.

Derivation of a UL. The LOAEL of 5 mg/day of folate was divided by the UF of 5 to obtain the UL for adults of 1 mg (or 1,000 µg) of folate added to fortified foods or consumed as supplements.

A UL of 1,000 µg/day is set for all adults rather than just for the elderly for the following reasons: (1) the devastating and irreversible nature of the neurological consequences, (2) data suggesting that pernicious anemia may develop at a younger age in some racial/ethnic groups (Carmel and Johnson, 1978), and (3) uncertainty about the occurrence of vitamin B₁₂ deficiency in younger age groups. In general, the prevalence of vitamin B₁₂ deficiency in females in the childbearing years is very low, and the consumption of supplementary folate at or above the UL in this subgroup is unlikely to produce adverse effects.

Folate UL Summary, Adults

UL for Adults	Ages 19 years and older	1,000 µg/day of folate added to fortified foods or consumed as supplements
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Other Life Stage Groups

There are no data on other life stage groups that can be used to identify a NOAEL or LOAEL and derive a UL. For infants, the UL was judged not determinable because of lack of data on adverse effects in this age group and concern about the infant's ability to handle excess amounts. To prevent high levels of intake, the only source of intake for infants should be from food, which would include that provided by fortified products. No data were found to suggest that other life stage groups have increased susceptibility to adverse effects of high supplemental folate intake. Therefore, the UL of 1,000 µg/day is also set for adult pregnant and lactating women. The UL of 1,000 µg/day for adults was adjusted for children and adolescents on the basis of relative body weight (see [Appendix C](#)). In some cases, values have been rounded down.

Life Stage	Ages	Supplemental Folate
UL For Infants	0 through 12 months	Not possible to establish for supplemental folate
UL for Children	1 through 3 years	300 µg/day
	4 through 8 years	400 µg/day
	9 through 13 years	600 µg/day
	14 through 18 years	800 µg/day

Life Stage	Ages	Supplemental Folate
UL for Pregnancy	14 through 18 years	800 µg/day
	19 through 50 years	1,000 µg/day
UL for Lactation	14 through 18 years	800 µg/day
	19 through 50 years	1,000 µg/day

Special Considerations

Individuals who are at risk of vitamin B₁₂ deficiency (e.g., those who eat no animal foods [vegans]) may be at increased risk of the precipitation of neurologic disorders if they consume excess folate (IOM, 1998).

Intake Assessment

It is not possible to use data from the Third National Health and Nutrition Examination Survey (NHANES III) or the Continuing Survey of Food Intake by Individuals (CSFII; USDA 1994–1996) to determine the population's exposure to supplemental folate. Currently available survey data do not distinguish between food folate and synthetic folate (folic acid) added as a fortificant or taken as a supplement. Based on data from NHANES III and excluding pregnant women (for whom folate supplements are often prescribed), the highest reported total folate intake from food and supplements at the ninety-fifth percentile, 983 µg/day, was found in females aged 30 through 50 years. This intake was obtained from food (which probably included fortified, ready-to-eat cereals, a few of which contain as much as 400 µg of folic acid/serving) and supplements. For the same group of women, the reported intake at the ninety-fifth percentile from food alone (which also probably included fortified, ready-to-eat cereal) was 438 µg/day. In Canada, the contribution of ready-to-eat cereals is expected to be lower because the maximum amount of folate that can be added to breakfast cereal is 60 µg of folic acid/100 g (Health Canada, 1996).

It would be possible to exceed the UL of 1,000 µg/day of supplemental folate through the ingestion of fortified foods and/or supplements in typical total diets in the U.S. and Canada (IOM, 1998).

Risk Characterization

The intake of folate is currently higher than indicated by NHANES III because enriched cereal grains in the U.S. food supply, to which no folate was added previously, are now fortified with 140 µg of folic acid/100 g of cereal grain. Using data from the 1987–1988 U.S. Department of Agriculture's Nationwide Food Consumption Survey, the U.S. Food and Drug Administration (FDA) estimated that the ninety-fifth percent percentile of folate intakes for

males aged 11 to 18 years would be 950 µg of total folate at this level of fortification; this value assumes that these young males would also take supplements containing 400 µg of folate (DHHS, 1993). Excluding pregnant women, for whom estimates were not provided, the ninety-fifth percentile for total folate for all other groups would be lower, and folate intake as folic acid would be lower still. Using a different method of analysis, the FDA estimated that those who follow the guidance of the Food Guide Pyramid and consume cereal grains at the upper end of the recommended range would obtain an additional 440 µg of folate as folic acid under the new U.S. fortification regulations (DHHS, 1993). (This estimate assumes 8 servings [16 slices] of bread at 40 µg of folic acid per serving and two ~ 1-cup servings of noodles or pasta at 60 µg of folic acid per serving.) Those who eat other fortified foods (such as cookies, crackers, and donuts) instead of bread might ingest a comparable amount of folic acid. Using either method of analysis and assuming regular use of an over-the-counter supplement that contains folic acid (ordinarily 400 µg per dose), it is unlikely that intake of folate added to foods or as supplements would exceed 1,000 µg on a regular basis for any of the life stage or gender groups.

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C. Riboflavin

Hazard Identification

No adverse effects associated with riboflavin consumption from food or supplements have been reported. Studies involving large doses of riboflavin (Schoenen et al., 1994; Stripp, 1965; Zempleni et al., 1996) have not been designed to systematically evaluate adverse effects. The limited evidence from studies involving large intakes of riboflavin is summarized here.

No adverse effects were reported in humans after single doses of up to 60 mg of supplemental riboflavin together with 11.6 mg of riboflavin given intravenously as a single bolus dose (Zempleni et al., 1996). This study is of limited use in setting a Tolerable Upper Intake Level (UL) because it was not designed to assess adverse effects. It is possible that chronic administration of these doses would pose some risk.

In a brief communication, a study by Schoenen and coworkers (1994) stated that no short-term side effects were reported by 48 of 49 patients complaining of migraine headaches and treated with 400 mg/day of riboflavin with or without aspirin (75 mg) taken with meals for at least 3 months. Schoenen and coworkers (1994) reported that one patient receiving riboflavin and aspirin withdrew from the study because of gastric upset. This isolated finding is probably an anomaly since no side effects were reported by other patients. Since no clinical or biochemical assessment was undertaken for possible adverse effects, this study by itself is inadequate to use as a basis for determining a no-observed-adverse-effect level (NOAEL).

The apparent lack of harm resulting from high oral doses of riboflavin may be due to its limited solubility, humans' limited capacity to absorb it from the gastrointestinal tract (Levy and Jusko, 1966; Stripp, 1965; Zempleni et al., 1996), and its rapid excretion in the urine (McCormick, 1997). Zempleni et al. (1996) showed that the maximal amount of riboflavin that was absorbed from a single oral dose was 27 mg. A study by Stripp (1965) found limited absorption of 50 to 500 mg of riboflavin with no adverse effects. The poor intestinal absorption of riboflavin is well recognized: riboflavin taken by mouth is sometimes used to mark the stool in experimental studies. There are no data from animal studies suggesting that uptake of riboflavin during pregnancy presents a specific potential hazard for the fetus or infant.

The only evidence of adverse effects associated with riboflavin comes from in vitro studies showing the formation of active oxygen species on intense exposure to visible or ultraviolet light (Ali et al., 1991; Floersheim, 1994; Spector et al., 1995). However, given the lack of any demonstrated functional or structural adverse effects in humans or animals following excess riboflavin intake, the relevance of this evidence to human health effects in vivo is highly questionable. Nevertheless, it is theoretically plausible that riboflavin increases photosensitivity to ultraviolet irradiation. Additionally, there is a theoretical risk

that excess riboflavin will increase the photosensitized oxidations of cellular compounds such as amino acids and proteins (McCormick, 1977) in infants treated for hyperbilirubinemia, with possible undesirable consequences.

Dose-Response Assessment

The data on adverse effects from high riboflavin intake are not sufficient for a quantitative risk assessment to establish a NOAEL (or lowest-observed-adverse-effect level [LOAEL]), and a UL cannot be derived.

Special Considerations

There is some in vitro evidence that riboflavin may interfere with detoxification of chrome VI by reduction to chrome III (Sugiyama et al., 1992). This may be of concern in people who may be exposed to chrome VI; for example, workers in chrome plating. Infants treated for hyperbilirubinemia may also be sensitive to excess riboflavin.

Intake Assessment

Although no UL can be set for riboflavin, an intake assessment is provided here for possible future use. Data from the Third National Health and Nutrition and Examination Survey (unpublished data, C.L. Johnson and J.D. Wright, National Center for Health Statistics, Centers for Disease Control and Prevention, 1997) showed that the highest mean intake of riboflavin from diet and supplements for any life stage and gender group reported was for males aged 31 through 50 years: 6.9 mg/day. The highest reported intake at the ninety-fifth percentile was 11 mg/day in females over age 70 years.

Risk Characterization

No adverse effects have been associated with excess intake of riboflavin from food or supplements. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of riboflavin intake are limited, caution may be warranted.

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Appendix E

Biographical Sketches of Subcommittee on Upper Reference Levels of Nutrients

IAN C. MUNRO, Ph.D., is a leading authority on toxicology and has over 30 years experience in dealing with complex regulatory issues related to product safety. He has in excess of 150 scientific publications in the fields of toxicology and risk assessment. Dr. Munro is currently a principal with CanTox, Inc. in Mississauga, Ontario. Formerly, he held senior positions at Health and Welfare Canada as director of the Bureau of Chemical Safety and director general of the Food Directorate, Health Protection Branch. He was responsible for research and standard-setting activities related to microbial and chemical hazards in food and the nutritional quality of the Canadian food supply. He has contributed significantly to the development of risk assessment procedures in the field of public health, both nationally and internationally, through membership on various committees dealing with the regulatory aspects of risk assessment and risk management of public health hazards. Dr. Munro is a graduate of McGill University in biochemistry and nutrition and holds a Ph.D. from Queen's University in pharmacology and toxicology. He is a fellow of the Royal College of Pathologists, London. He also was a former director of the Canadian Centre for Toxicology at Guelph, Ontario.

WALTER MERTZ, M.D., received his M.D. at the University of Mainz, Germany. He was intern surgeon at the County Hospital, Hersfeld, and assistant resident at the Medical University Hospital, Frankfurt, Germany. He came to the National Institute of Health in Bethesda in 1953 where he worked on nutritional aspects of liver disease and on the glucose tolerance factor, later identified as the trace element chromium. Dr. Mertz continued his work on chromium in clinical studies at the Walter Reed Army Institute of Research as chief, Department of Biological Chemistry. He later joined the Human Nutrition Research Division, Agricultural Research Service, United States Department of Agriculture, as chief, Vitamin and Mineral Nutrition Laboratory. In 1972, he was appointed director of the Nutrition Institute, now the Beltsville Human Nutrition Research

Center, a position that he held until his retirement in 1993. Dr. Mertz is the author of more than 200 scientific publications.

RITA B. MESSING, Ph.D., received her Ph.D. in physiological psychology from Princeton University and did postdoctoral research in the Department of Nutrition and Food Science at Massachusetts Institute of Technology in the Laboratory of Neuroendocrine Regulation. Dr. Messing has been in the Department of Pharmacology, University of Minnesota Medical School since 1981, and is currently an associate professor. Since 1990 her primary employment has been at the Minnesota Department of Health in Environmental Toxicology, where she supervises the Site Assessment and Consultation Unit, which conducts public health activities at hazardous waste sites and other sources of uncontrolled toxic releases. Dr. Messing has 70 publications in toxicology and risk assessment, neuropharmacology, psychobiology and experimental psychology. She has taught at Rutgers University, Northeastern University, University of California at Irvine, and the University of Minnesota, and had visiting appointments at Organon Pharmaceuticals in the Netherlands and the University of Paris.

SANFORD A. MILLER, Ph.D., is dean of the Graduate School of Biomedical Sciences and professor in the Departments of Biochemistry and Medicine at The University of Texas Health Science Center at San Antonio. He is the former director of the Center for Food Safety and Applied Nutrition at the Food and Drug Administration. Previously, he was professor of nutritional biochemistry at the Massachusetts Institute of Technology (MIT). Dr. Miller has served on many national and international government and professional society advisory committees, including the Federation of American Societies for Experimental Biology Expert Committee on GRAS Substances, the National Advisory Environmental Health Sciences Council of the National Institutes of Health, the Food and Nutrition Board and its Food Forum, the Joint WHO/FAO Expert Advisory Panel on Food Safety (Chairman), and the steering committees of several WHO/FAO panels. He also served as chair of the Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues. 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.

SUZANNE P. MURPHY, Ph.D., R.D., is adjunct associate professor in the Department of Nutritional Sciences at the University of California, Berkeley and director of the California Expanded Food and Nutrition Program at the University of California, Davis. She received her B.S. in mathematics from Temple University and her Ph.D. in nutrition from the University of California, Berkeley. Dr. Murphy's research interests include dietary assessment

methodology, development of food composition databases, and nutritional epidemiology. She is a member of the National Nutrition Monitoring Advisory Council, and serves on the editorial boards for the *Journal of Nutrition*, the *Journal of Food Composition and Analysis*, and *Family Economics and Nutrition Review*. Dr. Murphy is a member of numerous professional organizations including the American Dietetic Association, the American Society for Nutritional Sciences, the American Public Health Association, American Society for Clinical Nutrition, and the Society for Nutrition Education. She has over 50 publications on dietary assessment methodology and has lectured nationally and internationally on this subject.

JOSEPH V. RODRICKS, Ph.D., is one of the founding principals of the ENVIRON Corporation, with internationally recognized expertise in assessing the risks to human health of exposure to toxic substances. He received his B.S. from Massachusetts Institute of Technology and his Ph.D. in biochemistry from the University of Maryland. Dr. Rodricks is certified as a diplomate of the American Board of Toxicology. Before working as a consultant, he spent fifteen years at the Food and Drug Administration (FDA). In his final three years at the FDA, he was Deputy Associate Commissioner for Science, with special responsibility for risk assessment. He was a member of the National Academy of Sciences (NAS) Board on Toxicology and Environmental Health Hazards, and has also served on or chaired ten other NAS Committees. Dr. Rodricks has more than 100 scientific publications on food safety and risk assessment and has lectured nationally and internationally on these subjects. He is the author of *Calculated Risks*, a nontechnical introduction to toxicology and risk assessment.

IRWIN H. ROSENBERG, M.D., is an internationally recognized leader in nutrition science who serves as professor of physiology, medicine and nutrition at Tufts University School of Medicine and School of Nutrition, as well as director, Jean Mayer United States Department of Agriculture (USDA) Human Nutrition Research Center on Aging at Tufts University and dean for nutrition sciences, Tufts University. He is the first holder of the Jean Mayer Chair in Nutrition at Tufts. Prior to joining Tufts, Dr. Rosenberg held faculty positions at Harvard Medical School and the University of Chicago where he served as the first director of the Clinical Nutrition Research Center. As a clinical nutrition investigator, he has helped develop a nutritional focus within the field of gastroenterology with his primary research interest being in the area of folate metabolism. His research for the past decade has focused on nutrition and the aging process. Among his many honors are the Josiah Macy Faculty Award, Grace Goldsmith Award of the American College of Nutrition, Robert H. Herman Memorial Award of the American Society of Clinical Nutrition, the Jonathan B. Rhoads Award of the American Society for Parenteral and Enteral Nutrition, and the 1994 W.O. Atwater Memorial Lectureship of the USDA. Dr. Rosenberg was elected to the Institute of Medicine in 1994 and recently

received the Bristol Myers Squibb/Mead Johnson Award for Distinguished Achievement in Nutrition Research, 1996.

STEVE L. TAYLOR, Ph.D., serves as professor and head of the Department of Food Science and Technology and director of the Food Processing Center at the University of Nebraska. He also maintains an active research program in the area of food allergies through the Food Allergy Research and Resource Program at the University of Nebraska. He received his B.S. and M.S. in food science and technology from Oregon State University, and his Ph.D. in biochemistry from the University of California, Davis. Dr. Taylor's primary research interests involve naturally occurring toxicants in foods, especially food allergens. His research involves the development of immunoassays for the detection of residues of allergenic foods contaminating other foods, the effect of processing on food allergens, and the assessment of the allergenicity of genetically engineered foods. Dr. Taylor has over 160 publications. He is a member of numerous professional associations including Institute of Food Technologists; American Chemical Society; American Academy of Allergy, Asthma, and Immunology; and Society of Toxicology.

ROBERT H. WASSERMAN, Ph.D., is James Law Professor of Physiology, College of Veterinary Medicine, Cornell University. He received his B.S. in microbiology and his Ph.D. in nutritional microbiology from Cornell University. Dr. Wasserman's research interest is the mechanisms and control of epithelial transport of mineral ions with emphasis given to the role of vitamin D on the intestinal absorption of calcium and phosphorus. He was elected to the National Academy of Sciences in 1980, chaired its Committee on the Scientific Basis of Meat and Poultry Inspection, and was a member of the Food and Nutrition Board. Dr. Wasserman has served on the editorial boards of *Proceedings of the Society for Experimental Biology and Medicine*, *The Cornell Veterinarian*, *Calcified Tissue International*, and *Journal of Nutrition*. Included among his numerous awards are the Mead Johnson Lectureship at Iowa State University, the Lichtwitz Prize of the Institut National de la Sante et de la Recherche Medicale in Paris, the MERIT status award of the National Institutes of Health, William F. Neuman Research Award from the American Society of Bone and Mineral Research, the Career Recognition Award from Vitamin D Workshop, Inc., and election as a fellow of the American Institute of Nutrition.

FNB Staff

ALLISON A. YATES, Ph.D., R.D., is director of the Food and Nutrition Board (FNB), Institute of Medicine, National Academy of Sciences, and also serves as study director for the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dr. Yates received a B.S. in dietetics and an M.S. in

public health (nutrition) from U.C.L.A., a Ph.D. in nutrition from the University of California, Berkeley, and is a registered dietitian. She is a member of the American Society for Nutrition Sciences, American Society of Clinical Nutrition, American Dietetic Association, Institute of Food Technologists, and the American Public Health Association. Dr. Yates served as a member of the FNB Committee on Military Nutrition Research prior to assuming her position at IOM in 1994. Most recently, Dr. Yates was professor of food and nutrition and dean of the College of Health and Human Sciences at the University of Southern Mississippi.

SANDRA A. SCHLICKER, Ph.D., is a senior program officer at the Food and Nutrition Board (FNB), and serves as the study director for the Subcommittee on Upper Reference Levels of Nutrients. Prior to joining the FNB, she was vice president of a Washington, D.C.-based consulting/research firm that focused on public policy issues in the fields of agriculture, health, and nutrition. Dr. Schlicker has served as a government relations representative, media spokesperson, and nutrition consultant to food manufacturers and trade associations. She is a licensed nutritionist and holds a B.S. in science and an M.S. and Ph.D. in food and nutrition from The Pennsylvania State University. An active member of the American Dietetic Association, Dr. Schlicker has authored numerous nutrition articles in professional and consumer publications.

ELISABETH A. REESE, M.P.H., is a research associate with the Food and Nutrition Board (FNB). In addition to her work with the Subcommittee on Upper Reference Levels of Nutrients, Ms. Reese has worked on several Institute of Medicine and National Research Council reports including those of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes on calcium and related nutrients, and of the Committee to Ensure Safe Food from Production to Consumption. She also serves as president of the Society for Risk Analysis' Dose Response Specialty Group. Prior to joining the FNB in 1996, Ms. Reese was a staff scientist at an environmental consulting firm where she assessed and summarized the human health hazards of environmental chemicals and provided technical support for risk assessment projects. She earned a B.A. in chemistry and history from New York University, an M.P.H. in toxicology from the University of Michigan, and has since taken additional course work in epidemiology.